

Article

Palladium-Catalyzed Room Temperature Acylative Cross-Coupling of Activated Amides with Trialkylboranes

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Abstract: A highly efficient acylative cross-coupling of trialkylboranes with activated amides has been effected at room temperature to give the corresponding alkyl ketones in good to excellent yields by using 1,3-bis(2,6-diisopropyl)phenylimidazolylidene and 3-chloropyridine co-supported palladium chloride, the PEPPSI catalyst, in the presence of K_2CO_3 in methyl *tert*-butyl ether. The scope and limitations of the protocol were investigated, showing good tolerance of acyl, cyano, and ester functional groups in the amide counterpart while halo group competed via the classical Suzuki coupling. The trialkylboranes generated in situ by hydroboration of olefins with BH_3 or 9-BBN performed similarly to those separately prepared, making this protocol more practical.

Keywords: acylative cross-coupling; trialkylborane; amide activation; palladium; *N*-heterocyclic carbene

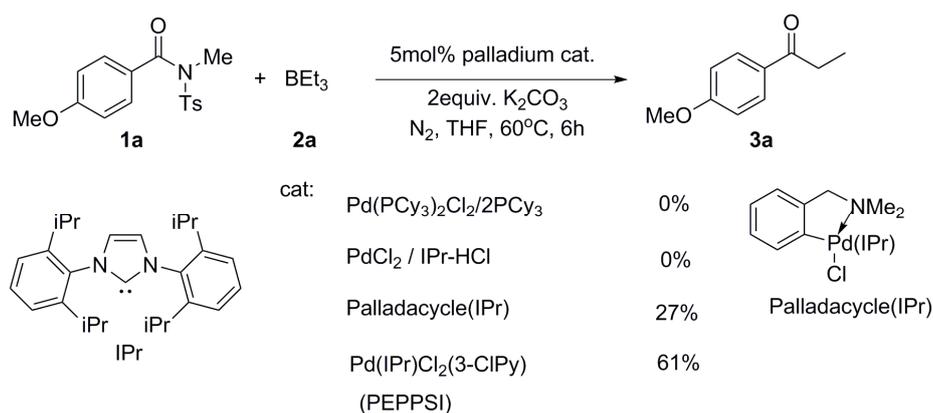
1. Introduction

Amides are unique and ubiquitous substructures in natural and artificial organic functional molecules, because the strong resonance between the carbonyl and amino groups leads to a highly inert and significantly planar linkage. However, the synthetic utility of amides as an acyl source had remained underdeveloped until the seminal publications in 2015 independently from Garg [1], Szostak [2], and ourselves [3], taking advantage of palladium or nickel catalysis for cleavage of electronically or sterically activated amide C-N bond, and formation of new carbon-carbon or carbon-oxygen bonds. In the past three years, many efforts have been made to expand the scope of amide counterparts, developing a variety of activated amides suitable for the acylative cross-coupling, e.g., *N*-acyl imides [4–6], *N*-Boc and *N*-Ts/Ms amides [7–15], *N*-acylsaccharins [16–20], and amides of heteroaromatic compounds [21,22]. Comparably, the carbon-centered nucleophile counterparts are still rather undeveloped, in particular, with respect to alkyl ones, although alkyl ketones have been widely found in biologically important molecules and synthetic building blocks for fine chemicals. In fact, besides the closely related esters [23–25], there are only two reports on the acylative cross-coupling of amides with alkyl reagents effected by using nickel catalysts. Garg and co-workers reported the first alkylation of amide derivatives by nickel-catalyzed acylative coupling with alkyl zinc reagents in 2016 [26]. Early this year, Rueping and co-workers described the other nickel-catalyzed cross-coupling of *B*-alkyl-9-BBN with amides [27]. After extension of the nucleophile counterparts from arylboronic acids to cost-effective diarylboronic acids and tetraarylboronates in palladium-catalyzed acylative cross-coupling of amides [28,29], we are interested in the reactivity of trialkylboranes, which could be readily prepared from alkyl Grignard reagents or olefins via hydroboration. Herein we report a highly efficient palladium-catalyzed acylative cross-coupling of activated amides with trialkylboranes at

room temperature by using 1,3-bis(2,6-diisopropyl)phenylimidazolylidene (IPr) and 3-chloropyridine (3-ClPy) co-supported palladium chloride, the PEPPSI catalyst developed by Organ et al. [30].

