Synthesis of Conformationally Constrained Esters and Amines by Pd-Catalyzed α-Arylation of Hindered Substrates

Anthony Martin,[†] Jean-Pierre Vors,[‡] and Olivier Baudoin*[†,§]

[†]Université Claude Bernard Lyon 1, CNRS UMR 5246 - Institut de Chimie et Biochimie Moléculaires et Supramoléculaires, CPE Lyon, 43 Boulevard du 11 Novembre 1918, 69622 Villeurbanne, France.

[§]Current address: Department of Chemistry, University of Basel, St. Johanns-Ring 19, CH-4056 Basel, Switzerland.
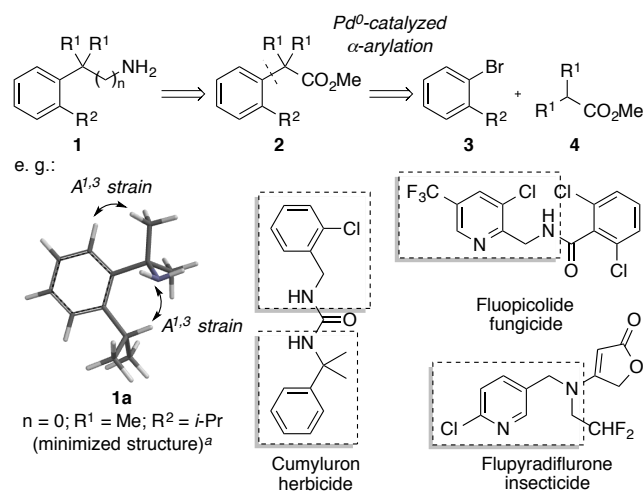
[‡]Bayer SAS, 14 Impasse Pierre Baizet, 69263 Lyon Cedex 09, France.

ABSTRACT: The α-arylation of sterically hindered silyl ketene acetals (SKAs) with sterically hindered aryl bromides occurs efficiently using $Pd[P(t-Bu)_3]_2$ as the optimal catalyst and ZnF_2 as a promoter. Less sensitive $P(t-Bu)_3$-based catalysts could be also employed, but showed a lower activity. The reaction showed broad scope with regard to both coupling partners, including heteroaryl bromides and cyclic SKAs. It also proved scalable to multigram quantities, which allowed to further transform the ester group and to access conformationally constrained benzyl- and phenethylamines, highly sought-after building blocks for the synthesis of new agrochemicals.

Keywords: arylation; C–C coupling; palladium; esters; amines.

Benzylamines and phenethylamines are widespread structural motifs in pharmaceuticals and agrochemicals. In particular, benzylamines can be found in all classes of active agrochemical ingredients (Scheme 1).[1] The introduction of substituents at both the benzylic (R^1) and the *ortho* (R^2) positions of these systems is highly desirable, because it would allow to restrict conformational freedom by virtue of the minimization of allylic 1,3-strains (see **1a**),[2] and hence to possibly enhance the binding to their cellular target.[3] Additional beneficial effects on the physicochemical properties can be also expected due to increased lipophilicity and metabolic stability.[4] However, the synthesis of such very sterically hindered benzyl- and phenethylamines **1** by the current available methods is a significant challenge.[5]

Scheme 1. Access to Sterically Hindered Primary Amines via Pd-Catalyzed α-Arylation of Esters

e. g.:

1a
n = 0; R^1 = Me; R^2 = *i*-Pr
(minimized structure)[a]

Fluopicolide fungicide

Cumyluron herbicide

Flupyradiflurone insecticide

[a] B3LYP, 6-31G*.

