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Stereoselective Synthesis of Nipecotic Acid Derivatives via Palladium-Catalyzed Decarboxylative Cyclization of γ-Methylidene-δ-valerolactones with Imines

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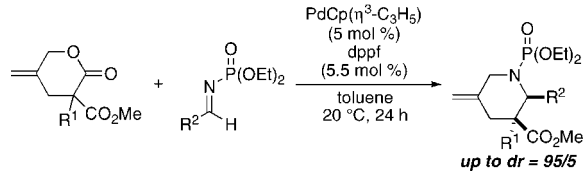
ABSTRACT



A new synthetic method of multisubstituted nipecotic acid (piperidine-3-carboxylic acid) derivatives has been developed by way of palladium-catalyzed decarboxylative cyclization of γ-methylidene-δ-valerolactones with imines. By employing the diethoxyphosphinoyl group as the N-protecting group for imines, the reaction proceeds smoothly with high diastereoselectivity. The products thus obtained can be further derivatized with high efficiency under simple reaction conditions.

Nipecotic acid derivatives are widely spread as a common structural motif in natural and synthetic biologically active compounds such as GABA uptake inhibitors.[1,2] It is therefore of high value to devise an efficient synthetic method for these compounds. Functional group manipulation of preformed nipecotic or nicotinic acid derivatives is most commonly utilized for their preparation,[2,3] and construction of the piperidine ring in a convergent manner is very rare in this context. Herein we describe the development of a palladium-catalyzed decarboxylative cyclization of γ-methylidene-δ-valerolactones[4] with *N*-diethoxyphosphinoyl imines to produce multisubstituted nipecotic acid derivatives in a diastereoselective fashion.[5,6]

We began our investigation by conducting reactions of γ-methylidene-δ-valerolactone **1a** with benzaldimines (1.2 equiv) in the presence of 5 mol % of Pd/dppf catalyst in

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(6) For a review on piperidine synthesis, see: Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953.

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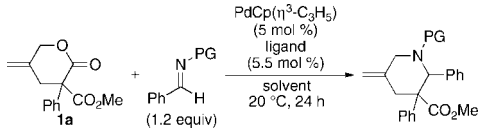
toluene at 20 °C to evaluate the effect of nitrogen substituents on reactivity and stereoselectivity (Table 1). The use of *N*-phenyl benzaldimine resulted in no formation of the desired product presumably due to the low electrophilicity of the imine (entry 1), and we decided to focus on the use of electron-deficient substituents on nitrogen. It turned out that both *N*-tosyl and *N*-diphenylphosphinoyl imines are suitable substrates to produce the desired heterocycles in high yield (90−93% yield; entries 2 and 3), but the diastereoselectivities were only moderate in both cases. We subsequently found that the diastereoselectivity was significantly improved by changing the nitrogen substituent to dialkoxyphosphinoyl groups with maintenance of the high reactivity (91−95% yield, dr = 91/9; entries 4 and 5).

Table 1. Palladium-Catalyzed Decarboxylative Cyclization of γ-Methylidene-δ-valerolactone **1a** with Benzaldimines: Effect of N-Substituents, Ligands, and Solvents



entry	PG	ligand	solvent	convn (%)[a]	yield (%)[b]	dr[a]
1	Ph	dppf	toluene	48	0	–
2	Ts	dppf	toluene	100	90	58/42
3	$P(O)Ph_2$	dppf	toluene	100	94	69/31
4	**$P(O)(OEt)_2$**	**dppf**	**toluene**	**100**	**95**	**91/9**
5	$P(O)(OR)_2$[c]	dppf	toluene	100	91	91/9
6	$P(O)(OEt)_2$	dppf	THF	100	94	91/9
7	$P(O)(OEt)_2$	dppf	CH_2Cl_2	72	64	83/17
8[d]	$P(O)(OEt)_2$	dppf	toluene	100	81	72/28
9	$P(O)(OEt)_2$	dppe	toluene	36	32	84/16
10[e]	$P(O)(OEt)_2$	PPh_3	toluene	100	55	97/3
11[e]	$P(O)(OEt)_2$	$P(Oi\text{-}Pr)_3$	toluene	100	91	83/17