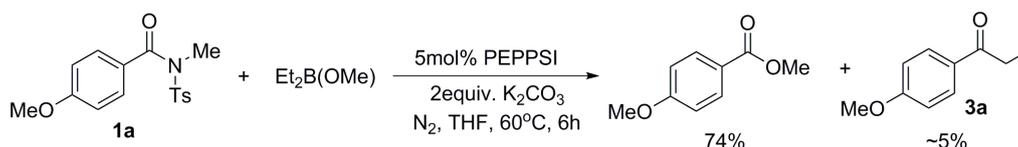
2. Results and Discussion

Reaction of 4-methoxy-*N*-methyl-*N*-tosylbenzamide (**1a**) with the commercially available triethylborane (**2a**) (BEt₃, 1M in THF) was chosen as the model to establish an optimal catalyst system for the acyl alkylation of activated amides (Scheme 1).



Scheme 1. Screening of palladium catalyst for acyl alkylation of amides with alkylboranes.

The catalyst system Pd(PCy₃)₂Cl₂/PCy₃, which we previously established for acylative cross-coupling of amides with aryl boron compounds, was investigated, at first, in the presence of K₂CO₃ as base in THF. Unfortunately, palladium black developed immediately upon heating and no reaction was detected after 6h at 60 °C, indicating the incompatibility of the Pd(PCy₃)₂Cl₂/PCy₃ system with the high reducing ability of trialkylboranes. We then turned to the sterically demanding *N*-heterocyclic carbene (NHC) supported palladium catalysts pioneered by Nolan group [31], for example, 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (IPr-HCl)/palladium chloride (IPr-HCl/PdCl₂) [32], IPr supported 2-((dimethylamino)methyl)phenyl palladium chloride (Palladacycle(IPr)) [33], and IPr and 3-chloropyridine co-supported PEPPSI catalyst (IPr)PdCl₂(3-ClPy) [30]. Although the IPr-HCl/PdCl₂ system also rapidly decomposed to palladium black and lost activity, the palladacycle/IPr and PEPPSI catalysts provided the desired cross-coupling product **3a** in 27% and 61% yields, respectively, from **1a** with 1.0 equiv **2a** in the presence of 2 equiv K₂CO₃. To test if dialkylboranes could be used in the acyl alkylation with amides, we also carried out the model reaction by using diethylborinate (Et₂B(OMe), 1M in THF) under otherwise identical conditions (Scheme 2). Surprisingly, the C-O cross-coupling product, methyl 4-methoxybenzoate, was obtained in 74% yield, while the C-C coupling product **3a** was isolated in low (~5%) yield, implying a much slower transmetalation of alkyl group from boron to palladium than that of alkoxy group in dialkylborinates.

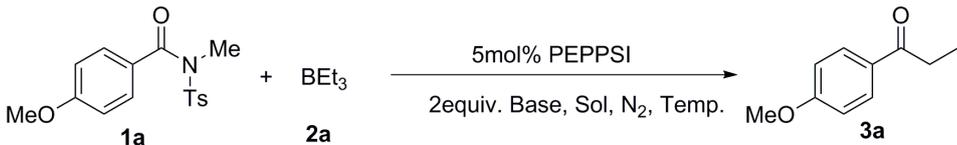


Scheme 2. Unexpected acyl C-O cross-coupling of methyl diethylborinate.

To increase the yield of the desired C-C coupling product in the PEPPSI-catalyzed acyl alkylation of amides, the reaction conditions were optimized with respect to substrate ratio, solvent, base, and reaction temperature, etc. Bases proved to be crucial since no reaction took place in the absence of bases or in the presence of organic base, e.g., NEt₃ and pyridine (Table 1, entries 2, 8 and 9).