We envisaged that amines **1** could be obtained from the common ester precursor **2** via hydrolysis followed by Curtius rearrangement or reductive amination, respectively. In turn, one could consider building the very bulky ester **2** by Pd[0]-catalyzed α-arylation of an enolate equivalent of carboxylic ester **4** with aryl bromide **3**. This cross-coupling reaction is a well-established method to construct a variety of arylated esters and carbonyl compounds.[6] However, the developed methods have been very rarely tested against steric hindrance on both coupling partners.[7,8] To the best of our knowledge, the most sterically encumbered partners employed so far feature a cyclohexyl group on the ester (R^1,R^1 = –(CH_2)_2-CHMe-(CH_2)_2–) and a methyl group as R^2, with a yield of only 37%.[8b] Herein, we report an operationally simple and efficient method which allows to couple a variety of sterically hindered esters and (hetero)aryl bromides, by using stable silyl ketene acetals as ester enolate equivalents and commercially available catalysts.

At the onset of our studies, we tried to optimize the coupling of *in situ*-generated metal (Li, Na, or K) enolates of methyl isobutyrate **4a** with 1-bromo-2-isopropylbenzene **3a** (Scheme 2). Despite extensive efforts, the highest achieved yield was only 40% under the shown conditions employing the lithium enolate of **4a** and $P(t-Bu)_3$ as the ligand.[7d]

**Scheme 2. Optimized Coupling of Metal Enolates**
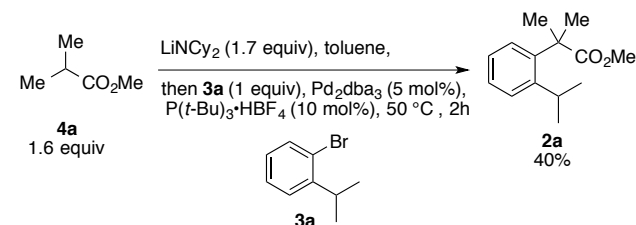
Based on previous observations,[9] we ascribed this lack of efficiency to catalyst deactivation by the amine (Cy₂NH in Scheme 2), which is generated in stoichiometric amounts during the enolate formation. Hence, we turned to the coupling of silyl ketene acetal (SKA) **5a**, a commercially available, stable and practical enolate equivalent which allows to perform the α-arylation reaction under amine-free conditions.[7e-f,10] A careful optimization of the coupling of SKA **5a** with aryl bromide **3a** was thus conducted (Table 1). Under conditions close to those reported by Hartwig and co-workers,[7e-f] i. e. with P(*t*-Bu)₃ as the ligand and ZnF₂ as a Lewis acid promoter in DMF at 90 °C, the desired coupling product was obtained in 65% GC yield, thereby validating the choice of **5a** as a superior enolate equivalent (entry 1). Gratifyingly, the well-defined Pd⁰L₂ complex significantly improved the yield (entry 2). The amount of SKA **5a** was varied, and 1.6 equiv proved the best compromise, although a decent yield (74%) was obtained at 1 equiv (entry 2, note). The amount of ZnF₂ could be also decreased, but a longer reaction time was required to reach full conversion (entry 3). Besides, a reaction temperature of 90 °C proved to be optimal (entries 2, 4).

**Table 1. Optimization of the Coupling of Silyl Ketene Acetal 5a with Aryl Bromide 3a**

Entry	Pd catalyst (mol%)	Promoter (equiv)	Temp. (°C)	t (h)	GC Yield (%)[a]
1	Pd₂dba₃ (5)/ P(*t*-Bu)₃ (10)	ZnF₂ (1)	90	2	65
2	Pd[P(*t*-Bu)₃]₂ (10)	ZnF₂ (1)	90	2	92[a] (86)
3	Pd[P(*t*-Bu)₃]₂ (10)	ZnF₂ (0.5)	90	15	90
4	Pd[P(*t*-Bu)₃]₂ (10)	ZnF₂ (1)	70	2	16
5	Pd[P(*t*-Bu)₃]₂ (10)	CsF (1)[c]	90	15	<5
6	Pd[P(*t*-Bu)₃]₂ (10)	ZnCl₂ (1)	90	15	32
7	Pd[P(*t*-Bu)₃]₂ (10)	LiCl (1)	90	15	79 (66)
8	Pd₂dba₃ (5)/ P(*t*-Bu)₃•HBF₄ (10)/ K₂CO₃ (10)[d]	ZnF₂ (1)	90	2	63
9	[PdBrP(*t*-Bu)₃]₂ (5)	ZnF₂ (1)	110[e]	2	91 (84)
10	**6** (4)/NEt₃ (4)[f]	ZnF₂ (1)	110[g]	15	76 (72)
11	Pd[P(*t*-Bu)₃]₂ (5)	ZnF₂ (1)	90	7	95 (89)
12	Pd[P(*t*-Bu)₃]₂ (1)	ZnF₂ (1)	90	7	100 (91)

