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Regioselective Pd-Catalyzed Synthesis of 2,3,6-Trisubstituted Pyridines from Isoxazolinones

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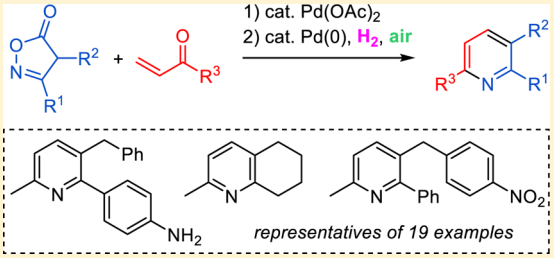
Supporting Information

ABSTRACT: Substituted pyridines are prevalent heterocycles of fundamental importance. Their efficient regioselective preparation is often still a challenge despite a large number of reported synthetic methodologies. In this letter we report an operationally simple approach that makes use of readily accessible isoxazolinones. The protocol involves a Pd(II)-catalyzed C-regioselective 1,4-addition to vinylketones, followed by a Pd(0)-catalyzed transformation, which is assumed to proceed via vinylnitrene-Pd intermediates. Both hydrogen and air are necessary for the pyridine formation step and could be employed at ratios above the upper explosive limit thus avoiding a safety issue. This new strategy allows an effective, scalable and practical access to various previously unknown 2,3,6-trisubstituted pyridines.



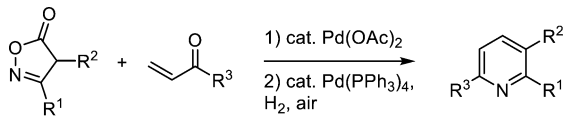
INTRODUCTION

On account of their wide range of applications in very different fields, pyridines are among the most important aromatic heterocycles.[1] They are present as a structural motif in many bioactive compounds[2] including active pharmaceutical ingredients or drug candidates,[3] as well as agrochemicals.[4] They are also frequently utilized as synthetic building blocks,[1,5] as ligands in metal complexes[6] or in supramolecular chemistry,[7] polymer chemistry and materials science.[8] In addition they are useful as nucleophilic/basic catalysts[9] or for the development of cooperative Lewis acid/onium salt catalysts.[10]

Because of the significance of pyridines, much effort has been devoted toward their synthesis.[1,11] A very attractive strategy is the metal-catalyzed [2 + 2 + 2] cycloaddition of a nitrile and two alkyne molecules.[12] Unfortunately, the intermolecular version of this methodology often suffers from regioselectivity problems. The condensation of dicarbonyl substrates with ammonia also plays a prominent role,[1,13] but only certain substitution patterns are efficiently accessible. Several methods which make use of substrates containing a relatively labile N−O bond have also been reported, often avoiding the oxidation step of a dihydropyridine intermediate, which is usually necessary for the traditional condensation of dicarbonyl substrates with ammonia.[14] Various recently developed methodologies for the de novo construction of substituted pyridines have efficiently addressed the issues of regioselectivity, diversity and step economy.[11,14d−j] In this context, and as a consequence of the great importance of substituted pyridine derivatives,[2−10] we found that there is still a demand for practical, atom-economic, catalytic routes for a rapid, cost-efficient, regioselective access of 2,3,6-trisubstituted pyridines starting from readily available precursors.

Herein, we report an operationally simple, divergent methodology for a step-economic regioselective synthesis toward 2,3,6-trisubstituted pyridines (Scheme 1). It involves a regioselective Pd(II)-catalyzed 1,4-addition of isoxazolinones

Scheme 1. Two-Step Synthesis of 2,3,6-Trisubstituted Pyridines 3 from Isoxazolinones 1



1 2 3

(systematic name: 4*H*-isoxazol-5-ones), which are readily prepared from *β*-ketoesters and hydroxylamine,[15] to enones. The 1,4-adducts are subsequently transformed into pyridines catalyzed by Pd(0) in the presence of H_2 and air. This latter reaction is assumed to take place via vinylnitrene intermediates, which have recently been proposed to be generated on exposure of isoxazolinones to Pd(0) via oxidative addition of the reactive N−O bond followed by a decarboxylation.[16]

RESULTS AND DISCUSSION

Conjugate additions of isoxazolinones are known to typically suffer from regioselectivity problems.[17,18] It has been reported that C-alkylations are usually accompanied by formation of significant amounts of N-alkylation products. Very recently we have reported the first enantio- and regioselective Michael addition of isoxazolinones to vinylketones forming quaternary carbons.[19] This reaction is efficiently catalyzed by a planar chiral pentaphenylferrocenyl palladacycle. However, as achiral aromatic products were targeted in the present investigation,

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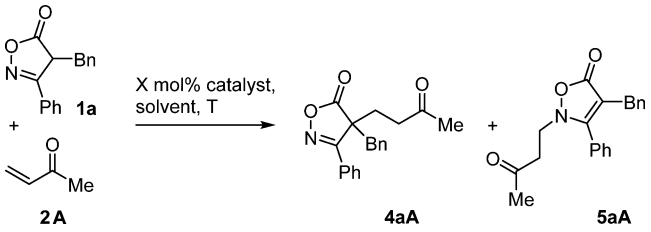
we have reinvestigated the 1,4-addition of isoxazolinones to develop an operationally simple and nonenantioselective catalytic method (Table 1) still offering high levels of regioselectivity, which is more cost-efficient than using the above-mentioned palladacycle.[20]

Table 1. Optimization of the 1,4-Addition of Isoxazolinones to Vinylketones



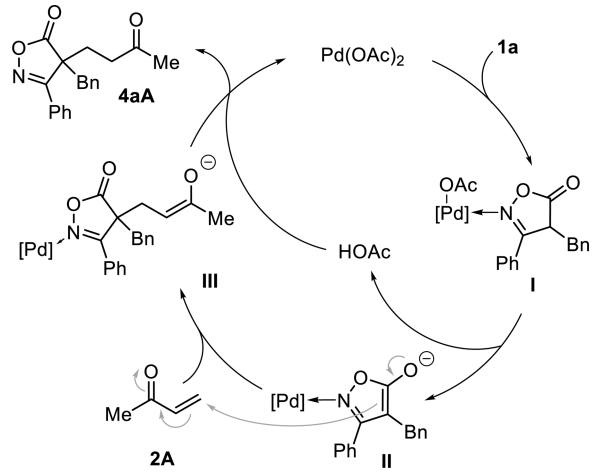
#	catalyst	X mol %	solvent	T (°C)	ratio **4aA**:**5aA**[a]	yield **4aA** (%)[b]
1	KO*t*Bu	10	THF	25	47:53	43
2	NaOMe	10	MeOH	25	31:69	24
3	NaOMe	10	CH_2Cl_2	−78	50:50	46
4	Cs_2CO_3	10	CH_2Cl_2	25	23:77	20
5	NaOAc	10	CH_2Cl_2	25	23:77	15
6	HOAc	360	EtOH	25	–	0
7	NEt_3	10	MeOH	25	28:72	22
8	NEt_3	120	MeOH	25	71:29	65
9	$Pd(OAc)_2$	1	CH_2Cl_2	25	89:11	89
10	$Pd(OAc)_2$	0.5	CH_2Cl_2	25	87:13	87
11	$Pd(OAc)_2$	0.1	CH_2Cl_2	25	84:16	80
12	$Pd(OAc)_2$	0.05	CH_2Cl_2	25	78:22	71
13[c]	$Ni(OAc)_2$	10	CH_2Cl_2	25	32:68	27
14[c]	$Mn(OAc)_2$	10	CH_2Cl_2	25	23:77	16
15	–	–	CH_2Cl_2	25	–	–

[a]Determined by ^{1}H NMR of the crude product. [b]Determined by ^{1}H NMR analysis of the crude product using mesitylene as an internal standard. [c]The corresponding tetrahydrate complex was used as catalyst.

Promoting the 1,4-addition by catalytic amounts of alkoxide bases (10 mol %) provided mainly the undesired N-alkylation regioisomer **5aA** for the model reaction of isoxazolinone **1a** and methylvinylketone (**2A**, MVK, entries 1−3). A similar preference was found for inorganic bases like Cs_2CO_3 (entry 4) or simple alkaline acetate salts like NaOAc (entry 5). With an excess of acetic acid (entry 6) no product was formed, whereas catalytic amounts of NEt_3 in MeOH gave mainly the N-alkylation product (entry 7). With an excess of NEt_3 the C-alkylation product became the dominant product,[17b] but still with a moderate regioselectivity (entry 8). Because of the above-mentioned efficiency of a neutral palladacycle in the asymmetric version of this reaction,[19] $Pd(OAc)_2$ (1 mol %) was investigated and provided the targeted C-alkylation regioisomer **4aA** with a significant excess and in good yield (entry 9).[21] A useful reaction outcome was still noticed with $Pd(OAc)_2$ loads of 0.5, 0.1, 0.05 mol % (entries 10−12). Other divalent acetate salts like $Ni(OAc)_2$ or $Mn(OAc)_2$ were not efficient for the C-alkylation even with loadings of 10 mol % (entry 13 and 14) and the N-alkylation was dominating. In the absence of a catalyst, no alkylation product was formed (entry 15).