The stronger inorganic bases, Cs₂CO₃ (25%) and K₃PO₄ (33%), gave the lower yields of **3a** than that of K₂CO₃, albeit the reaction proceeded faster while the weaker ones, e.g., Na₂CO₃, NaOAc, and NaHCO₃, resulted in recovering most of amide substrate **1a** (Table 1, entries 3–7). The yield of **3a** could be increased to 80% with 1.5 equiv BEt₃ (Table 1, entry 10). Methyl *tert*-butyl ether (MTBE) appeared to be the choice of solvent, giving **3a** in 90% yield (Table 1, entry 12). The reaction occurred even at room temperature and an excellent yield (98%) for **3a** was obtained in 24 h (Table 1, entry 14). Given the advantages of room temperature organic synthesis [34], we reinvestigated the model reaction in THF or MTBE with K₂CO₃ or K₃PO₄ as the base (Table 1, entries 15–17). The results confirmed the best performance of the combination of MTBE with K₂CO₃.

Table 1. PEPPSI-catalyzed acyl alkylation reaction of amide **1a** with triethylborane. ^a



Entry	Equiv of 2a	Solvent	Base ^b	T (°C)	Time (h)	Yield (%) ^c
1	1.1	THF	K ₂ CO ₃	60	5	61
2	1.1	THF	/	60	5	NR ^d
3	1.1	THF	Cs ₂ CO ₃	60	5	25
4	1.1	THF	K ₃ PO ₄	60	5	33
5	1.1	THF	Na ₂ CO ₃	60	8	15
6	1.1	THF	NaHCO ₃	60	8	Trace ^d
7	1.1	THF	NaOAc	60	8	Trace ^d
8	1.1	THF	Et ₃ N	60	8	NR ^d
9	1.1	THF	Pyridine	60	8	NR ^d
10	1.5	THF	K ₂ CO ₃	60	5	80
11	1.5	Dioxane	K ₂ CO ₃	60	8	35
12	1.5	MTBE	K ₂ CO ₃	55	8	90
13	1.5	MeCN	K ₂ CO ₃	60	8	17
14	1.5	MTBE	K ₂ CO ₃	rt	24	98
15	1.5	MTBE	K ₃ PO ₄	rt	24	84
16	1.5	THF	K ₂ CO ₃	rt	24	82
17	1.5	THF	K ₃ PO ₄	rt	12	40

^a Reaction was run at 0.5 mol scale with respect to **1a**; ^b 2 equiv base used but no base used in Entry 2; ^c Isolated yield; ^d Amide **1a** recovered.

Scope and limitations of the PEPPSI-catalyzed room temperature acylative cross-coupling of activated amides with trialkylboranes were briefly explored (Table 2). Influence of the amide structure was investigated at first under the optimized reaction conditions. Similar to tosyl-activated amide **1a**, mesyl (Ms, **1b**) analog also reacted efficiently to give **3a** in 98% yield, while *tert*-butyloxycarbonyl (Boc) activated amide (**1c**) showed comparably lower reactivity (75%) (Table 2, entries 1 and 2). Reaction of benzamides bearing an electron-withdrawing group, acyl (**1e**), cyano (**1f**), or ester (**1g**), at the *para*-position of the benzene ring gave the corresponding ketones (**3b**, **3c**, or **3d**) in 92%, 70%, or 91% yields, respectively, indicating good functional group compatibility of the PEPPSI-catalyzed acyl alkylation (Table 2, entries 4–6). When 4-chloro-*N*-methyl-*N*-tosylbenzamide (**1h**) was used as the substrate, the desired acylative cross-coupling product 1-(4-chlorophenyl)propanone was not obtained. Instead, double alkylation product 1-(4-ethylphenyl)propanone (**3e**) was isolated in 47% yield, which could be increased to 88% yield with 2.5 equiv BEt₃ (Table 2, entry 7), similar to our previous investigation on the palladium-catalyzed acylative Suzuki coupling of arylboronic acids [3]. A small *ortho*-substituent at the benzene ring appeared to slightly hamper the coupling. In fact, 1-(*o*-tolyl)propan-1-one (**3f**) was isolated in 72% yield from *N*-methyl-*N*-tosyl-2-methylbenzamide (**1i**) (Table 2, entry 8). Alkyl amides (**1j** and **1k**) reacted similarly to give dialkyl ketones **3g** and **3h** in 95% and 98% yields, respectively (Table 2, entries 9 and 10).

