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Intermolecular palladium-catalyzed coupling of 2-halopyridines and alcohols for the preparation of pyridine ether PPAR agonists

Paul S. Humphries,* Simon Bailey,* Quyen-Quyen T. Do, Jack H. Kellum, Guy A. McClellan and David M. Wilhite

Pfizer Global R&D, Department of Medicinal Chemistry, 10614 Science Center Drive, San Diego, CA 92121, USA

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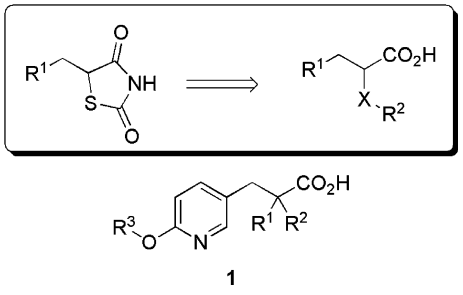
Abstract—A series of pyridine ether PPAR agonists were synthesized through intermolecular palladium-catalyzed coupling of 2-halopyridines and alcohols. This method proved to be versatile, efficient, and amenable to parallel synthesis.

Peroxisome proliferator-activated receptors (PPARs) are pharmaceutical targets of great importance. Their wide-ranging effects on key transcriptional pathways for lipid handling, insulin sensitivity, inflammation, and other functions have led to marketed drugs and vast clinical and preclinical research efforts.[1–4]

In 1991, a series of PPAR analogues were disclosed, which for the first time did not contain a thiazolidine-2,4-dione pharmacophore.[5] These were propanoic acid derivatives with a substituent placed in the α-position such that the whole group could mimic the thiazolidine-2,4-dione ring. Based on the above and a knowledge of PPAR ligands publicly disclosed, we wished to synthesize compounds represented by the general structure **1** (Fig. 1). We envisaged the pyridyl ether moiety of **1** to be efficiently formed via intermolecular palladium-catalyzed coupling of the requisite 2-halopyridines and alkyl alcohols.

Aromatic ethers are structural motifs in many naturally occurring and medicinal compounds.[6] Although there are numerous methods for their synthesis,[7] a mild and general method remained elusive for a considerable period of time. Recently, the Buchwald group developed an efficient catalyst for the palladium-catalyzed intermolecular coupling of aryl bromides and chlorides and primary alcohols.[8,9] Prior to this work, successful intermolecular palladium-catalyzed C–O bond forming processes were limited to the reactions of activated aryl halides and alcohols lacking β-hydrogens.[10] This new general procedure minimizes β-hydride elimination from **A**, thus allowing the productive reductive elimination step to occur at a faster rate (Scheme 1).[11] This is made possible by the use of bulky phosphine ligand **2**, which balances the subtle interplay of both sterics and electronics, allowing for successful C–O bond formation.



1

Figure 1. Thiazolidine-2,4-dione mimic and chosen lead scaffold.

In the original publication, only one example of the use of a 2-halopyridine was described. We felt that this efficient and practically simple protocol had utility as a versatile method. Our first attempt at this reaction involved the coupling of 2-chloropyridine **3** and alcohol **4** to afford pyridyl ether **5** in good yield (Scheme 2).[12]

With the above result in hand, we then pursued a variety of targets by performing the intermolecular palladium-catalyzed coupling of bromopyridine **6** and a variety

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* Corresponding authors. Tel.: +1 858 622 7956; fax: +1 858 526 4438 (P.S.H.); tel.: +1 858 526 4692; fax: +1 858 526 4315 (S.B.); e-mail addresses: paul.humphries@pfizer.com; simon.bailey@pfizer.com