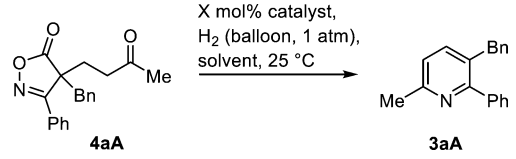
We assume that the mechanism of the $Pd(OAc)_2$ catalyzed 1,4-addition is related to the above-mentioned enantioselective reaction catalyzed by a planar chiral palladacycle.[19] The N atom of the isoxazolinone is supposed to coordinate to the Lewis-acidic Pd(II), thus facilitating the substrate enolization in **I** by the basic acetate ligand to form the heteroaromatic nucleophile **II** (Scheme 2).[22] Protonation of the initial 1,4-adduct **III** would close the catalytic cycle and release the product.

Scheme 2. Possible Simplified Mechanistic Scenario for the $Pd(OAc)_2$-Catalyzed 1,4-Addition



With the 1,4-adduct **4aA** the pyridine formation was investigated under various conditions using Pd(0) catalysts (Table 2).

Table 2. Optimization of the Pyridine Formation



#	catalyst	X mol %	solvent	yield (%)[a]
1	Pd/C	5	MeOH	73
2[b]	$Pd(PPh_3)_4$	5	THF	0
3[b]	$Pd(PPh_3)_4$	5	dioxane	0
4	$Pd(PPh_3)_4$	5	THF	94
5	$Pd(PPh_3)_4$	5	dioxane	89
6	$Pd(PPh_3)_4$	5	MeCN	84
7	$Pd(PPh_3)_4$	5	toluene	68
8	$Pd(PPh_3)_4$	0.5	dioxane	98
9	$Pd(PPh_3)_4$	0.1	dioxane	0

[a]Determined by ^{1}H NMR analysis of the crude product using mesitylene as internal standard. [b]This reaction was performed in the absence of H_2.

With catalytic amounts of Pd/C (5 mol %) in MeOH at 25 °C the product was formed in a promising yield of 73% under an atmosphere of H_2 provided by a balloon (entry 1). H_2 was initially just employed in order to activate an old batch of Pd/C. However, the investigation of $Pd(PPh_3)_4$ as catalyst revealed, that the presence of H_2 is−in contrast to our initial expectations−essential for the product formation. Neither in THF nor in 1,4-dioxane there was any product formation in the absence of H_2 (entries 2 and 3). In contrast, under 1 bar of H_2 the product was formed in good yields in both solvents (entries 4 and 5). A similar result was obtained in MeCN (entry 6) and toluene (entry 7). Gratifyingly, when the catalyst loading was

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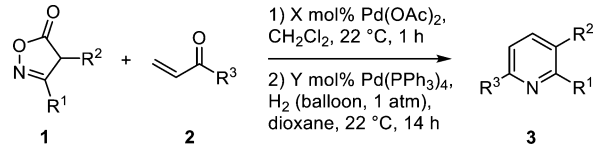
Table 3. Investigation of the Scope



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entry	3	R^1	R^2	R^3	X mol %	Y mol %	yield step 1/2 (%)[a]
1	**3aA**	Ph	Bn	Me	5	0.5	89/98
2	**3bA**	Ph	Me	Me	5	0.5	89/97
3	**3cA**	Ph	*n*Pr	Me	5	1	92/96
4	**3dA**	Ph	$CH_2C_6H_4$-4-Me	Me	5	0.5	71/94
5	**3eA**	Ph	$CH_2C_6H_4$-4-OMe	Me	5	0.5	50/95
6	**3fA**	Ph	CH_2-2-naphthyl	Me	5	1	95/92
7	**3gA**	Ph	$CH_2C_6H_4$-4-NO_2	Me	5	1	69/93
8[b]	**3gA***	Ph	$CH_2C_6H_4$-4-NO_2	Me	5	5	69/99
9	**3hA**	Ph	Ph	Me	5	1	44/99
10	**3iA**	C_6H_4-4-OMe	Bn	Me	5	1	33/89
11[b]	**3jA***	C_6H_4-4-NO_2	Bn	Me	5	1	69/91
12	**3kA**	C_6H_4-3-OMe	Bn	Me	5	1	60/87
13	**3lA**	Me	Bn	Me	5	1	87/89
14	**3aB**	Ph	Bn	Et	5	1	88/93
15	**3aC**	Ph	Bn	$(CH_2)_2$Ph	10	1	95/97
16	**3aD**	Ph	Bn	Ph	5	1	50/85
17	**3aE**	Ph	Bn	C_6H_4-4-OMe	10	1	64/95
18	**3mA**		$(CH_2)_4$	Me	5	5	68/82
19[c]	**3n′A**	Ph	$CH_2CH_2C(=O)Me$	Me	5	1	99/88

[a]Yield of isolated product. [b]The nitro group was reduced to a primary amino function. [c]R^2 = H in the starting isoxazolinone **1n**, which was applied to a double alkylation with MVK.

reduced to 0.5 mol % the reaction in 1,4-dioxane resulted in nearly quantitative product formation. A further decrease to 0.1 mol % gave no product, possibly due to catalyst inhibition by small amounts of substrate impurities below the detection level of ^{1}H NMR.

As both steps require the use of a Pd catalyst, the possibility of a one-pot procedure using only one catalyst portion was also considered, in which CH_2Cl_2 was exchanged by 1,4-dioxane and PPh_3 was added as a ligand. However, in this case using 5 mol % of the Pd source there was nearly no conversion of the 1,4-adduct **4aA** to the pyridine **3aA**. Purification of **4aA** might be mandatory to avoid catalyst inhibition.

The 2-step sequence was then applied to different isoxazolinones and vinylketones (Table 3). Various types of residues R^2 at the CH-acidic isoxazolinone position were well tolerated. With alkyl residues such as methyl and *n*-propyl (entries 2 and 3) similarly high yields were obtained as with a benzyl residue (entry 1). A range of isoxazolinones carrying electron withdrawing (*p*-NO_2) or donating (*p*-Me, *p*-OMe) substituents at a benzylic residue or a 2-naphthylmethylene group R^2 furnished useful results (entries 4−7). Surprisingly, the *p*-NO_2-group was not reduced during the second step when 1 mol % of catalyst was employed (entry 7). In contrast, using 5 mol % of $Pd(PPh_3)_4$ the corresponding aniline was obtained in high yield (entry 8). An aromatic substituent directly bound to the isoxazolinone 4-position led to a decreased yield for the 1,4-addition step (44%), but the subsequent pyridine generation proceeded almost quantitatively (entry 9).

Variation of the R^1-residue at the 3-position is also possible (entries 10−13). An electron rich aryl moiety somewhat hampered the 1,4-addition, but again the following step furnished high yields of the aromatic heterocycles (entry 10). Also in this case the *p*-NO_2-group was reduced to a primary amino function, even with 1 mol % of $Pd(PPh_3)_4$ (entry 11). Isoxazolinones with an alkyl residue R^1 (entry 13) and vinylketones with alkyl and aryl groups R^3 can be employed, too (entries 14−17). Moreover, it is possible to form bicyclic pyridine derivatives as entry 18 shows in which a tetrahydroquinoline **3mA** was obtained in good overall yields starting from a [4.3.0]-bicyclic isoxazolidinone **1n**. Variation of the ring size of the second ring would in principle allow access to other bicyclic pyridine skeletons.[23] Entry 19 describes a double alkylation of an isoxazolinone, in which R^2 = H. The efficiency of the subsequent pyridine generation demonstrates the compatibility with an additional keto group in the product.[24]

In addition we have shown for both reactions described in entry 1 that the pyridine formation is scalable. In the first step the $Pd(OAc)_2$ loading was reduced to 0.1 mol % (0.4 mg $Pd(OAc)_2$ for 449.0 mg starting material **1a**) resulting in a yield of 76% of the isolated pure C-alkylation isomer **4aA** (C/N-alkylation ratio of the crude product: 84/16). The second step was repeated using 621 mg of **4aA** to provide 500 mg of **3aA** (1 mol % catalyst, quantitative yield).