Table 2. Scope and limitations of the PEPPSI-catalyzed acyl alkylation reaction of amides with trialkylboranes ^a.

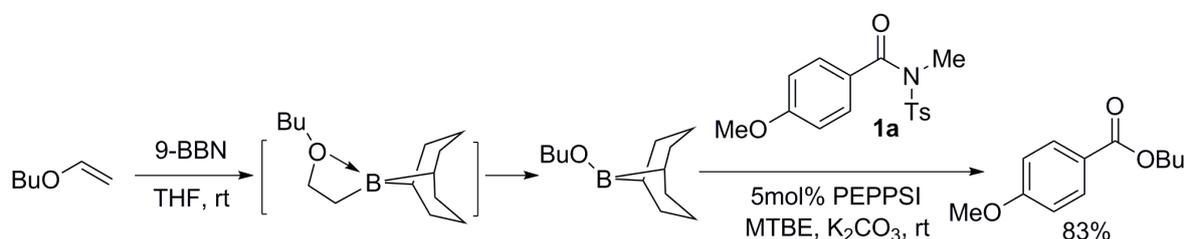
Entry	Amide	Borane	Product	Entry	Amide	Borane	Product ^b
1		BEt ₃ 2a		10		2a	
2		2a		11		B(<i>n</i> -Bu) ₃ 2b	
3		2a		12		B(<i>n</i> -C ₈ H ₁₇) ₃ 2c	
4		2a		13			
5		2a		14			
6		2a		15		2e	
7		2a		16		2e	
8		2a		17		2d	
9		2a					

^a Reaction was run at 0.5 mol scale with respect to amides with 1.5 equiv trialkylboranes; ^b Isolated yield; ^c With 2.5 equiv BEt₃; ^d B(*n*-C₈H₁₇)₃ and branched isomers in situ generated from hydroboration of octene with 1.0 equiv BH₃ in THF at room temperature was used.

Tri(*n*-butyl)borane (**2b**) reacted with **1a** similarly to triethylborane (**2a**) while no reaction of tricyclohexylborane was observed, implying the failure of transmetalation of *secondary*-alkyl group from boron to palladium. Hydroboration of alkenes represents an alternative route to primary alkyl boranes. However, the long-chain primary alkyl boranes prepared by hydroboration of alkenes are generally contaminated by the presence of branched-isomers due to the non-regiospecific addition of B-H to C=C double bonds [35]. Due to the inertness of the *secondary*-alkyl group in alkylboranes, reaction of **1a** with tri(octyl)boranes prepared by hydroboration of 1-octene proceeded comparably to that of tri(*n*-octyl)borane (**2c**) from Grignard reagent [36], giving **3j** in 91% and 99% yields, respectively (Table 2, entry 12). Given the fact that only one primary alkyl group of trialkylboranes is useful in the palladium-catalyzed acylative cross-coupling, it is more practical to use long-chain alkyl boranes prepared by hydroboration of corresponding olefins by dialkylborane, a more stable B-H source,

e.g., 9-borabicyclo[3.3.1]nonane (9-BBN). Therefore, we further investigated use of B-octyl-9-BBN formed in situ from octene as the trialkylborane counterpart and obtained **3j** in 93% yield (Table 2, entry 13). β -Phenyl propiophenones, which show intrinsic deactivation of the lowest and thermally populated n, π^* -triplet excited states in aryl alkyl ketones [37], could be readily obtained in 98% yield (**3k**) by the acyl alkylation of amide **1a** with B-(2-phenylpropyl)-9-BBN generated in situ from 9-BBN and α -methylstyrene. Alkyl and heterocyclic analogs, e.g., 1-cyclohexyl-3-phenylbutanone (**3l**, 90%) and 3-phenyl-1-(thiophen-2-yl)butanone (**3m**, 97%) could also be prepared efficiently (Table 2, entries 14–16).