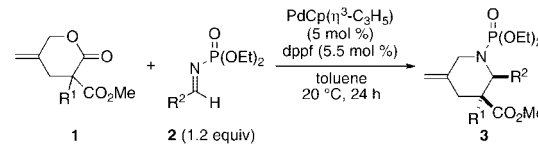
[a] Determined by ^{1}H NMR of the crude material. [b] Combined yield of the two diastereomers (determined by ^{1}H NMR against an internal standard). [c] $(OR)_2 = (OCH_2CMe_2CH_2O)$. [d] Methyl ester of **1a** was replaced by *tert*-butyl ester. [e] 10 mol % of ligand was used.

With these imines in hand, we also found that similar reactivity and stereoselectivity could be observed in THF (entry 6), but the use of dichloromethane as a solvent gave the product with somewhat lower efficiency (entry 7). The change of ester group on **1a** from Me to *t*-Bu resulted in significantly lower diastereoselectivity (dr = 72/28; entry 8).[7] With regard to the effect of ligands on palladium, the use of other bisphosphines, such as dppe, or monodentate phosphorus ligands, such as PPh_3 and $P(Oi\text{-}Pr)_3$, gave the product in lower yield (entries 9 and 10) and/or lower diastereoselectivity (entries 9 and 11).

Under the optimized conditions, various α-(hetero)aryl-γ-methylidene-δ-valerolactones **1** undergo decarboxylative cyclization with imine **2a** in high yield with good to excellent diastereoselectivity (dr = 87/13 to 95/5; Table 2, entries 1−5).[8] α-Alkyl lactones such as **1f** can also give the corresponding product in high yield, albeit with somewhat lower diastereoselectivity (dr = 74/26; entry 6). With regard to the imine component, various aryl groups can be tolerated to give the products with high diastereoselectivity (entries 7−11), but the use of a heteroaryl or an alkenyl imine results in lower stereoselectivity (entries 12 and 13). The relative configuration of the major diastereomer of **3ea** (entry 5) was determined by X-ray crystallographic analysis as shown in Figure 1.

(7) Lactones without an ester group cannot be employed under the present conditions.

Table 2. Palladium-Catalyzed Decarboxylative Cyclization of γ-Methylidene-δ-valerolactones **1** with Imines **2**: Scope



entry	R^1	R^2	product	dr[a]	yield (%)[b]
1	(1a)	(2a)	**3aa**	91/9	85
2	OMe (1b)		**3ba**	87/13	82
3	Me (1c)		**3ca**	91/9	79
4	(1d)		**3da**	95/5	83
5	S (1e)		**3ea**	90/10	82
6	(1f)		**3fa**	74/26	84[c]
7	(1a)	OMe (2b)	**3ab**	93/7	73
8		Br (2c)	**3ac**	88/12	80
9		OMe (2d)	**3ad**	87/13	82
10		Cl (2e)	**3ae**	85/15	84
11		Me (2f)	**3af**	94/6	84
12		S (2g)	**3ag**	71/29	95[c]
13		(2h)	**3ah**	59/41	51[c]

[a] Determined by ^{1}H NMR of the crude material. [b] Isolated yield of the major diastereomer unless otherwise noted. [c] Combined isolated yield of the two diastereomers.