Mechanistically the pyridine formation might be explained by the intermediacy of a vinylnitrene-Pd species **7** formed by oxidative addition of Pd(0) to the N−O bond of **4** followed by a decarboxylation of **6**. Vinylnitrene-Pd intermediates have recently been proposed by Ohe.[16,25] The vinylnitrene might then undergo an intramolecular [2 + 2] cycloaddition with the ketone moiety to give the bicyclic [4.2.0] oxazapalladetidine **8**, which would then undergo a cycloreversion to give dihydropyridine **9** and a Pd(II)-species (Scheme 3).[26]

The existence of intermediate **9** is supported by ESI-MS measurements performed after a reaction time of 1.5 h, which showed next to the starting material **4c** a prominent species with *m*/*z* = 214.1583 (calculated: 214.1596, R^3 = Me). Initially

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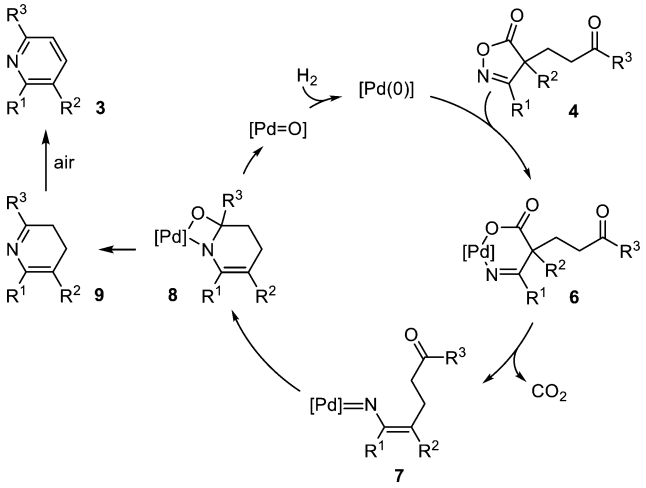
Scheme 3. Possible Mechanism of the Pyridine Formation from Isoxazolinone 4

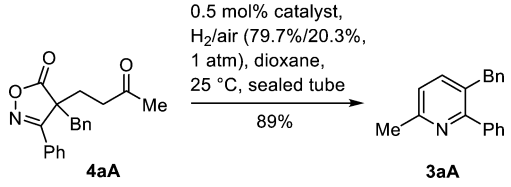


we were hoping that **9** might be aromatized by the generated Pd(II) species to close the catalytic cycle in a redox-neutral pathway. The observation though that hydrogen is required points to a different scenario in which hydrogen is essential to turnover the catalytic cycle by regeneration of a catalytically active Pd(0) species.

The stoichiometric oxidant for the aromatization step is most likely air, which apparently entered the reaction vessel via the H_2-balloon used.[27] This is supported by the fact that in an autoclave in the absence of oxygen using otherwise identical conditions there is almost no conversion. Dihydropyridine **9** is then also not generated in significant quantities, which might be explained by inhibition of the catalyst by, e.g., **9** or the corresponding 1,4-dihydropyridine tautomer or follow-up products of these species forming relatively inert complexes, if oxidation is not taking place.

As the amount of oxygen inside will depend on the quality of the balloon type used, we also investigated a different setup to ensure reproducibility on the one hand and avoiding safety issues on the other hand caused by potentially explosive H_2/O_2 mixtures. For that reason we have repeated the reaction using **4aA** in a sealed tube and added a calculated amount of air to generate a H_2/air mixture with a ratio 79.7/20.3% (Scheme 4).

Scheme 4. Use of a Nonexplosive H_2/Air Mixture for the Pyridine Generation Step



This ratio is above the upper explosive limit and should thus avoid a risk of explosion.[28] The data obtained under these conditions are comparable to the data obtained using a balloon.

CONCLUSION

In conclusion, we have reported a straightforward methodology that allows a rapid and regioselective entry to substituted pyridines starting from readily accessible isoxazolinones. In this synthetic sequence a C-regioselective alkylation is followed by a Pd-catalyzed reaction sequence that possibly involves vinylnitrene intermediates. The synthetic utility of the new method is underscored by the fact that only two out of 19 pyridines described in Table 3 are to our knowledge currently known compounds. We thus anticipate that the operationally simple route will help to contribute to new developments using pyridines.

EXPERIMENTAL SECTION

General Procedure for the 1,4-Additions Using Palladium(II) Acetate as Catalyst (GP1). To a solution of the corresponding isoxazol-5(4*H*)-one (1 equiv, recrystallized from EtOH prior to use)[19] in CH_2Cl_2 (0.6 M) was added palladium(II) acetate (1−10 mol %) and subsequently the corresponding vinyl ketone (4 equiv). After 1 h of stirring at room temperature, the solvent was removed and the crude product was subjected to column chromatography (silica, petrol ether/ethyl acetate: 4/1).

General Procedure for the Pyridine Formation (GP2). To a solution of the 1,4-adduct (1 equiv) in 1,4-dioxane was added tetrakis(triphenylphosphine)palladium(0) (0.5−5 mol %) as stock solution, so that a substrate concentration of 0.1 M was achieved. Hydrogen (over a balloon) was bubbled through the solution for 10 min. Thereafter the solution was set under a hydrogen atmosphere and it was stirred for 24 h at room temperature. The solvent was evaporated and the crude product was subjected to column chromatography (silica, petrol ether/ethyl acetate: 4/1) to give the respective pyridine.

1,4-Additions of Isoxazolinones to Vinyl Ketones. *4-Benzyl-4-(3-oxobutyl)-3-phenylisoxazol-5(4H)-one (**4aA**).* According to GP1, to **1a** (50.0 mg, 0.20 mmol, 1.0 equiv) was added palladium(II) acetate (2.2 mg, 9.80 μmol, 5 mol %). Subsequently, **2A** (67 μL, 0.79 mmol, 4 equiv) was added to yield **4aA** (57.0 mg, 0.18 mmol, 89%) as a colorless solid.

$C_{20}H_{19}NO_3$: MW 321.38 g/mol; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.81−7.75 (*m*, 2H), 7.62−7.46 (*m*, 3H), 7.22−7.09 (*m*, 3H), 6.87−6.80 (*m*, 2H), 3.32 (*d*, *J* = 13.7, 1H), 3.29 (*d*, *J* = 13.7, 1H), 2.67−2.16 (*m*, 4H), 2.08 (*s*, 3H).

The analytical data are in accordance with literature data for enantioenriched material.[19]

*4-Methyl-4-(3-oxobutyl)-3-phenylisoxazol-5(4H)-one (**4bA**).* According to GP1, to **1b** (50.0 mg, 0.29 mmol, 1.0 equiv) was added palladium(II) acetate (3.2 mg, 14.27 μmol, 5 mol %). Subsequently, **2A** (96 μL, 1.14 mmol, 4 equiv) was added to yield **4bA** (63.3 mg, 0.26 mmol, 89%) as a colorless oil.

$C_{14}H_{15}NO_3$: MW 245.28 g/mol; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.78−7.22 (*m*, 2H), 7.58−7.44 (*m*, 3H), 7.49−2.10 (*m*, 4H), 2.06 (*s*, 3H), 1.62 (*s*, 3H).

The analytical data are in accordance with literature data for enantioenriched material.[19]

*4-(3-Oxobutyl)-3-phenyl-4-propylisoxazol-5(4H)-one (**4cA**).* According to GP1, to **1c** (50.0 mg, 0.25 mmol, 1.0 equiv) was added palladium(II) acetate (2.8 mg, 12.30 μmol, 5 mol %). Subsequently, **2A** (83 μL, 0.98 mmol, 4 equiv) was added to yield **4cA** (61.2 mg, 0.22 mmol, 91%) as a colorless solid.

$C_{16}H_{19}NO_3$: MW 273.33 g/mol; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.79−7.73 (*m*, 2H), 7.58−7.44 (*m*, 3H), 2.46−2.15 (*m*, 4H), 2.06 (*s*, 3H), 2.05−1.95 (*m*, 2H), 1.30−1.06 (*m*, 2H), 0.85 (*t*, *J* = 7.8 Hz, 3H).

The analytical data are in accordance with literature data for enantioenriched material.[19]

*4-(4-Methylbenzyl)-4-(3-oxobutyl)-3-phenylisoxazol-5(4H)-one (**4dA**).* According to GP1, to **1d** (50.0 mg, 0.19 mmol, 1.0 equiv) was added palladium(II) acetate (2.1 mg, 9.42 μmol, 5 mol %). Subsequently, **2A** (64 μL, 0.75 mmol, 4 equiv) was added to yield **4dA** (44.9 mg, 0.13 mmol, 71%) as a colorless solid.

$C_{21}H_{21}NO_3$: MW 335.40 g/mol; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.81−7.75 (*m*, 2H), 7.58−7.45 (*m*, 3H), 6.91 (*d*, *J* = 7.9 Hz, 2H), 6.71 (*d*, *J* = 7.9 Hz, 2H), 3.30 (*d*, *J* = 13.8, 1H), 3.23 (*d*, *J* = 13.8, 1H), 2.62−2.25 (*m*, 4H), 2.21 (*s*, 3H), 2.05 (*s*, 3H).

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The analytical data are in accordance with literature data for enantioenriched material.[19]

*4-(4-Methoxybenzyl)-4-(3-oxobutyl)-3-phenylisoxazol-5(4H)-one (**4eA**).* According to GP1, to **1e** (50.0 mg, 0.18 mmol, 1.0 equiv) was added palladium(II) acetate (2.0 mg, 8.88 μmol, 5 mol %). Subsequently, **2A** (60 μL, 0.71 mmol, 4 equiv) was added to yield **4eA** (31.2 mg, 0.09 mmol, 50%) as a colorless solid.