However, when amide **1a** was subjected to the hydroboration solution of *n*-butyl vinyl ether with 9-BBN the C-O coupling product (vide supra) butyl 4-methoxybenzoate, instead of the desired β -butoxy-4-methoxypropiophenone, was obtained in 83% yield, probably due to the facile β -alkoxy elimination of labile B-(2-butoxyethyl)-9-BBN via intramolecular O-B coordination to B-butoxy-9-BBN for the subsequent C-O cross-coupling (Scheme 3).



Scheme 3. Formation of borinate and subsequent acyl C-O cross-coupling.

3. Materials and Methods

3.1. General

Chemicals obtained commercially were used as received. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker DPX-400 spectrometer (Bruker Co., Billerica, MA, USA) using residue of the deuterated solvent or tetramethylsilane (TMS) as the internal standard (Cambridge Isotope Lab. Inc., Tewksbury, MA, USA). For copies of ^1H and ^{13}C -NMR spectra of the products, please see Supplementary Materials. All products were isolated by flash chromatography using petroleum ether (Sinopharm Chemical Reagent Co. Ltd., Shanghai, China) (60–90 °C)/ethyl acetate (Sinopharm Chemical Reagent Co. Ltd., Shanghai, China) as eluents. Triethylborane (1 M in THF), tributylborane, 9-BBN (1 M in THF) and BH_3 (1 M in THF) were purchased from J&K chemicals (Beijing, China). Amides [3], PEPPSI catalyst [30], 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (IPr-HCl) [32], palladacycle (IPr) [33], and tri(*n*-octyl)borane [36] were prepared according to the procedures reported previously. Solvents, methyl *tert*-butyl ether (MTBE), tetrahydrofuran (THF), and dioxane were dried over sodium while acetonitrile was distilled over CaH_2 prior to use.

3.2. General Procedure for the PEPPSI-Catalyzed Cross-Coupling of *N*-Methyl-*N*-Tosylamides with Trialkylboranes

A Schlenk tube (20 mL) charged with amide (0.5 mmol), PEPPSI (0.025 mmol, 5 mol%), and K_2CO_3 (2 equiv) was degassed and then refilled with nitrogen, three times. Then, solvent MTBE (6.0 mL) was added via syringe followed by 0.75 mL (1.5 equiv) borane solution (1 M in THF), which was commercially available or was in situ prepared by hydroboration of olefin. The resulted mixture was stirred for 24 h at room temperature under N_2 atmosphere. The reaction was quenched with iced water (5 mL) and extracted with MTBE (2×5 mL). The combined MTBE extracts were dried over anhydrous Na_2SO_4 . After filtration, solvents were removed by rotavapor to afford the crude product, which was purified by flash column chromatography on silica gel using petroleum ether/EtOAc as the eluents.

1-(4-Methoxyphenyl)propanone (**3a**) [38]: Colorless oil (80.3 mg, 98%). ^1H -NMR (400 MHz, CDCl_3) δ (ppm): 7.91 (d, $J = 8.8$ Hz, 2H, Ar), 6.89 (d, $J = 8.8$ Hz, 2H, Ar), 3.82 (s, 3H, OMe), 2.91 (q, $J = 7.2$ Hz,

2H, CH₂), 1.18 (t, *J* = 7.2 Hz, 3H, CH₃). ¹³C-NMR (100 MHz, CDCl₃) δ(ppm): 199.34 (C=O), 163.16 (C⁴_{Ar}), 130.06 (C^{2,6}_{Ar}), 129.85 (C¹_{Ar}), 113.52 (C^{3,5}_{Ar}), 55.29 (OMe), 31.26 (CH₂), 8.29 (CH₃).