[a] Determined by GCMS using tetradecane as the internal standard. Yield of the isolated product in parentheses. [b] Yield with 1.0 equiv **5a**: 74%. [c] Yield with KF: 32%. [d] Yield without K₂CO₃: 41%. [e] Yield at 90 °C: 65%. [f] Yield without NEt₃: 47%. [g] Yield at 90 °C: 57%.
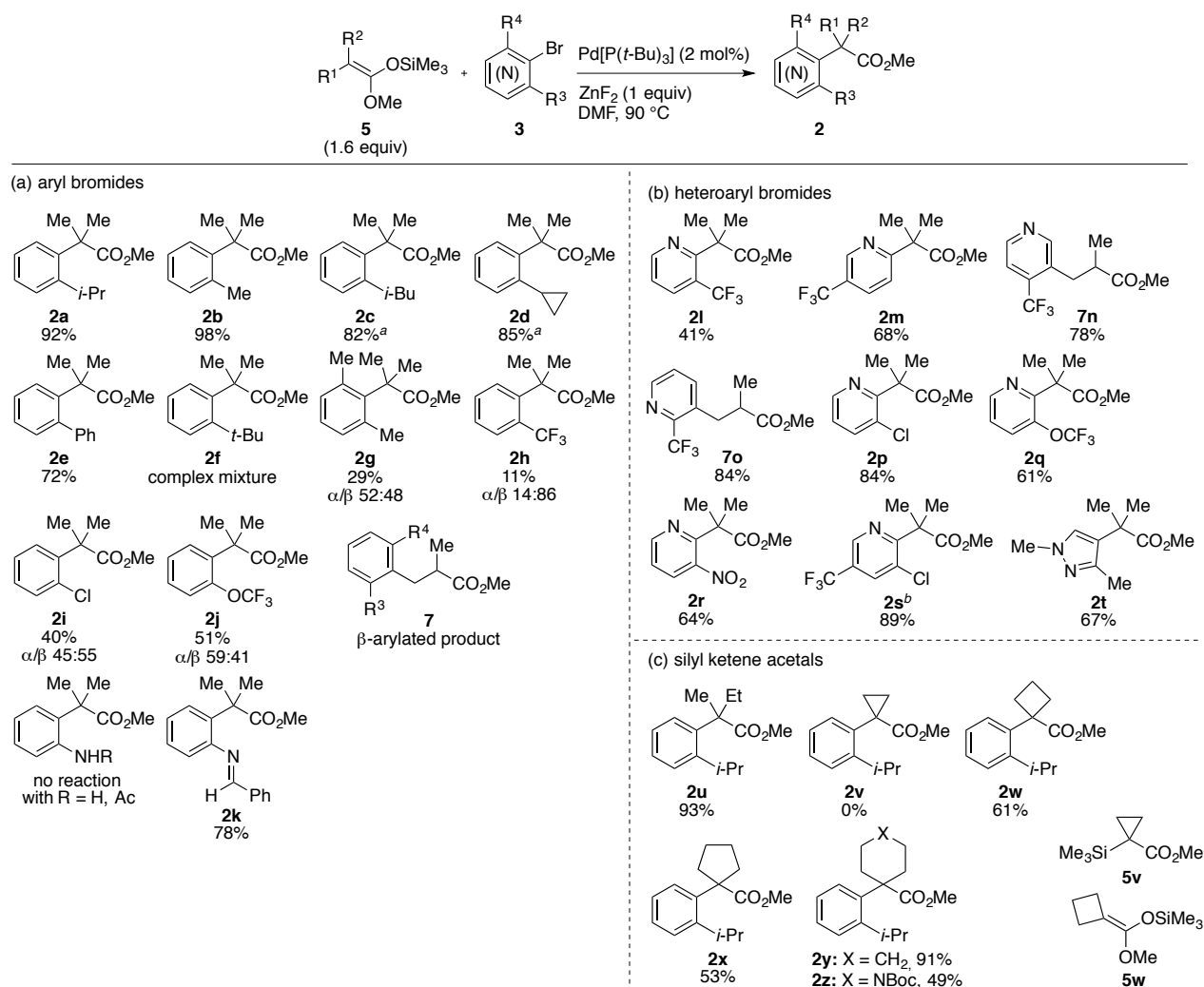
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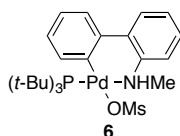
Other reaction promoters were tested, including fluorides and zinc salts. The yield with KF or CsF (entry 5) was lower, due to the competitive desilylation of **5a** to give ester **4a**, as observed by GCMS. On the other hand, with ZnCl₂ the conversion and yield were low (entry 6). Interestingly, the more economical LiCl could be also employed instead of ZnF₂, albeit with a lower yield (entry 7). These results further confirm that ZnF₂ plays a unique role as a Lewis-acidic promoter in the α-arylation of SKAs. Next, different precatalysts were tested. The air-stable phosphonium tetrafluoroborate, P(*t*-Bu)₃•HBF₄,[11] could be employed instead of the free phosphine in combination with Pd₂dba₃ (entry 8, compare to entry 1), however a co-catalytic amount of a base such as K₂CO₃ was required. Indeed ZnF₂ does not seem to be sufficiently basic to fully deprotonate the phosphonium *in situ* (entry 8, note). Nevertheless, the well-defined Pd⁰L₂ complex was more efficient than the *in situ* mixture (compare to entry 2). Other well-defined P(*t*-Bu)₃-containing precatalysts were assessed, starting with the commercially available [PdBrP(*t*-Bu)₃]₂ dimer (entry 9).[12c,e] The reaction was slow at 90 °C (entry 9, note), but could be performed at 110 °C with a similar efficiency to the Pd⁰L₂ complex. However, the Pd⁰ monomer and the Pdᴵ dimer are both air-sensitive, and thus we looked for a more stable Pdᴵᴵ precatalyst which could be employed out of the glove-box. The recently introduced, commercially available palladacycle precatalyst **6**[13] provided a satisfying solution in combination with co-catalytic NEt₃ to favor the generation of the active Pd⁰L species by reductive elimination (entry 10).[14] However, among all tested precatalysts, Pd[P(*t*-Bu)₃]₂ clearly remained the most active. Gratifyingly, the catalyst loading could be lowered to 1 mol% without affecting the reaction efficiency (entries 11-12).