$C_{21}H_{21}NO_4$: MW 351.40 g/mol; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.81−7.76 (*m*, 2H), 7.61−7.47 (*m*, 3H), 6.77−6.73 (*m*, 2H), 6.68−6.63 (*m*, 2H), 3.72 (*s*, 3H), 3.29 (*d*, *J* = 13.9, 1H), 3.23 (*d*, *J* = 13.9, 1H), 2.63−2.14 (*m*, 4H), 2.08 (*s*, 3H, $COCH_3$).

The analytical data are in accordance with literature data for enantioenriched material.[19]

*4-(Naphthalen-2-ylmethyl)-4-(3-oxobutyl)-3-phenylisoxazol-5(4H)-one (**4fA**).* According to GP1, to **1f** (50.0 mg, 0.17 mmol, 1.0 equiv) was added palladium(II) acetate (1.9 mg, 8.30 μmol, 5 mol %). Subsequently, **2A** (56 μL, 0.66 mmol, 4 equiv) was added to yield **4fA** (58.5 mg, 0.16 mmol, 95%) as colorless solid.

$C_{24}H_{21}NO_3$: MW 371.44 g/mol; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.81−7.70 (*m*, 3H), 7.64−7.48 (*m*, 5H), 7.47−7.37 (*m*, 2H), 7.30−7.24 (*m*, 1H), 6.99−6.91 (*m*, 1H), 3.36 (*s*, 2H), 2.75−2.20 (*m*, 4H), 2.09 (*s*, 3H).

The analytical data are in accordance with literature data for enantioenriched material.[19]

*4-(4-Nitrobenzyl)-4-(3-oxobutyl)-3-phenylisoxazol-5(4H)-one (**4gA**).* According to GP1, to **1g** (50.0 mg, 0.17 mmol, 1.0 equiv) was added palladium(II) acetate (1.9 mg, 8.43 μmol, 5 mol %). Subsequently, **2A** (57 μL, 0.68 mmol, 4 equiv) was added to yield **4gA** (42.7 mg, 0.12 mmol, 69%) as a colorless solid.

$C_{20}H_{18}N_2O_5$: MW 366.37 g/mol; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.93 (*d*, *J* = 11.4, 2H), 7.71 (*d*, *J* = 6.9, 2H), 7.59−7.43 (*m*, 3H), 6.93 (*d*, *J* = 8.4, 2H), 3.36 (*d*, *J* = 13.5, 1H), 3.30 (*d*, *J* = 13.5, 1H), 2.65−2.11 (*m*, 4H), 2.03 (*s*, 3H).

The analytical data are in accordance with literature data for enantioenriched material.[19]

*4-(3-Oxobutyl)-3,4-diphenylisoxazol-5(4H)-one (**4hA**).* According to GP1, to **1h** (50.0 mg, 0.21 mmol, 1.0 equiv) was added palladium(II) acetate (2.4 mg, 10.53 μmol, 5 mol %). Subsequently, **2A** (71 μL, 0.84 mmol, 4 equiv) was added to yield **4hA** (28.5 mg, 0.09 mmol, 44%) as a colorless oil.

$C_{19}H_{17}NO_3$: MW 307.35 g/mol; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.53−7.48 (*m*, 2H), 7.46−7.29 (*m*, 8H), 2.92−2.79 (*m*, 1H), 2.66−1.37 (*m*, 2H), 2.31−2.16 (*m*, 1H), 2.09 (*s*, 3H).

The analytical data are in accordance with literature data for enantioenriched material.[19]

*4-Benzyl-3-(4-methoxyphenyl)-4-(3-oxobutyl)isoxazol-5(4H)-one (**4iA**).* According to GP1, to **1i** (50.0 mg, 0.18 mmol, 1.0 equiv) was added palladium(II) acetate (2.0 mg, 8.89 μmol, 5 mol %). Subsequently, **2A** (60 μL, 0.71 mmol, 4 equiv) was added to yield **4iA** (20.6 mg, 0.06 mmol, 33%) as colorless solid.

$C_{21}H_{21}NO_4$: MW 351.40 g/mol; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.78−7.71 (*m*, 2H), 7.21−7.09 (*m*, 3H), 7.03−6.98 (*m*, 2H), 6.88−6.83 (*m*, 2H), 3.89 (*s*, 3H), 3.32 (*d*, *J* = 13.6, 1H), 3.26 (*d*, *J* = 13.6, 1H), 2.63−2.12 (*m*, 4H), 2.07 (*s*, 3H).

The analytical data are in accordance with literature data for enantioenriched material.[19]

*4-Benzyl-3-(4-nitrophenyl)-4-(3-oxobutyl)isoxazol-5(4H)-one (**4jA**).* According to GP1, to **1j** (50.0 mg, 0.17 mmol, 1.0 equiv) was added palladium(II) acetate (1.9 mg, 8.44 μmol, 5 mol %). Subsequently, **2A** (57 μL, 0.68 mmol, 4 equiv) was added to yield **4jA** (42.7 mg, 0.12 mmol, 69%) as a colorless solid.

$C_{20}H_{18}N_2O_5$: MW 366.37 g/mol; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 8.34 (*d*, *J* = 9.7, 2H), 7.93 (*d*, *J* = 10.3, 2H), 7.22−7.06 (*m*, 3H), 6.77 (*d*, *J* = 8.0, 2H), 3.35 (*d*, *J* = 14.0, 1H), 3.25 (*d*, *J* = 14.0, 1H), 2.66−2.36 (*m*, 3H), 2.26−2.11 (*m*, 1H), 2.07 (*s*, 3H).

The analytical data are in accordance with literature data for enantioenriched material.[19]

*4-Benzyl-3-(3-methoxyphenyl)-4-(3-oxobutyl)isoxazol-5(4H)-one (**4kA**).* According to GP1, to **1k** (50.0 mg, 0.18 mmol, 1.0 equiv) was added palladium(II) acetate (2.0 mg, 8.89 μmol, 5 mol %). Subsequently, **2A** (60 μL, 0.71 mmol, 4 equiv) was added to yield **4kA** (37.5 mg, 0.11 mmol, 60%) as a colorless solid.

$C_{21}H_{21}NO_4$: MW 351.40 g/mol; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.43 (*t*, *J* = 7.4 Hz, 1H), 7.37−7.29 (*m*, 2H), 7.19−7.08 (*m*, 4H), 6.89−6.84 (*m*, 2H), 3.85 (*s*, 3H), 3.35 (*d*, *J* = 13.7, 1H), 3.28 (*d*, *J* = 13.8, 1H), 2.64−2.15 (*m*, 4H), 2.08 (*s*, 3H).

The analytical data are in accordance with literature data for enantioenriched material.[19]

*4-Benzyl-3-methyl-4-(3-oxobutyl)isoxazol-5(4H)-one (**4lA**).* According to GP1, to **1l** (50.0 mg, 0.26 mmol, 1.0 equiv) was added palladium(II) acetate (3.0 mg, 13.21 μmol, 5 mol %). Subsequently, **2A** (90 μL, 1.06 mmol, 4 equiv) was added to yield **4lA** (61.0 mg, 0.24 mmol, 87%) as colorless solid.

$C_{15}H_{17}NO_3$: MW 259.12 g/mol; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.32−7.22 (*m*, 3H), 7.13−7.04 (*m*, 2H), 3.21 (*d*, *J* = 13.6, 1H), 2.91 (*d*, *J* = 14.5, 1H), 2.55−2.41 (*m*, 1H), 2.29−2.09 (*m*, 3H), 2.15 (*s*, 3H), 2.04 (*s*, 3H).

The analytical data are in accordance with literature data for enantioenriched material.[19]

*4-Benzyl-4-(3-oxopentyl)-3-phenylisoxazol-5(4H)-one (**4aB**).* According to GP1, to **1a** (50.0 mg, 0.20 mmol, 1.0 equiv) was added palladium(II) acetate (2.2 mg, 9.95 μmol, 5 mol %). Subsequently, **2B** (67.0 mg, 0.80 mmol, 4 equiv) was added to yield **4aB** (58.7 mg, 0.18 mmol, 88%) as a colorless solid.

$C_{21}H_{21}NO_3$: MW 335.40 g/mol; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.80−7.73 (*m*, 2H), 7.60−7.45 (*m*, 3H), 7.21−7.08 (*m*, 3H), 6.87−6.80 (*m*, 2H), 3.33 (*d*, *J* = 13.8, 1H), 3.28 (*d*, *J* = 14.1, 1H), 2.67−2.54 (*m*, 1H), 2.48−2.28 (*m*, 4H), 2.26−2.12 (*m*, 1H), 0.98 (*t*, *J* = 7.6 Hz, 3H).