1-(4-Acetylphenyl)propanone (3b) [39]: White powder (80.9 mg, 92%), mp 69–71 °C. ¹H-NMR (400 MHz, CDCl₃) δ(ppm): 8.00 (s, 4H, Ar), 3.01 (q, *J* = 7.2 Hz, 2H, CH₂), 2.62 (s, 3H, Ac), 1.21 (t, *J* = 7.2 Hz, 3H, CH₃). ¹³C-NMR (100 MHz, CDCl₃) δ(ppm): 200.13 (C=O), 197.46 (C=O), 139.96 (C^{1/4}_{Ar}), 139.90 (C^{1/4}_{Ar}), 128.41 (C_{Ar}), 128.07 (C_{Ar}), 32.15 (CH₂), 26.81 (MeCO), 7.97 (CH₃).

4-Propionylbenzotrile (3c) [40]: White powder (55.8 mg, 70%), mp 53–55 °C. ¹H-NMR (400 MHz, CDCl₃) δ(ppm): 7.97 (d, *J* = 8.4 Hz, 2H, Ar), 7.69 (d, *J* = 8.4 Hz, 2H, Ar), 2.95 (q, *J* = 7.2 Hz, 2H, CH₂), 1.15 (t, *J* = 7.2 Hz, 3H, CH₃). ¹³C-NMR (100 MHz, CDCl₃) δ(ppm): 199.16 (C=O), 139.64 (C⁴_{Ar}), 132.33 (C_{Ar}), 128.23 (C_{Ar}), 117.84 (CN/C¹_{Ar}), 115.95 (CN/C¹_{Ar}), 32.01 (CH₂), 7.75 (CH₃).

Methyl 4-propionylbenzoate (3d) [41]: White crystalline powder, (87.1 mg, 91%), mp 81–83 °C. ¹H-NMR (400 MHz, CDCl₃) δ(ppm): 8.08 (d, *J* = 8.4 Hz, 2H, Ar), 7.97 (d, *J* = 8.4 Hz, 2H, Ar), 3.92 (s, 3H, OMe), 3.05 (q, *J* = 7.2 Hz, 2H, CH₂), 1.21 (t, *J* = 7.2 Hz, 3H, CH₃). ¹³C-NMR (100 MHz, CDCl₃) δ(ppm): 200.15 (C=O), 166.17 (OC=O), 140.01 (C^{1/4}_{Ar}), 133.59 (C^{1/4}_{Ar}), 129.72 (C_{Ar}), 127.78 (C_{Ar}), 52.35 (OMe), 32.10 (CH₂), 7.96 (CH₃).

1-(4-Ethylphenyl)propanone (3e) [42]: Colorless oil (71.1 mg, 88%, with 2.5 equiv BEt₃). ¹H-NMR (400 MHz, CDCl₃) δ(ppm): 7.81 (d, *J* = 8.4 Hz, 2H, Ar), 7.19 (d, *J* = 8.4 Hz, 2H, Ar), 2.90 (q, *J* = 7.2 Hz, 2H, COCH₂), 2.61 (q, *J* = 7.6 Hz, 2H, ArCH₂), 1.17 (t, *J* = 7.6 Hz, 3H, COCH₂CH₃), 1.13 (t, *J* = 7.2 Hz, 3H, ArCH₂CH₃). ¹³C-NMR (100 MHz, CDCl₃) δ(ppm): 200.51 (C=O), 149.71 (C⁴_{Ar}), 134.59 (C¹_{Ar}), 128.14 (C_{Ar}), 127.97 (C_{Ar}), 31.60 (COCH₂), 28.85 (ArCH₂), 15.16 (ArCH₂CH₃), 8.27 (COCH₂CH₃).