To further compare the various P(*t*-Bu)₃-containing catalysts, the kinetic profiles of three representative examples were determined at 90 °C (Figure 1).[15] The Pd⁰L₂ complex (2 mol%) clearly showed the highest conversion of aryl bromide **3a** into product **2a** (blue lines).
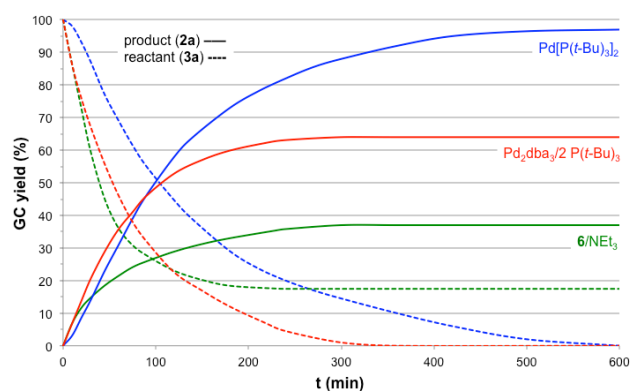
Figure 1. Kinetic profiles for the formation of **2a** from **3a** and **5a** with various P(*t*-Bu)₃-based catalysts. All reactions were performed in DMF at 90 °C at the same reactant concentrations and at 2 mol% Pd. Solid lines: GC yield of **2a**; dashed lines: GC yield of **3a**. Blue lines: Pd[P(*t*-Bu)₃]₂ (2 mol%); green lines: Pd₂dba₃ (1 mol%)/ P(*t*-Bu)₃ (4 mol%); red lines: palladacycle **6** (2 mol%)/NEt₃ (2 mol%).

