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

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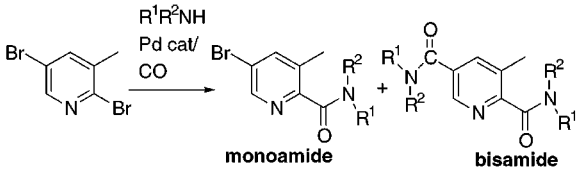
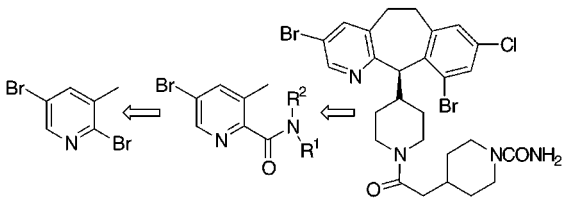
ABSTRACT



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 66336[1] required an efficient method for the preparation of secondary and tertiary 3-methyl-5-bromo-2-pyridinecarboxyamides. Most of the reported methods 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]



Sch 66336

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 Et_3N 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-methylpyridine[5] and later purchased

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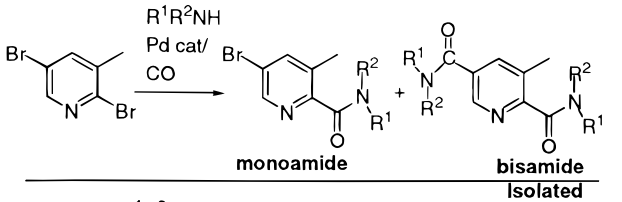
commercially.[6] Carbonylation with alkylamines proceeded even more smoothly and gave better than 95:5 regioselectivity as determined by both HPLC and NMR analyses. This better selectivity was apparently due to the stronger nucleophilicity of amines than alcohols. The synthetic versatility of the carbonylation 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

Table 1. Regioselective Carbonylation



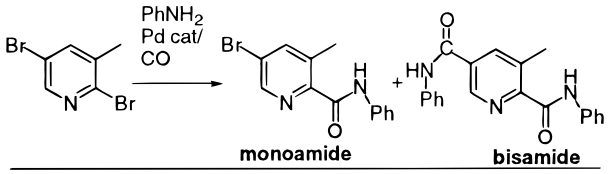
entry	R^1R^2NH	Temp C	Time h	mono:bis	Isolated monoamide
1	*t*-$BuNH_2$	55	6	95:5	67%
2		55	6	95:5	62%
3		55	6	95:5	70%
4		55	6	95:5	69%
5		55	6	95:5	64%
6	$(MeO(CH_2))_2NH$	55	6	95:5	59%
7	$Me_2N(CH_2)_2NHMe$	55	6	95:5	72%
8	$CyclohexylNH_2$	55	6	95:5	64%
9		75	18	80:20	50%
10	4-$BnOC_6H_4NH_2$	55	18	80:20	59%
11	4-$MeOC_6H_4NH_2$	55	18	80:20	57%
12	$PhNH_2$	55	18	75:25	55%
13	4-$ClC_6H_4NH_2$	75	18	70:30	40%
14	4-$FC_6H_4NH_2$	75	24	60:40	24%
15	PhNHMe	75	18	70:30	30%

Pd cat = 0.5-3 mol % $(Ph_3P)_2PdCl_2$, CO = 10 to 100 psi, 1:1 mixture of toluene and MeCN.

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. $(PPh_3)_2PdCl_2$ (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.

Table 2. Base Effect



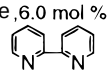
entry	Base	Temp C	Time h	Conversion	mon:bis
1	*i*-Pr_2NEt	55	18	75%	78:22
2	Et_3N	55	18	93%	75:25
3	DBU	45	5	95%	67:33
4	K_2CO_3	50	18[a]	99%	23:77

a) Over reacted. b) All reactions were carried out using 3 mol % of $(PPh_3)_2PdCl_2$, 1.2 eq. of $PhNH_2$, CO (80 psi), and 2.0 eq. of base.

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 Bu_3P 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

entry	Pd cat[a]	Ligand	Reaction Temp C	Reaction Time h	mon:bis	Isol. Yield
1	$Pd(OAc)_2$	PBu_3	80	40	n/a	n/a
2	$Pd(OAc)_2$	$Ph_2P(CH_2)_2PPh_2$	70	6	75:25	50%
3	$PdCl_2$	PPh_3	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 % Pd cat., 3.3 mol % $Ph_2P(CH_2)_2PPh_2$ or bipyridine ,6.0 mol % of other ligands, CO(80 psi), 1.4 eq DBU. b) Bipyridine = 

(6) D & O Chemicals, Inc. 401 South Van Brunt Street, Englewood, NJ 07631.

reactivity with Bu_3P 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 phosphine-based ligand and selected 2,2-bipyridine[8] 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.

Table 4. Carbonylation with 2,2-Bipyridine Ligand

entry	R^1R^2NH	Reaction Temp C	Reaction Time h	mon:bis	HPLC yield	Isol. yield
1	$PhNH_2$	65	40	98:2	90%	82%
2	$4\text{-}ClC_6H_4NH_2$	65	40	98:2	80%	72%
3	PhNHMe	65	40	95:5	66%	n/a

3 mol % Pd cat, 3.3 mol % Bipyridine,1.5 eq DBU, and 80 psi CO.

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 ^{13}C 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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(8) Recently, chrial derivatives of 2,2-bipyridine were used as chiral ligands for palladium reactions: Chelucci, G.; Pinna, G. A.; Saba, A. *Tetrahedron: Asymmetry* **1998**, *9*, 531.

(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.