Novel 2,2-Bipyridine Ligand for Palladium-Catalyzed Regioselective Carbonylation

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ABSTRACT



A palladium-catalyzed highly regioselective one-step carbonylation of 2,5-dibromo-3-methylpyridine is reported. A range of alkyl esters and amides can be prepared in good yield with better than 95:5 regioselectivity via this method. Key to the high regioselectivity for the formation aromatic amides is the introduction of a novel nonphosphine-based 2,2-bipyridine ligand. This novel reaction was scaled up smoothly in the plant to a 130-kg batch size and facilitated the delivery of bulk material for the clinical trials of Sch 66336, a candidate for oncologic treatments.

The synthesis of Sch 66336¹ required an efficient method for the preparation of secondary and tertiary 3-methyl-5bromo-2-pyridinecarboxyamides. Most of the reported meth-



ods for amide formation required multistep synthesis and did not give regioselectivity for the 2-position.² Palladium-catalyzed carbonylative amide formation could provide an

easy access to our desired intermediate. Although underutilized in industry, this reaction forms an amide in one step and reduces the cost of goods since the starting materials are carbon monoxide and a simple amine.³ Our major concern was the regioselectivity, since we required the selective reaction of the more hindered bromo group. Without the 3-methyl group, it was reported that the 2-bromo was more reactive toward palladium-catalyzed reactions.⁴

The first carbonylation reaction we carried out between 2,5-dibromo-3-methylpyridine and carbon monoxide (60 psi) in methanol using 3 mol % of $(PPh_3)_2PdCl_2$ as a catalyst and Et₃N as a base gave the desired 5-bromo-3-methyl-2-pyridine ester and the diester in a ratio of 90:10. 2,5-Dibromo-3-methylpyridine was initially prepared in two steps starting from 2-amino-3-methylpyridine⁵ and later purchased

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commercially.⁶ Carbonylation with alkylamines proceeded even more smoothly and gave better than 95:5 regioselectivity as determined by both HPLC and NMR analyses. This better selectivity was apparently due to the stronger nucleophilicity of amines than alcohols. The synthetic versatility of the carbonylation met the challenge of the preparation of a variety of amides in a single step for our process optimization. As shown in Table 1, the reaction worked well



with both primary and secondary amines as well as with cyclic amines. For alkylamines, the reaction time was 6 h and the isolated yields ranged from 59 to 72%. Over 20 amides were prepared via this regioselective carbonylation and some of the representative examples are listed in Table 1.

Further studies indicated that aromatic amides are better suited for our synthetic efforts toward Sch 66336. The regioselectivity, however, decreased from 95:5 for alkylamines to about 70:30 for anilines, and the isolated yields dropped accordingly to between 24 and 50%. Anilines with electron-donating substituents gave better selectivity and yield than those bearing electron-withdrawing groups. It was further observed that the regioselectivity deteriorates with time and eventually bisamides become the dominant product. This, coupled with the fact that no 5-monoamide was observed, suggested a sequential reaction mechanism. This may account for the lower selectivity with anilines since their reaction rates were three times slower than those for alkylamines. Thus, we first sought to shorten the reaction time with aniline by varying the base. (PPh₃)₂PdCl₂ (3 mol %) was used as a catalyst for this study. As shown in Table 2, the stronger the base the faster the reaction rate. However, both the regioselectivity and the yield deteriorate with the base strength.



We then studied the ligand effect on the regioselectivity using 1.4 equiv of DBU as a base. We thought that initial Pd coordination with the pyridine nitrogen followed by insertion to the neighboring Br–C bond accounted for the selectivity and that a weaker ligand should enhance the selectivity. In fact, pyridine is known to coordinate with palladium and forms stable complexes.⁷ Examination of the effect of several ligands on the selectivity validated our thinking, and these results are summarized in Table 3. While a strong ligand such as Bu₃P completely inhibits the carbonylation, reaction without any ligand such as palladium on carbon also gives only a trace of product. The lack of

Table 3.	Ligand	Effect
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		ReactionReaction Isol.				
entry	Pd cat ^a	Ligand	Temp C	Time h	mon:bi	s Yield
1	Pd(OAc) ₂	PBu ₃	80	40	n/a	n/a
2	Pd(OAc) ₂	Ph ₂ P(CH ₂) ₂ PPh	2 70	6	75:25	50%
3	PdCl ₂	PPh3	50	6	80:20	55%
4	Pd(OAc) ₂	Bipyridine ^b	65	40	98:2	75%
5	PdCl ₂	PhCN	70	40	n/a	n/a
6	Pd/C	No	70	40	n/a	n/a
3 mol 9	% Pd cat., 3	.3 mol % Ph ₂ P(C	H ₂) ₂ PPh ₂	or bipyri	dine ,6.0	mol %

of other ligands, CO(80 psi), 1.4 eq DBU. b) Bipyridine = (N - N)

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reactivity with Bu₃P may come from the decrease in reaction rate of the migratory insertion step. It is clear from Table 3 that we need a ligand that is weak enough not to inhibit the coordination of 2,5-dibromo-3-methylpyridine with palladium and strong enough to keep palladium in solution. We shifted our attention away from the ubiquitous phosphinebased ligand and selected 2,2-bipyridine⁸ for this task. This novel ligand improved the regioselectivity from 75:25 to 98:2 for aromatic amides. It was also observed that less polar solvents such as toluene give better selectivity than polar ones such as MeCN or DMF. The amount of catalyst used can be further dropped from 3 to 0.5 mol % without sacrificing the yield.

A simple workup procedure was developed for the isolation of amides as described in ref 9. Under the optimized conditions, the isolated yields for amides derived from aniline and 4-chloroaniline increased from 55% and 40% to 82% and 72%, respectively. As shown in Table 4, the solution yield for *N*-methylphenyl amide **15** also improved from 35% to 66%. The reaction with aniline was scaled up successfully and safely in the plant and produced more than 600 kg of bulk intermediate for our antitumor project.

		Reaction	Reaction		HPLC Isol.	
entry	R ¹ R ² NH	Temp C	Time h	mon:bis	yield	yield
1	PhNH ₂	65	40	98:2	90%	82%
2	4-CIC ₆ H ₄ NH ₂	65	40	98:2	80%	72%
3	PhNHMe	65	40	95:5	66%	n/a

In summary, we have developed a palladium-catalyzed regioselective carbonylation and applied it to the manufacture of a pharmaceutical intermediate. This reaction replaced multiple steps in previous syntheses and reduced the cost significantly.

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Supporting Information Available: Experimental procedures, full characterization data, and ¹H and ¹³C NMR spectra for compounds **1–15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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⁽⁹⁾ **Representative Experimental Section**. To a 4-L autoclave were added sequentially 250 g (950 mmol) of 2,5-dibromo-3-methylpyridine, 6.7 g (30 mmol) of Pd(OAc)₂, 5.0 g (32 mmol) of 2,2-bipyridine, 2.5 L of toluene, 127 mL (1.1 mol) of aniline, and 194 mL (1.4 mol) of DBU. The autoclave was sealed, evacuated, purged with nitrogen, and charged with CO to 80 psi. The mixture was heated to 65 °C for about 40 h while keeping the pressure at 80 psi, cooled to 25 °C, and filtered through a pad of Celite with aid of water. The layers were separated, and the organic layer was concentrated. Crystallization of the residue from 2-PrOH gave the desired amide in 76–82% isolated yield. The purity of the isolated product was >98% and the solution yield was 90% as determined by HPLC.