1-(*o*-Tolyl)propanone (3f) [43]: Colorless oil (53.4 mg, 72%). ¹H-NMR (400 MHz, CDCl₃) δ(ppm): 7.53 (d, *J* = 7.6 Hz, 1H), 7.29–7.25 (m, 1H, Ar), 7.16–7.14 (m, 2H, Ar), 2.82 (q, *J* = 7.2 Hz, 2H, CH₂), 2.41 (s, 3H, ArCH₃), 1.11 (t, *J* = 7.2 Hz, 3H, CH₃). ¹³C-NMR (100 MHz, CDCl₃) δ(ppm): 205.04 (C=O), 138.01 (C^{1/2}_{Ar}), 137.76 (C^{1/2}_{Ar}), 131.81 (C_{Ar}), 130.97 (C_{Ar}), 128.19 (C_{Ar}), 125.56 (C_{Ar}), 34.64 (CH₂), 21.19 (ArCH₃), 8.31 (CH₃).

1-Phenylpentan-3-one (3g) [44]: Colorless oil (77.1 mg, 95%). ¹H-NMR (400 MHz, CDCl₃) δ(ppm): 7.33–7.29 (m, 2H, Ph), 7.23–7.20 (m, 3H, Ph), 2.93 (t, *J* = 7.6 Hz, 2H, PhCH₂CH₂CO), 2.76 (t, *J* = 7.6 Hz, 2H, PhCH₂), 2.43 (q, *J* = 7.2 Hz, 2H, COCH₂CH₃), 1.07 (t, *J* = 7.2 Hz, 3H, CH₃). ¹³C-NMR (100 MHz, CDCl₃) δ(ppm): 210.61 (C=O), 141.10 (C¹_{Ph}), 128.41 (Ph), 128.24 (Ph), 126.00 (C⁴_{Ph}), 43.81 (PhCH₂CH₂CO), 36.05 (COCH₂CH₃), 29.77 (PhCH₂), 7.69 (CH₃).

1-(4-Methoxyphenyl)pentan-3-one (3h) [45]: Colorless oil (94.3 mg, 98%). ¹H-NMR (400 MHz, CDCl₃) δ(ppm): 7.09 (d, *J* = 8.8 Hz, 2H, Ar), 6.81 (d, *J* = 8.8 Hz, 2H, Ar), 3.77 (s, 3H, OMe), 2.84 (t, *J* = 7.6 Hz, 2H, PhCH₂CH₂CO), 2.64 (t, *J* = 7.6 Hz, 2H, PhCH₂), 2.39 (q, *J* = 7.6 Hz, 2H, COCH₂CH₃), 1.03 (t, *J* = 7.6 Hz, 3H, CH₃). ¹³C-NMR (100 MHz, CDCl₃) δ(ppm): 210.80 (C=O), 157.85 (C⁴_{Ar}), 133.12 (C¹_{Ar}), 129.16 (C_{Ar}), 113.79 (C_{Ar}), 55.17 (OMe), 44.09 (PhCH₂CH₂CO), 36.08 (COCH₂CH₃), 28.93 (PhCH₂), 7.68 (CH₃).

1-(4-Methoxyphenyl)pentanone (3i) [46]: Colorless oil (93.5 mg, 97%). ¹H-NMR (400 MHz, CDCl₃) δ(ppm): 7.93 (d, *J* = 8.8 Hz, 2H, Ar), 6.91 (d, *J* = 9.2 Hz, 2H, Ar), 3.85 (s, 3H, OMe), 2.90 (t, *J* = 7.6 Hz, 2H, COCH₂), 1.73–1.66 (m, 2H, COCH₂CH₂), 1.44–1.34 (m, 2H, COCH₂CH₂CH₂), 0.94 (t, *J* = 7.6 Hz, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ(ppm): 199.20 (C=O), 163.23 (C⁴_{Ar}), 130.25 (C^{2,6}_{Ar}), 130.11 (C¹_{Ar}), 113.59 (C^{3,5}_{Ar}), 55.37 (OMe), 37.95 (COCH₂), 26.68 (CH₂), 22.48 (CH₂), 13.90 (CH₃).