The analytical data are in accordance with literature data for enantioenriched material.[19]

*4-Benzyl-4-(3-oxo-5-phenylpentyl)-3-phenylisoxazol-5(4H)-one (**4aC**).* According to GP1, to **1a** (50.0 mg, 0.20 mmol, 1.0 equiv) was added palladium(II) acetate (4.4 mg, 19.90 μmol, 10 mol %). Subsequently, **2C** (127.5 mg, 0.80 mmol, 4 equiv) was added to yield **4aC** (77.8 mg, 0.19 mmol, 95%) as a colorless solid.

$C_{27}H_{25}NO_3$: MW 411.50 g/mol; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.76 (*d*, *J* = 7.7, 2H), 7.61−7.47 (*m*, 3H), 7.24−7.05 (*m*, 8H), 6.83 (*d*, *J* = 8.3, 2H), 3.32 (*d*, *J* = 13.8, 1H), 3.29 (*d*, *J* = 13.8, 1H), 2.89−2.77 (*m*, 2H), 2.70−2.51 (*m*, 3H), 2.48−2.32 (*m*, 2H), 2.25−2.10 (*m*, 1H).

The analytical data are in accordance with literature data for enantioenriched material.[19]

*4-Benzyl-4-(3-oxo-3-phenylpropyl)-3-phenylisoxazol-5(4H)-one (**4aD**).* According to GP1, to **1a** (50.0 mg, 0.20 mmol, 1.0 equiv) was added palladium(II) acetate (2.2 mg, 9.95 μmol, 5 mol %). Subsequently, **2D** (105.7 mg, 0.80 mmol, 4 equiv) was added to yield **4aD** (38.3 mg, 0.10 mmol, 50%) as a colorless solid.

$C_{25}H_{21}NO_3$: MW 383.45 g/mol; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.88−7.79 (*m*, 4H), 7.59−7.48 (*m*, 4H), 7.21−7.11 (*m*, 3H), 6.90−6.85 (*m*, 2H), 3.41 (*d*, *J* = 13.4, 1H), 3.35 (*d*, *J* = 13.8, 1H), 3.12−2.97 (*m*, 1H), 2.86−2.55 (*m*, 3H).

The analytical data are in accordance with literature data for enantioenriched material.[19]

*4-Benzyl-4-(3-(4-methoxyphenyl)-3-oxopropyl)-3-phenylisoxazol-5(4H)-one (**4aE**).* According to GP1, to **1a** (50.0 mg, 0.20 mmol, 1.0 equiv) was added palladium(II) acetate (2.2 mg, 9.95 μmol, 5 mol %). Subsequently, **2E** (129.8 mg, 0.80 mmol, 4 equiv) was added to yield **4aE** (52.7 mg, 0.13 mmol, 64%) as a colorless solid.

$C_{26}H_{23}NO_4$: MW 413.47 g/mol; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.87−7.77 (*m*, 4H), 7.62−7.44 (*m*, 3H), 7.24−7.09 (*m*, 3H), 6.93−6.83 (*m*, 4H), 3.85 (*s*, 3H), 3.40 (*d*, *J* = 14.2, 1H), 3.35 (*d*, *J* = 14.2, 1H), 3.06−2.53 (*m*, 4H).

The analytical data are in accordance with literature data for enantioenriched material.[19]

*3a-(2-Oxopropyl)-4,5,6,7-tetrahydrobenzo[c]isoxazol-3(3aH)-one (**4mA**).* According to GP1, to **1m** (50.0 mg, 0.36 mmol, 1.0 equiv) was added palladium(II) acetate (4.0 mg, 18.00 μmol, 5 mol %). Subsequently, **2A** (121 μL, 1.44 mmol, 4 equiv) was added to yield **4mA** (51.1 mg, 0.24 mmol, 68%) as a colorless oil.

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$C_{11}H_{15}NO_3$: MW 209.25 g/mol; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 2.68−1.34 (*m*, 12H), 2.11 (*s*, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 206.2, 180.8, 172.2, 49.8, 37.6, 34.2, 30.1, 27.3, 25.6, 25.2, 20.5; IR (ATR) $\tilde{\nu}$ = 2944, 2867, 2254, 1781, 1714, 1621, 1448, 1366, 1315, 1279, 1213, 1166, 1144, 1079, 1043, 1014, 986, 941, 912, 861, 838, 727, 647, 592, 566, 552; MS (ESI) *m*/*z* 232.10 (100%, $[M + Na]^+$); HRMS (ESI) *m*/*z* calcd. for $[C_{11}H_{15}NO_3 + Na]^+$ 232.0944, found 232.0958.

*4,4′-(5-Oxo-3-phenyl-4,5-dihydroisoxazole-4,4-diyl)bis(butan-2-one) (**4n′A**).* To a suspension of **1n** (50.0 mg, 0.31 mmol, 1.0 equiv) in DCM (0.4 mL) was added palladium(II) acetate (3.4 mg, 15.00 μmol, 5 mol %). Subsequently, **2A** (105 μL, 1.24 mmol, 4 equiv) was added to yield **4n′A** (92.6 mg, 0.31 mmol, 99%) as a colorless oil.

$C_{17}H_{19}NO_4$: MW 301.34 g/mol; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.76 (*d*, 2H), 7.58−7.45 (*m*, 3H), 2.44−2.15 (*m*, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 205.5, 180.1, 166.7, 132.3, 129.6, 127.1, 126.5, 53.5, 38.0, 29.9, 29.7; IR (ATR) $\tilde{\nu}$ = 2929, 1789, 1714, 1551, 1499, 1447, 1420, 1366, 1264, 1231, 1162, 1119, 1087, 949, 883, 804, 775, 693, 634, 590, 569; MS (ESI) *m*/*z* 324.12 (100%, $[M + Na]^+$); HRMS (ESI) *m*/*z* calcd. for $[C_{17}H_{19}NO_4 + Na]^+$ 324.1206, found 324.1207.

Pyridine Synthesis. *3-Benzyl-6-methyl-2-phenylpyridine (**3aA**).* According to GP2, to a solution of **4aA** (50.0 mg, 0.16 mmol, 1 equiv) was added tetrakis(triphenylphosphine)palladium(0) (0.9 mg, 0.78 μmol, 0.5 mol %), and the reaction was set under hydrogen to yield **3aA** (40.6 mg, 0.16 mmol, 98%) as a colorless oil.

$C_{19}H_{17}N$: MW 259.35 g/mol; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.48−7.43 (*m*, 2H), 7.43−7.34 (*m*, 4H), 7.28−7.15 (*m*, 3H), 7.08 (*d*, *J* = 7.6, 1H), 7.01 (*d*, *J* = 7.6, 2H), 3.98 (*s*, 2H), 2.61 (*s*, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 158.5, 155.9, 140.69, 140.67, 138.7, 130.7, 129.0, 128.8, 128.5, 128.3, 127.9, 126.2, 122.0, 38.1, 24.3; IR (ATR) $\tilde{\nu}$ = 3082, 3058, 3026, 2920, 2846, 1589, 1565, 1493, 1451, 1439, 1384, 1372 1294, 1244, 1169, 1119, 1074, 1057, 1028, 1001, 968, 908, 841, 802, 772, 725, 695, 643, 633, 618, 596, 541, 524; MS (ESI) *m*/*z* 260.14 (100%, $[M + H]^+$); HRMS (ESI) *m*/*z* calcd. for $[C_{19}H_{17}N + H]^+$ 260.1434, found 260.1424.

*3,6-Dimethyl-2-phenylpyridine (**3bA**).* According to GP2, to a solution of **4bA** (50.0 mg, 0.20 mmol, 1 equiv) was added tetrakis(triphenylphosphine)palladium(0) (1.2 mg, 1.01 μmol, 0.5 mol %), and the reaction was set under hydrogen to yield **3bA** (35.6 mg, 0.19 mmol, 97%) as a colorless oil.

$C_{13}H_{13}N$: MW 183.25 g/mol; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.55−7.48 (*m*, 2H), 7.48−7.41(*m*, 3H), 7.41−7.33 (*m*, 1H), 7.03 (*d*, *J* = 7.5 Hz, 1H), 2.59 (*s*, 3H), 2.29 (*s*, 3H).

The analytical data are in accordance with the literature.[29]

*6-Methyl-2-phenyl-3-propylpyridine (**3cA**).* According to GP2, to a solution of **4cA** (50.0 mg, 0.18 mmol, 1 equiv) was added tetrakis(triphenylphosphine)palladium(0) (2.1 mg, 1.83 μmol, 1.0 mol %), and the reaction was set under hydrogen to yield **3cA** (36.5 mg, 0.17 mmol, 96%) as a colorless oil.