Scheme 3. Scope and Limitations of the α-Arylation of Hindered SKAs with Hindered (Hetero)aryl Bromides

(a) aryl bromides

2a 92%
2b 98%
2c 82%[a]
2d 85%[a]

2e 72%
2f complex mixture
2g 29% α/β 52:48
2h 11% α/β 14:86

2i 40% α/β 45:55
2j 51% α/β 59:41
7 β-arylated product

no reaction with R = H, Ac
2k 78%

(b) heteroaryl bromides

2l 41%
2m 68%
7n 78%

7o 84%
2p 84%
2q 61%

2r 64%
2s[b] 89%
2t 67%

(c) silyl ketene acetals

2u 93%
2v 0%
2w 61%

2x 53%
2y: X = CH₂, 91%
2z: X = NBoc, 49%

5v
5w

[a] Reaction performed at 110 °C. [b] From the pyridyl chloride instead of the bromide.

The Pd₂dba₃/L combination using the same amount of Pd (2 mol%) and ligand (4 mol%) showed a faster and complete conversion of **3a** (red lines), but the yield of **2a** plateaued at ca. 65% with concomitant formation of cumene, indicating that protodebromination competes with the arylation pathway. This behavior may be imputed to the known inhibitory effect of dba.[9,16] The combination of palladacycle **6** and NEt₃ showed the lowest activity (green lines), with incomplete (ca. 80%) conversion of **3a** and <40% yield of arylated product. This behavior can be ascribed to both competitive protodebromination and catalyst deactivation due to the lack of extra stabilizing ligand. As can be seen in Table 1 (entry 10), precatalyst **6** requires a higher temperature (110 °C) and loading (4 mol%) to furnish a good yield of product. Overall, the activity of Pd[P(t-Bu)₃]₂ at lower temperature and catalyst loading could not be surpassed by the considered alternatives. This complex seems to be the most efficient in delivering the active species that catalyzes the arylation reaction, presumably the monoligated species Pd[P(t-Bu)₃].[17]

The scope of the α-arylation process was then examined under optimized conditions at 2 mol% catalyst loading (Scheme 3). First, various *ortho* substituents (R³, R⁴) on the aryl bromide were examined in combination with SKA **5a** (Scheme 3a). High yields were achieved for substrates bearing a single alkyl (including cyclopropyl) or phenyl *ortho*-substituent (**2a-e**). A limitation was found for compounds bearing one *t*-butyl group (**2f**) or two *ortho* methyl groups (**2g**), presumably due to the excessive allylic strain disfavoring C–C reductive elimination (see computed structure in Scheme 1). The formation of **2g** was accompanied by the corresponding β-arylated isomer **7g** (R³ = R⁴ = Me), arising from Pd migration at the terminal carbon. Similar α/β mixtures were obtained with electron-withdrawing substituents (CF₃, Cl, OCF₃), in line with our previous studies showing that such electronically-biased substituents favor Pd migration and long-range arylation.[9,18] Nevertheless, α-arylated products **2g-j** could all be separated from their β isomers by preparative HPLC and isolated in low to moderate yield (11-51%), depending on the α/β selectivity. Finally, we were interested in the introduction of an electron-donating *ortho* nitrogen substituent that would both give minimal β-arylation product and constitute a convenient precursor for the free amino group. Whereas the free aniline itself and the acetanilide did not provide any arylation product, the corresponding benzaldimine was found to be