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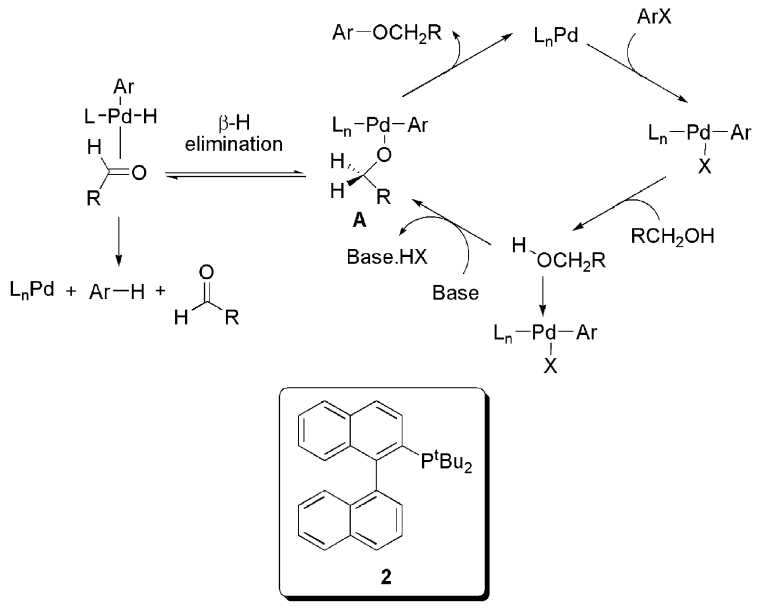
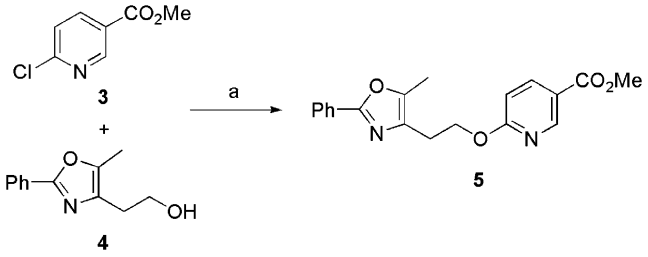


Scheme 1. Mechanism of intermolecular palladium-catalyzed synthesis of aryl ethers.

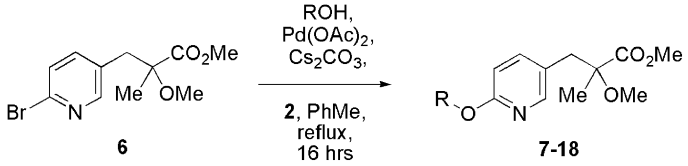


Scheme 2. Reagents and conditions: (a) $Pd(OAc)_2$ (cat.), racemic-2-(di-*tert*-butylphosphino)-1,1′-binaphthyl **2** (cat.), Cs_2CO_3, PhMe, reflux, 16 h, 58%.

of primary alcohols (Table 1).[13,14] In general, a variety of diverse alcohols afforded the expected products in excellent yield. As expected, alcohols containing oxazoles, thiazoles, and pyridines are tolerated in this chemistry. In a limited number of cases, functionality (e.g., basic amines, pyrazoles, benzimidazoles, indoles) caused palladium sequestration and no reaction occurred (data not shown).

We then shifted our attention to variation of halopyridine, whilst holding constant the 2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethanol reactant **19** (Table 2).

Table 1. Intermolecular palladium-catalyzed coupling of bromopyridine **6** and a variety of primary alcohols[a]