$C_{15}H_{17}N$: MW 211.30 g/mol; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.49 (*d*, *J* = 7.9, 1H), 7.46−739 (*m*, 4H), 7.39−7.32 (*m*, 1H), 7.08 (*d*, *J* = 7.7, 1H), 2.57 (*s*, 3H), 2.56 (*t*, *J* = 7.7, 2H), 1.50 (*m*, 2H), 0.83 (*t*, *J* = 7.6, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 158.2, 155.2, 141.0, 137.6, 132.3, 128.9, 128.2, 127.6, 121.8, 34.1, 24.2, 24.1, 13.9; IR (ATR) $\tilde{\nu}$ = 3056, 2958, 2928, 2870, 1590, 1566, 1494, 1459, 1440, 1375, 1293, 1245, 1179, 1128, 1073, 1054, 1027, 916, 828, 806, 778, 751, 735, 699, 633, 609, 568, 535; MS (ESI) *m*/*z* 212.14 (100%, $[M + H]^+$); HRMS (ESI) *m*/*z* calcd. for $[C_{15}H_{17}N + H]^+$ 212.1434, found 212.1423.

*4-(4-Methylbenzyl)-4-(3-oxobutyl)-3-phenylisoxazol-5(4H)-one (**3dA**).* According to GP2, to a solution of **4dA** (50.0 mg, 0.15 mmol, 1 equiv) was added tetrakis(triphenylphosphine)palladium(0) (0.9 mg, 0.75 μmol, 0.5 mol %), and the reaction was set under hydrogen to yield **3dA** (38.3 mg, 0.14 mmol, 94%) as a colorless oil.

$C_{20}H_{19}N$: MW 273.37 g/mol; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.48−7.44 (*m*, 2H), 7.43−7.33 (*m*, 4H), 7.09−7.03 (*m*, 3H), 6.94−6.88 (*m*, 2H), 3.94 (*s*, 2H), 2.60 (*s*, 3H), 2.32 (*s*, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 158.4, 155.8, 140.7, 138.7, 137.6, 135.6, 130.9, 129.2, 129.0, 128.7, 128.2, 127.8, 122.0, 37.6, 24.3, 21.0; IR (ATR) $\tilde{\nu}$ = 3050, 3020, 2919, 1590, 1564, 1511, 1494, 1458, 1438, 1380, 1293, 1243, 1180, 1119, 1075, 1056, 1027, 948, 913, 883, 847, 812, 785, 749, 698, 632, 609, 578, 535; MS (ESI) *m*/*z* 274.16 (100%, $[M + H]^+$); HRMS (ESI) *m*/*z* calcd. for $[C_{20}H_{19}N + H]^+$ 274.1590, found 274.1593.

*4-(4-Methoxybenzyl)-4-(3-oxobutyl)-3-phenylisoxazol-5(4H)-one (**3eA**).* According to GP2, to a solution of **4eA** (50.0 mg, 0.14 mmol, 1 equiv) was added tetrakis(triphenylphosphine)palladium(0) (0.8 mg, 0.71 μmol, 0.5 mol %), and the reaction was set under hydrogen to yield **3eA** (39.1 mg, 0.14 mmol, 95%) as a colorless oil.

$C_{20}H_{19}NO$: MW 289.37 g/mol; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.48−7.31 (*m*, 6H), 7.07 (*d*, *J* = 7.9, 1H), 6.92 (*d*, *J* = 9.0, 2H), 6.79 (*d*, *J* = 8.9, 2H), 3.90 (*s*, 2H), 3.78 (*s*, 3H), 2.59 (*s*, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 158.3, 158.0, 155.8, 140.7, 138.6, 132.8, 131.1, 129.8, 129.0, 128.3, 127.9, 122.0, 113.9, 55.3, 37.3, 24.4; IR (ATR) $\tilde{\nu}$ = 3000, 2932, 2834, 1610, 1588, 1565, 1510, 1461, 1440, 1384, 1301, 1247, 1176, 1119, 1034, 910, 820, 798, 748, 700, 633, 536; MS (EI) *m*/*z* 289.20 (100%, $[M]^+$); HRMS (EI) *m*/*z* calcd. for $[C_{20}H_{19}NO]^+$ 289.1467, found 289.1458.

*6-Methyl-3-(naphthalen-2-ylmethyl)-2-phenylpyridine (**3fA**).* According to GP3, to a solution of **4fA** (50.0 mg, 0.13 mmol, 1 equiv) was added tetrakis(triphenylphosphine)palladium(0) (1.6 mg, 1.35 μmol, 1.0 mol %), and the reaction was set under hydrogen to yield **3fA** (38.3 mg, 0.12 mmol, 92%) as a colorless oil.

$C_{23}H_{19}NO$: MW 309.40 g/mol; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.84−7.48 (*m*, 1H), 7.77−7.70 (*m*, 2H), 7.53−7.36 (*m*, 8H), 7.18−7.14 (*m*, 1H), 7.09 (*d*, *J* = 7.7, 1H), 4.15 (*s*, 2H), 2.63 (*s*, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 158.5, 156.1, 140.7, 138.8, 128.3, 133.6, 132.1, 130.5, 129.1, 128.3, 128.2, 128.0, 127.6, 127.5, 127.4, 127.2, 126.1, 125.5, 122.1, 38.4, 24.4; IR (ATR) $\tilde{\nu}$ = 3051, 2919, 1632, 1590, 1565, 1507, 1495, 1458, 1438, 1371, 1285, 1271, 1243, 1169, 1149, 1120, 1075, 1057, 1027, 956, 928, 858, 813, 799, 756, 741, 699, 633, 620, 608, 580, 538; MS (ESI) *m*/*z* 310.16 (100%, $[M + H]^+$); HRMS (ESI) *m*/*z* calcd. for $[C_{23}H_{19}N + H]^+$ 310.1590, found 310.1595.

*6-Methyl-3-(4-nitrobenzyl)-2-phenylpyridine (**3gA**).* According to GP2, to a solution of **4gA** (50.0 mg, 0.14 mmol, 1 equiv) was added tetrakis(triphenylphosphine)palladium(0) (1.6 mg, 1.36 μmol, 1.0 mol %), and the reaction was set under hydrogen to yield **3gA** (38.6 mg, 0.13 mmol, 92%) as a colorless oil.

$C_{19}H_{16}N_2O_2$: MW 304.34 g/mol; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 8.05 (*d*, *J* = 7.84, 2H), 7.43−7.30 (*m*, 6H), 7.11 (*d*, *J* = 7.6, 1H), 7.07 (*d*, *J* = 8.5, 2H), 4.06 (*s*, 2H), 2.59 (*s*, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 158.7, 156.8, 148.3, 146.5, 140.3, 138.6, 129.5, 129.1, 128.8, 128.4, 128.1, 123.7, 122.3, 38.2, 24.4; IR (ATR) $\tilde{\nu}$ = 3056, 2922, 2852, 1596, 1566, 1513, 1492, 1459, 1439, 1372, 1342, 1245, 1179, 1109, 1075, 1057, 1027, 1015, 919, 858, 826, 803, 775, 754, 733, 700, 632, 606, 566, 534; MS (ESI) *m*/*z* 305.13 (100%, $[M + H]^+$); HRMS (ESI) *m*/*z* calcd. for $[C_{19}H_{16}N_2O_2 + H]^+$ 305.1285, found 305.1291.

*4-((6-Methyl-2-phenylpyridin-3-yl)methyl)aniline (**3gA***).* According to GP2, to a solution of **4gA** (50.0 mg, 0.14 mmol, 1 equiv) was added tetrakis(triphenylphosphine)palladium(0) (7.9 mg, 6.8 μmol, 5.0 mol %), and the reaction was set under hydrogen to yield **3gA*** (37.1 mg, 0.14 mmol, 99%) as a colorless oil.

$C_{19}H_{18}N_2$: MW 274.37 g/mol; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.48−7.32 (*m*, 6H), 7.05 (*d*, *J* = 7.6, 1H), 6.78 (*d*, *J* = 8.1, 2H), 6.58 (*d*, *J* = 8.1, 2H), 3.84 (*s*, 2H), 2.58 (*s*, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 158.3, 155.7, 144.5, 140.8, 138.5, 131.5, 130.7, 129.7, 129.0, 128.2, 127.8, 122.0, 115.3, 37.2, 24.3; IR (ATR) $\tilde{\nu}$ = 3445, 3336, 3214, 3054, 3026, 2919, 2848, 2210, 1886, 1621, 1589, 1565, 1513, 1458, 1438, 1373, 1275, 1244, 1177, 1122, 1075, 1057, 1027, 909, 883, 816, 797, 757, 731, 699, 633, 609, 579, 537, 500; MS (ESI) *m*/*z* 275.15 (100%, $[M + H]^+$); HRMS (ESI) *m*/*z* calcd. for $[C_{19}H_{18}N_2 + H]^+$ 275.1543, found 275.1530.

*6-Methyl-2,3-diphenylpyridine (**3hA**).* According to GP2, to a solution of **4hA** (50.0 mg, 0.16 mmol, 1 equiv) was added tetrakis(triphenylphosphine)palladium(0) (1.9 mg, 1.63 μmol, 1.0 mol %), and the reaction was set under hydrogen to yield **3hA** (39.5 mg, 0.16 mmol, 99%) as a colorless oil.