(8) **General Procedure.** A solution of $PdCp(\pi\text{-}C_3H_5)$ (2.1 mg, 10 μmol) and dppf (6.1 mg, 11 μmol) in toluene (0.50 mL) was stirred for 10 min at room temperature. Lactone **1** (0.20 mmol) and imine **2** (0.24 mmol) were added to it with additional toluene (0.50 mL), and the resulting solution was stirred for 24 h at 20 °C. The reaction mixture was directly passed through a pad of silica gel with EtOAc, and the solvent was removed under vacuum. The residue was purified by silica gel preparative TLC to afford compound **3.**

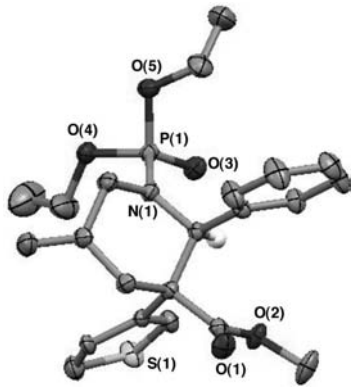
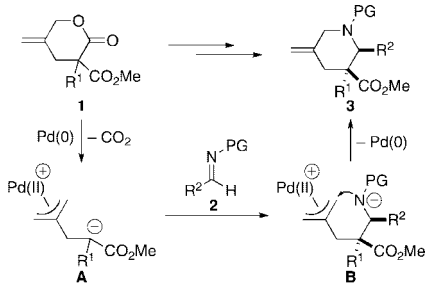


Figure 1. X-ray structure of **3ea** with thermal ellipsoids drawn at the 50% probability level.

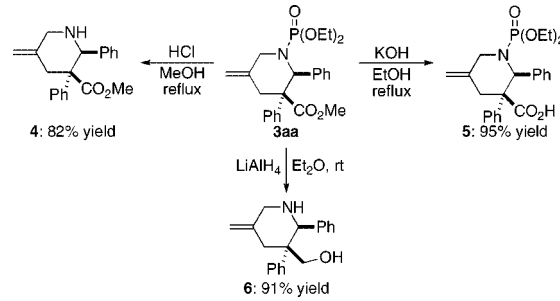
A proposed catalytic cycle of this process is illustrated in Scheme 1. Thus, oxidative addition of the allyl ester moiety of **1** to palladium(0), followed by decarboxylation,[9,10] gives 1,4-zwitterionic species **A**. The anionic carbon of **A** then attacks the electrophilic carbon of **2** to give intermediate **B**, which undergoes a ring-closure through a nucleophilic attack of the nitrogen atom to the π-allylpalladium moiety, leading to the formation of **3** along with regeneration of palladium(0).

Scheme 1. Proposed Catalytic Cycle for the Palladium-Catalyzed Decarboxylative Cyclization of **1** with **2** (PG = P(O)(OEt)$_2$)



The products obtained under the present catalysis can be further manipulated with high efficiency (Scheme 2). For example, selective removal of the diethoxyphosphinoyl group on nitrogen of compound **3aa** is accomplished under acidic conditions to give deprotected amine **4** in 82% yield. In contrast, treatment of **3aa** with KOH in EtOH leads to carboxylic acid **5** with its N-protecting group intact in 95% yield. Furthermore, a reaction of **3aa** with $LiAlH_4$ simultaneously reduces the ester and cleaves the N-protecting group to give aminoaocohol **6** in 91% yield.

Scheme 2. Derivatization of Compound **3aa**



In summary, we have developed a new synthetic method of highly functionalized nipecotic acid derivatives through palladium-catalyzed decarboxylative cyclization of γ-methylidene-δ-valerolactones with imines. By employing the diethoxyphosphinoyl group as the nitrogen protecting group for imines, the reaction proceeds smoothly with high diastereoselectivity. The products thus obtained can be further derivatized under simple reaction conditions. Future studies will be directed toward further expansion of the reaction scope as well as the development of an asymmetric variant.[11]

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Supporting Information Available: Experimental procedures and compound characterization data (PDF) and X-ray data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) In our preliminary experiment, a reaction of **1a** with **2a** in the presence of (*R*)-binap as the ligand gave **3aa** with 38% ee, and chiral phosphoramidites are less effective for this reaction.