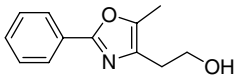
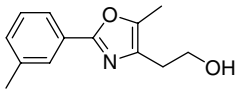
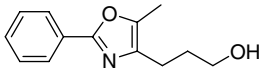
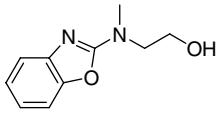
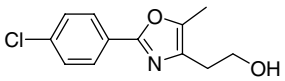
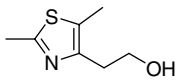
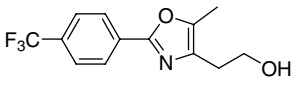
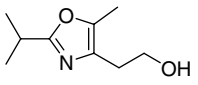
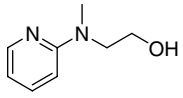
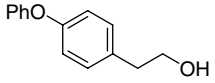
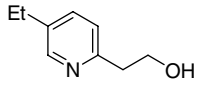
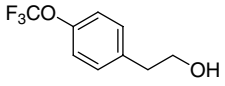
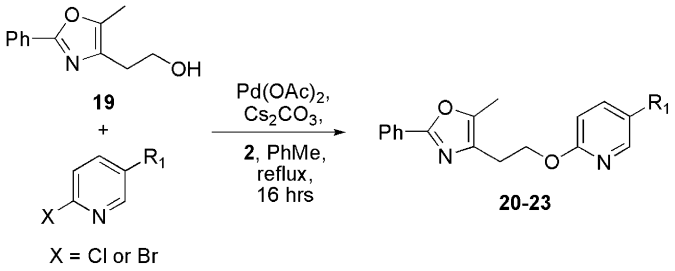
Entry	Alcohol	Product	Yield (%)	Entry	Alcohol	Product	Yield (%)
1		**7**	85	7		**13**	69
2		**8**	79	8		**14**	90
3		**9**	56	9		**15**	68
4		**10**	67	10		**16**	59

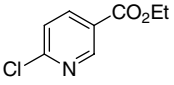
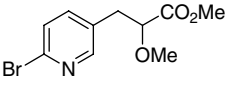
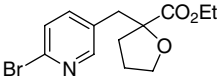
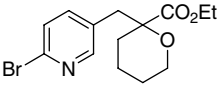
Table 1 (*continued*)

Entry	Alcohol	Product	Yield (%)	Entry	Alcohol	Product	Yield (%)
5		**11**	79	11		**17**	64
6		**12**	100	12		**18**	67

[a] Reactions were run using 0.5 mmol halopyridine, 1.0 mmol alcohol, 1.5 mmol cesium carbonate, 8 mol % $Pd(OAc)_2$, 10 mol % racemic-2-(di-*tert*-butylphosphino)-1,1′-binaphthyl **2** and 5 mL toluene.

Table 2. Intermolecular palladium-catalyzed coupling of alcohol **19** and a variety of halopyridines[a]

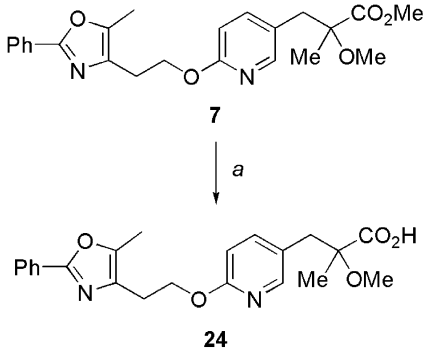


Entry	Halopyridine	Product	Yield (%)	Entry	Halopyridine	Product	Yield (%)
1		**20**	93	3		**22**	74
2		**21**	72	4		**23**	70

[a] Reactions were run using 0.5 mmol halopyridine, 1.0 mmol alcohol, 1.5 mmol cesium carbonate, 8 mol % $Pd(OAc)_2$, 10 mol % racemic-2-(di-*tert*-butylphosphino)-1,1′-binaphthyl **2** and 5 mL toluene.

Switching from 2-bromopyridines to 2-chloropyridines had no effect on isolated yields. Similarly, variation of the 5-substituent of the pyridine ring resulted in equally high yields.

Having efficiently synthesized a diverse set of intermediate esters, we then sought an expedient method for obtaining the final carboxylic acids. We opted for a microwave-assisted procedure for this basic hydrolysis step. As shown in Scheme 3, the carboxylic acids (e.g., **24**) could be obtained in a matter of minutes.[15] The significant reduction in reaction time resulted in a productivity enhancement due to increased sample processing.



Scheme 3. Reagents and conditions: (a) 1 N aq NaOH, MeCN, 100 °C, μW, 10 min, 92%.