$C_{18}H_{15}N$: MW 245.32 g/mol; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.60 (*d*, *J* = 7.6 Hz, 1H), 7.34−7.32 (*m*, 1H), 7.23−7.12 (*m*, 10H), 2.65 (*s*, 3H).

The analytical data are in accordance with the literature.[30]

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*3-Benzyl-2-(4-methoxyphenyl)-6-methylpyridine (**3iA**).* According to GP2, to a solution of **4iA** (50.0 mg, 0.14 mmol, 1 equiv) was added tetrakis(triphenylphosphine)palladium(0) (1.6 mg, 1.42 μmol, 1.0 mol %), and the reaction was set under hydrogen to yield **3iA** (36.6 mg, 0.13 mmol, 89%) as a colorless oil.

$C_{20}H_{19}NO$: MW 289.37 g/mol; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.34−7.26 (*m*, 3H), 7.20−7.13 (*m*, 2H), 7.13−7.06 (*m*, 1H), 6.96 (*d*, *J* = 7.9, 1H), 6.93 (*d*, *J* = 7.5, 2H), 6.85 (*d*, *J* = 8.9, 2H), 3.91 (*s*, 2H), 3.76 (*s*, 3H), 2.50 (*s*, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 159.5, 158.1, 155.9, 140.8, 138.9, 133.2, 130.6, 130.3, 128.9, 128.5, 126.2, 121.8, 113.7, 55.4, 38.2, 24.3; IR (ATR) $\tilde{\nu}$ = 3025, 3000, 2930, 2835, 1737, 1608, 1590, 1574, 1512, 1493, 1450, 1413, 1382, 1295, 1243, 1174, 1119, 1108, 1074, 1058, 1029, 937, 890, 835, 797, 763, 731, 721, 697, 642, 618, 584, 549, 527; MS (ESI) *m*/*z* 290.15 (100%, $[M + H]^+$); HRMS (ESI) *m*/*z* calcd. for $[C_{20}H_{19}NO + H]^+$ 290.1539, found 290.1550.

*4-(3-Benzyl-6-methylpyridin-2-yl)aniline (**3jA***).* According to GP2, to a solution of **4jA** (50.0 mg, 0.14 mmol, 1 equiv) was added tetrakis(triphenylphosphine)palladium(0) (1.6 mg, 1.36 μmol, 1.0 mol %), and the reaction was set under hydrogen to yield **3jA*** (34.0 mg, 0.12 mmol, 91%) as a colorless oil.

$C_{19}H_{18}N_2$: MW 274.36 g/mol; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.35 (*d*, *J* = 7.6, 1H), 7.29−7.21 (*m*, 4H), 7.20−7.12 (*m*, 1H), 7.05−6.97 (*m*, 3H), 6.70 (*d*, *J* = 8.2, 2H), 4.0 (*s*, 2H), 2.57 (*s*, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 158.4, 155.8, 146.2, 140.9, 138.7, 130.9, 130.4, 130.2, 128.9, 128.5, 126.1, 121.4, 114.8, 38.2, 24.3; IR (ATR) $\tilde{\nu}$ = 3365, 3218, 3058, 3026, 2922, 1762, 1714, 1611, 1589, 1518, 1493, 1450, 1377, 1288, 1243, 1178, 1118, 1074, 1057, 1029, 910, 835, 794, 764, 729, 698, 645, 619, 580, 545; MS (ESI) *m*/*z* 275.15 (100%, $[M + H]^+$); HRMS (ESI) *m*/*z* calcd. for $[C_{19}H_{18}N_2 + H]^+$ 275.1543, found 275.1542.

*3-Benzyl-2-(3-methoxyphenyl)-6-methylpyridine (**3kA**).* According to GP2, to a solution of **4kA** (50.0 mg, 0.14 mmol, 1 equiv) was added tetrakis(triphenylphosphine)palladium(0) (1.6 mg, 1.42 μmol, 1.0 mol %), and the reaction was set under hydrogen to yield **3kA** (35.8 mg, 0.12 mmol, 87%) as a colorless oil.

$C_{20}H_{19}NO$: MW 289.37 g/mol; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.33 (*d*, *J* = 7.2, 1H), 7.26−7.20 (*m*, 1H), 7.20−7.13 (*m*, 2H), 7.13−7.06 (*m*, 1H), 7.00 (*d*, *J* = 8.1, 1H), 6.96−6.90 (*m*, 3H), 6.87−6.80 (*m*, 2H), 3.88 (*s*, 2H), 3.65 (*s*, 3H), 2.51 (*s*, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 159.4, 158.3, 155.9, 141.9, 140.8, 138.8, 130.6, 129.3, 128.8, 128.5, 126.1, 122.1, 121.3, 114.2, 114.1, 55.2, 38.2, 24.3; IR (ATR) $\tilde{\nu}$ = 3059, 3026, 3001, 2935, 2834, 1715, 1679, 1599, 1579, 1492, 1452, 1427, 1382, 1318, 1286, 1246, 1231, 1165, 1119, 1074, 1041, 995, 918, 875, 845, 825, 782, 759, 729, 700, 635, 620, 558, 527; MS (ESI) *m*/*z* 290.16 (100%, $[M + H]^+$); HRMS (ESI) *m*/*z* calcd. for $[C_{20}H_{19}NO + H]^+$ 290.1515, found 290.1523.

*3-Benzyl-2,6-dimethylpyridine (**3lA**).* According to GP2, to a solution of **4lA** (50.0 mg, 0.19 mmol, 1 equiv) was added tetrakis(triphenylphosphine)palladium(0) (2.2 mg, 1.93 μmol, 1.0 mol %), and the reaction was set under hydrogen to yield **3lA** (33.9 mg, 0.17 mmol, 89%) as a colorless oil.

$C_{14}H_{15}N$: MW 197.28 g/mol; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.25−7.08 (*m*, 4H), 7.01 (*d*, *J* = 6.8, 2H), 6.84 (*d*, *J* = 7.6, 1H), 3.85 (*s*, 2H), 2.42 (*s*, 3H), 2.37 (*s*, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 156.4, 155.5, 139.5, 137.8, 130.9, 128.7, 128.6, 126.3, 120.8, 38.4, 24.1, 22.6; IR (ATR) $\tilde{\nu}$ = 3060, 3026, 2919, 1713, 1593, 1576, 1493, 1463, 1450, 1392, 1370, 1263, 1245, 1158, 1114, 1074, 1028, 971, 911, 838, 813, 786, 724, 696, 642, 613, 570, 549, 521; MS (ESI) *m*/*z* 198.13 (100%, $[M + H]^+$); HRMS (ESI) *m*/*z* calcd. for $[C_{14}H_{15}N + H]^+$ 198.1277, found 198.1255.

*3-Benzyl-6-ethyl-2-phenylpyridine (**3aB**).* According to GP2, to a solution of **4aB** (50.0 mg, 0.15 mmol, 1 equiv) was added tetrakis(triphenylphosphine)palladium(0) (1.7 mg, 1.49 μmol, 1.0 mol %), and the reaction was set under hydrogen to yield **3aB** (37.9 mg, 0.14 mmol, 93%) as a colorless oil.

$C_{20}H_{19}N$: MW 273.38 g/mol; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.40−7.24 (*m*, 5H), 7.19−7.12 (*m*, 2H), 7.12−7.06 (*m*, 1H), 7.00 (*d*, *J* = 7.9, 1H), 6.92 (*d*, *J* = 7.4, 2H), 3.89 (*s*, 2H), 2.78 (*q*, *J* = 7.6, 2H), 1.24 (*t*, *J* = 7.6, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 161.2, 158.3, 140.7, 138.8, 130.8, 129.1, 128.9, 128.5, 128.2, 127.9, 126.1, 120.6, 38.1, 31.2, 14.2; IR (ATR) $\tilde{\nu}$ = 3059, 3026, 2966, 2932, 2872, 1588, 1562, 1494, 1463, 1452, 1438, 1393, 1288, 1222, 1168, 1121, 1074, 1060, 1026, 1001, 973, 918, 872, 843, 819, 770, 725, 698, 632, 546; MS (ESI) *m*/*z* 274.16 (100%, $[M + H]^+$); HRMS (ESI) *m*/*z* calcd. for $[C_{20}H_{19}N + H]^+$ 274.1590, found 274.1591.

*3-Benzyl-6-phenethyl-2-phenylpyridine (**3aC**).* According to GP2, to a solution of **4aC** (50.0 mg, 0.12 mmol, 1 equiv) was added tetrakis(triphenylphosphine)palladium(0) (1.4 mg, 1.22 μmol, 1.0 mol %), and the reaction was set under hydrogen to yield **3aC** (41.2 mg, 0.12 mmol, 97%) as a colorless oil.