an excellent surrogate, which provided product **2k** in 78% yield and complete α selectivity.

The reaction of pyridyl bromides, relevant to the synthesis of active agrochemical ingredients (see examples in Scheme 1), was next investigated (Scheme 3b). When the pyridine nitrogen atom was located in *ortho* position to the bromine atom in **3**, the α-heteroarylated product was exclusively obtained, with no observable β isomer. This results contrasts with the selectivity observed with phenyl rings (compare **2l** with **2h**, **2p** with **2i**, **2q** with **2j**). The α-coupled products **2l** and **2p-r** bearing one *ortho* electron-withdrawing substituent were obtained in moderate to good yields (41-84%). In contrast, when the nitrogen atom of the pyridine ring was located in *meta* position to the bromine atom, the β isomer (**7n-o**) was exclusively obtained. In this case, the increased β selectivity compared to the corresponding benzene ring (**2h/7h** 14:86) can be imputed to the increased electron-deficiency of the pyridine ring which disfavors α-reductive elimination, in line with previous mechanistic data.[9] In contrast, for 2-bromopyridines, the total α selectivity might originate in the formation of pyridyl-bridged Pd dimers,[19] which would block β-H elimination and therefore would shut down the β-arylation pathway. Importantly, the reaction of SKA **5a** with 2,3-dichloro-5-trifluoromethylpyridine, relevant to the synthesis of Fluopicolide analogues (Scheme 1), furnished compound **2s** in 89% yield, in a completely site-selective manner. This site-selectivity, which was also observed for **2p**, can be inferred to the more electron-deficient character of the 2-position vs. the 3-position of the pyridine, favoring the initial oxidative addition to Pd[0]. Of note, control experiments, conducted for 2-halopyridine substrates without Pd catalyst, showed no coupling product, thereby excluding any contribution of S$_N$Ar mechanism. Finally, an *ortho*-methylbromopyrazole could be coupled successfully and selectively to **5a** (product **2t**), thereby demonstrating the feasibility of α-heteroarylation beyond pyridine.

The scope with regard to the SKA coupling partner was also examined, in combination with aryl bromide **3a** (Scheme 3c). SKAs were conveniently prepared in a standard fashion from the corresponding methyl ester **4** upon deprotonation by LDA and reaction with TMSCl, and were found to be stable for several weeks under moisture-free conditions. Both acyclic (**2u**) and cyclic (**2w-z**) SKAs, including a Boc-protected piperidine (**2z**), were coupled successfully. Interestingly, cyclobutyl compound **5w** predominantly exists as the O-enolate (O-Si/C-Si 9:1) whereas its cyclopropyl analogue **5v** exclusively occurs as the C-enolate. The lack of reactivity of **5v** vs. **5w** can be ascribed to the use of ZnF$_2$, which is suitable to promote the reaction of SKAs but not of organosilanes, for which a better fluoride source would likely be required.[20,21]