In summary, we have expanded the scope of the intermolecular palladium-catalyzed synthesis of aryl ethers. Utilization of this method resulted in a rapid, convenient, and high-yielding two step protocol for the preparation of PPAR agonists. In particular, the intermolecular palladium-catalyzed coupling of 2-halopyridines and alcohols proved to be versatile, efficient, and amenable to parallel synthesis. A full account of the medicinal chemistry of these compounds will be given elsewhere.

Acknowledgments

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12. All new compounds were characterized by full spectroscopic data, yields refer to chromatographed material with purity >95%.
13. General procedure for the intermolecular palladium-catalyzed synthesis of pyridyl ethers. An oven-dried flask was charged with palladium(II) acetate (8 mol %), racemic-2-(di-*tert*-butylphosphino)-1,1′-binaphthyl **2** (10 mol %) and cesium carbonate (3 equiv). The flask was then evacuated and back-filled with nitrogen and fitted with a rubber septum. Anhydrous toluene (2.5 mL) followed by halopyridine **6** (0.144 g, 0.5 mmol), alcohol **4** (0.203 g, 1.0 mmol) and additional anhydrous toluene (2.5 mL) was added via a syringe. The flask was then sealed under nitrogen and placed in a pre-heated oil bath to allow the solution to reflux for 16 h. The reaction mixture was cooled to ambient temperature, diluted with diethyl ether (2 mL), and filtered through a pad of Celite, washing with additional diethyl ether (10 mL). The filtrate was then concentrated in vacuo and purified (Biotage Sp4) by silica gel chromatography (hexanes to ethyl acetate over 10 column volumes) to afford ester **7** as a pale yellow oil (0.174 g, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97–7.95 (m, 1H), 7.92 (d, $J = 2.1$ Hz, 2H), 7.43–7.39 (m, 4H), 6.63 (d, $J = 8.5$ Hz, 1H), 4.52 (t, $J = 6.8$ Hz, 2H), 3.70 (s, 3H), 3.32–3.28 (m, 3H), 2.96–2.90 (m, 4H), 2.33 (s, 3H), 1.33 (s, 3H). ESIMS (*m*/*z*): 411 (M+H).
14. A modified microwave-assisted intermolecular palladium-catalyzed procedure was never attempted during these investigations.
15. General procedure for the microwave-assisted hydrolysis reaction. A Smith Process Vial (2–5 mL) was charged, under nitrogen, with a stir bar, methyl ester **7** (0.174 g, 0.42 mmol), 1 N aq sodium hydroxide (1.26 mL, 1.26 mmol), and acetonitrile (2 mL). The reaction vessel was sealed and heated at 100 °C for 10 min (fixed hold time) in a Biotage Emrys Creator. After cooling, the vessel was uncapped and the reaction mixture acidified to pH 5–7 with 1 N aq hydrochloric acid. The resulting mixture was extracted with ethyl acetate (3 × 15 mL) and the combined organic extracts were dried (anhydrous magnesium sulfate), filtered, and concentrated in vacuo. Purification (Biotage Sp4) by silica gel chromatography (ethyl acetate to 50% methanol/ethyl acetate over 10 column volumes) afforded acid **24** as a white solid (0.153 g, 92%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.93–7.89 (m, 3H), 7.52–7.46 (m, 4H), 7.42–7.38 (m, 3H), 6.69 (d, $J = 8.5$ Hz, 1H), 4.44 (t, $J = 6.7$ Hz, 2H), 3.45–3.43 (m, 2H), 3.18 (s, 3H), 2.91–2.87 (m, 2H), 2.31 (s, 3H), 1.19 (s, 3H). ESIMS (*m*/*z*): 395 (M−H). Anal. Calcd for $C_{22}H_{24}N_2O_5$: C, 66.65; H, 6.10; N, 7.07. Found: $C_{22}H_{24}N_2O_5.0.06H_2O$: C, 66.16; H, 6.15; N, 6.96.