$C_{26}H_{23}N$: MW 349.47 g/mol; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.49−7.33 (*m*, 6H), 7.32−7.15 (*m*, 8H), 7.05−6.99 (*m*, 3H), 3.99 (*s*, 2H), 3.13 (*m*, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 158.9, 158.5, 141.7, 140.7, 138.7, 131.1, 129.1, 128.8, 128.6, 128.5, 128.3, 128.2, 127.9, 126.2, 125.9, 121.6, 39.8, 38.2, 36.2; IR (ATR) $\tilde{\nu}$ = 3083, 3059, 3025, 2923, 2856, 1601, 1587, 1565, 1494, 1452, 1439, 1393, 1290, 1178, 1116, 1074, 1056, 1028, 918, 843, 809, 751, 728, 698, 670, 632, 542; MS (ESI) *m*/*z* 350.19 (100%, $[M + H]^+$); HRMS (ESI) *m*/*z* calcd. for $[C_{26}H_{23}N + H]^+$ 350.1903, found 350.1907.

*3-Benzyl-2,6-diphenylpyridine (**3aD**).* According to GP2, to a solution of **4aD** (50.0 mg, 0.13 mmol, 1 equiv) was added tetrakis(triphenylphosphine)palladium(0) (1.5 mg, 1.30 μmol, 1.0 mol %), and the reaction was set under hydrogen to yield **3aD** (35.7 mg, 0.11 mmol, 85%) as a colorless oil.

$C_{24}H_{19}N$: MW 321.41 g/mol; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 8.11−8.03 (*m*, 2H), 7.66 (*d*, *J* = 8.2, 1H), 7.62−7.54 (*m*, 3H), 7.50−7.35 (*m*, 6H), 7.32−7.16 (*m*, 3H), 7.07 (*d*, J = 7.4, 2H), 4.10 (*s*, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 158.7, 154.9, 140.7, 140.6, 139.3, 132.2, 129.3, 128.9, 128.8, 128.7, 128.6, 128.0, 126.9, 126.2, 119.0, 38.3; IR (ATR) $\tilde{\nu}$ = 3058, 3025, 2930, 2852, 1601, 1584, 1573, 1559, 1493, 1452, 1436, 1377, 1315, 1266, 1178, 1156, 1126, 1074, 1027, 1018, 1001, 918, 844, 792, 750, 724, 693, 635, 615, 581, 549, 529, 508; MS (ESI) *m*/*z* 322.16 (100%, $[M + H]^+$); HRMS (ESI) *m*/*z* calcd. for $[C_{24}H_{19}N + H]^+$ 322.1590, found 322.1589.

*3-Benzyl-6-(4-methoxyphenyl)-2-phenylpyridine (**3aE**).* According to GP2, to a solution of **4aE** (50.0 mg, 0.12 mmol, 1 equiv) was added tetrakis(triphenylphosphine)palladium(0) (1.4 mg, 1.21 μmol, 1.0 mol %), and the reaction was set under hydrogen to yield **3aE** (40.4 mg, 0.11 mmol, 95%) as a colorless oil.

$C_{25}H_{21}NO$: MW 351.45 g/mol; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 8.03 (*d*, *J* = 8.8, 2H), 7.63−7.51 (*m*, 4H), 7.50−7.34 (*m*, 3H), 7.32−7.15 (*m*, 3H), 7.06 (*d*, *J* = 7.3, 2H), 6.98 (*d*, *J* = 8.7, 2H), 4.08 (*s*, 2H), 3.86 (*s*, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 160.4, 158.5, 154.6, 140.8, 140.7, 139.2, 131.9, 131.4, 129.3, 129.0, 128.9, 128.5, 128.2, 128.1, 127.9, 126.2, 118.3, 114.1, 113.8, 55.4, 38.3; IR (ATR) $\tilde{\nu}$ = 3059, 3026, 2931, 2835, 1607, 1584, 1560, 1512, 1494, 1453, 1437, 1376, 1304, 1288, 1250, 1172, 1110, 1074, 1059, 1044, 1029, 919, 833, 815, 784, 766, 725, 699, 669, 638, 565, 526; MS (ESI) *m*/*z* 352.17 (100%, $[M + H]^+$); HRMS (ESI) *m*/*z* calcd. for $[C_{25}H_{21}NO + H]^+$ 352.1696, found 352.1689.

*2-Methyl-5,6,7,8-tetrahydroquinoline (**3mA**).* According to GP2, to a solution of **4mA** (50.0 mg, 0.24 mmol, 1 equiv) was added tetrakis(triphenylphosphine)palladium(0) (13.8 mg, 11.9 μmol, 5.0 mol %), and the reaction was set under hydrogen to yield **3mA** (28.8 mg, 0.20 mmol, 82%) as a colorless oil.

$C_{10}H_{13}N$: MW 147.22 g/mol; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.22 (*d*, *J* = 8.3, 1H), 6.86 (*d*, *J* = 7.3, 1H), 2.87 (*t*, *J* = 6.4, 2H), 2.69 (*t*, *J* = 6.2, 2H), 2.47 (*s*, 3H), 1.90−1.73 (*m*, 4H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ = 156.4, 155.0, 137.1, 129.0, 120.5, 32.6, 28.4, 24.1, 23.2, 22.8; IR (ATR) $\tilde{\nu}$ = 2928, 2858, 2836, 1713, 1594, 1573, 1469, 1438, 1425, 1401, 1372, 1309, 1263, 1243, 1158, 1116, 1034, 985, 936, 898, 862, 831, 806, 732, 710, 607, 562, 535; MS (EI) *m*/*z* 147.10 (100%, $[M]^+$); HRMS (EI) *m*/*z* calcd. for $[C_{10}H_{13}N]^+$ 147.1048, found 147.1042.

*4-(6-Methyl-2-phenylpyridin-3-yl)butan-2-one (**3n′A**).* According to GP2, to a solution of **4n′A** (50.0 mg, 0.17 mmol, 1 equiv) was added tetrakis(triphenylphosphine)palladium(0) (9.6 mg, 8.3 μmol, 5.0 mol %), and the reaction was set under hydrogen to yield **3n′A** (34.9 mg, 0.15 mmol, 88%) as a colorless oil.

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$C_{16}H_{17}NO$: MW 239.32 g/mol; ^1H NMR ($CDCl_3$, 500 MHz) δ = 7.45 (*d*, *J* = 7.7, 1H), 7.43 (*d*, *J* = 3.8, 4H), 7.40−7.33 (*m*, 1H), 7.07 (*d*, *J* = 8.2, 1H), 2.88 (*t*, *J* = 7.5, 2H), 2.56 (*s*, 3H), 2.51 (*t*, *J* = 7.6, 2H), 2.00 (*s*, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 207.5, 158.1, 155.9, 140.7, 137.9, 130.7, 128.7, 128.4, 127.9, 122.0, 44.2, 29.8, 26.2, 24.2; IR (ATR) $\tilde{\nu}$ = 3056, 2923, 1712, 1591, 1566, 1495, 1460, 1440, 1363, 1287, 1160, 1123, 1063, 1027, 967, 918, 820, 790, 748, 701, 634, 609, 596, 550; MS (ESI) *m*/*z* 240.14 (100%, $[M + H]^+$); HRMS (ESI) *m*/*z* calcd. for $[C_{16}H_{17}NO + H]^+$ 240.1377, found 240.1383.

Scale-up Experiment: 1,4-Addition. According to GP1, to **1a** (449.0 mg, 1.79 mmol, 1.0 equiv) was added palladium(II) acetate (0.4 mg, 1.79 μmol, 0.1 mol %). Subsequently, **2A** (604 μL, 7.14 mmol, 4 equiv) was added and the reaction was stirred for 24 h. Column chromatography (silica, petrol ether/ethyl acetate: 4/1) yielded **4aA** (436.1 mg, 1.36 mmol, 76%) as a colorless solid.

Scale-up Experiment: Pyridine Formation. According to GP2, to a solution of **4aA** (621.0 mg, 1.93 mmol, 1 equiv) was added tetrakis(triphenylphosphine)palladium(0) (35.9 mg, 19.3 μmol, 1.0 mol %), and the reaction was set under hydrogen. After 24 h the solvent was evaporated and the crude product was subjected to column chromatography (silica, petrol ether/ethyl acetate: 4/1) to yield **3aA** (500 mg, 1.93 mmol, 100%) as a colorless oil.

Pyridine Formation in a Sealed Tube. A 120 mL sealed tube was charged with **4aA** (30.7 mg, 0.095 mmol, 1 equiv), tetrakis-(triphenylphosphine)palladium(0) (0.55 mg, 0.47 μmol, 0.5 mol %) and 1,4-dioxane (1.5 mL). A constant stream of H_2 was bubbled through the solution for 10 min. Thereafter the tube was filled with H_2 (94 mL) and air (24 mL) via syringes and sealed. The reaction mixture was subsequently stirred for 24 h. Column chromatography (silica, petrol ether/ethyl acetate: 4/1) yielded **3aA** (22 mg, 0.085 mmol, 89%) as a colorless oil.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General experimental procedures, NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01065.

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Notes

The authors declare no competing financial interest.

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