Finally, the cross-coupling of aryl bromide **3d** and SKA **5y** was chosen for scale-up studies, which allowed to obtain multigram quantities of arylated ester **2aa** in 89% yield (Scheme 4). In this case, using 5 mol% catalyst and heating to 110 °c proved necessary to achieve full conversion. The ester group in **2aa** could then be further transformed to provide useful building blocks for the synthesis of potential new agrochemicals (see Scheme 1). It was first converted to benzylamine **9** by hydrolysis to the carboxylic acid (**8**) and Curtius rearrangement, both steps requiring microwave irradiation due to steric hindrance. Primary amide **10** was also obtained from the

same carboxylic acid intermediate **8** upon formation of the acid chloride and reaction of the latter with aqueous ammonia. Finally, phenethylamine **12** was synthesized from **2aa** by reduction to the primary alcohol (**11**), followed by conversion to the corresponding azide and Staudinger reduction.

In conclusion, the arylation of sterically hindered esters and aryl bromides has been realized by employing silyl ketene acetals as stable and convenient enolate surrogates, Pd[P(*t*-Bu)$_3$]$_2$ as the optimal catalyst and ZnF$_2$ as a promoter. Less sensitive catalysts could be also employed, but showed a reduced activity. The reaction showed broad scope with regard to both coupling partners, proved to be scalable, and the ester group could be further transformed to access very bulky benzyl- and phenethylamines, which are valuable new building blocks for the synthesis of agrochemicals with potentially improved properties.

Scheme 4. Scale-up and Post-Functionalization[a]
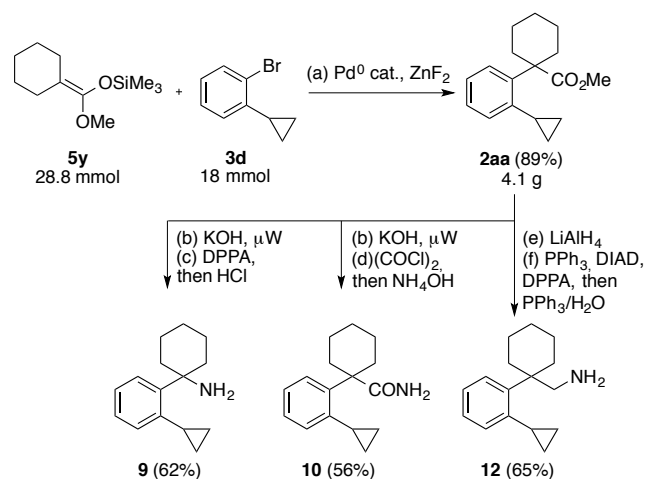
[a] Reaction conditions: (a) Pd[P(*t*-Bu)$_3$]$_2$ (5 mol%), ZnF$_2$ (1 equiv), DMF, 110 °C, 15 h. (b) KOH (20 equiv), THF/MeOH/H$_2$O 1:1:1, μW (150 °C), 30 min (75%). (c) (EtO)$_2$P(O)N$_3$ (1.04 equiv), NEt$_3$ (1.15 equiv), toluene, μW (110 °C), 45 min, then 37% aq. HCl, THF, 20 °C, 15 h (83%). (d) (COCl)$_2$ (1.1 equiv), DMF (5 mol%), CH$_2$Cl$_2$, 20 °C, 15 h, then 28% aq. NH$_4$OH, THF, 20 °C, 2 h. (e) LiAlH$_4$ (5 equiv), THF, 25 °C, 15 h (96%). (f) PPh$_3$ (1.2 equiv), *i*-PrO$_2$CN=NCO$_2$*i*-Pr (1.2 equiv), (EtO)$_2$P(O)N$_3$ (1.2 equiv), THF, 25 °C, 15 h then PPh$_3$ (1.3 equiv), 60 °C, 4 h, then H$_2$O, 80 °C, 1 h (68%).

ASSOCIATED CONTENT

Supporting Information.
Full characterization of all new compounds, detailed experimental procedures, copies of NMR spectra for target molecules. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author
*E-mail: olivier.baudoin@unibas.ch
Notes
The authors declare no competing financial interest.

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conformationally constrained
benzyl- and phenethylamines