1-(4-Methoxyphenyl)nonanone (3j) [47]: Colorless oil (123.0 mg, 99%, with tri(*n*-octyl)borane; 115 mg, 93% with hydroboration of octene with 9-BBN; 113 mg, 91% with hydroboration of octene with BH₃). ¹H-NMR (400 MHz, CDCl₃) δ(ppm): 7.86 (d, *J* = 9.2 Hz, 2H, Ar), 6.84 (d, *J* = 9.2 Hz, 2H, Ar), 3.78 (s, 3H, OMe), 2.82 (t, *J* = 7.6 Hz, 2H, COCH₂), 1.63 (t, *J* = 7.6 Hz, 2H, COCH₂CH₂), 1.29–1.19 (m, 10H, (CH₂)₅), 0.80 (t, *J* = 7.2 Hz, 3H, CH₃). ¹³C-NMR (100 MHz, CDCl₃) δ(ppm): 199.20 (C=O), 163.23 (C⁴_{Ar}), 130.25

(C^{2,6}_{Ar}), 130.13 (C¹_{Ar}), 113.60 (C^{3,5}_{Ar}), 55.37 (OMe), 38.26 (COCH₂), 31.79 (CH₂), 29.41 (CH₂), 29.39 (CH₂), 29.14 (CH₂), 24.59 (CH₂), 22.61 (CH₂), 14.05 (CH₃).

1-(4-Methoxyphenyl)-3-phenylbutanone (3k) [46]: White powder (125.0 mg, 98%), mp 84–86 °C. ¹H-NMR (400 MHz, CDCl₃) δ(ppm): 7.93 (d, *J* = 8.8 Hz, 2H, Ar), 7.34–7.30 (m, 4H, Ph), 7.23–7.19 (m, 1H, Ph), 6.92 (d, *J* = 8.8 Hz, 2H, Ar), 3.86 (s, 3H, OMe), 3.55–3.47 (m, 1H, CH), 3.26 (dd, *J*₁ = 16.4 Hz, *J*₂ = 5.6 Hz, 1H, CH₂), 3.14 (dd, *J*₁ = 16.0 Hz, *J*₂ = 8.4 Hz, 1H, CH₂), 1.34 (d, *J* = 7.8, 3H, CH₃). ¹³C-NMR (100 MHz, CDCl₃) δ(ppm): 197.59 (C=O), 163.31 (C⁴_{Ar}), 146.65 (C¹_{Ph}), 130.28 (C_{Ar}/C_{Ph}), 130.21 (C¹_{Ar}), 128.43 (C_{Ph}), 126.79 (C_{Ph}), 126.15 (C⁴_{Ph}), 113.61 (C^{3,5}_{Ar}), 55.37 (OMe), 46.59 (COCH₂), 35.67 (CH), 21.79 (CH₃).

1-Cyclohexyl-3-phenylbutanone (3l): Colorless oil (103.7 mg, 90%). ¹H-NMR (400 MHz, CDCl₃) δ(ppm): 7.33–7.29 (m, 2H, Ph), 7.25–7.19 (m, 3H, Ph), 3.41–3.32 (m, 1H, PhCH), 2.77 (dd, *J*₁ = 16.8 Hz, *J*₂ = 6.4 Hz, 1H, COCH), 2.69 (dd, *J*₁ = 16.4 Hz, *J*₂ = 8.0 Hz, 1H, COCH₂), 2.29–2.22 (m, 1H, COCH), 1.83–1.65 (m, 5H, Cy), 1.35–1.17 (m, 8H, Cy overlapped with CH₃). ¹³C-NMR (100 MHz, CDCl₃) δ(ppm): 212.83 (C=O), 146.54 (C¹_{Ph}), 128.39 (C_{Ph}), 126.75 (C_{Ph}), 126.11 (C⁴_{Ph}), 51.19 (COCH), 49.10 (COCH₂), 35.02 (CH), 28.22 (Cy), 28.05 (Cy), 25.78 (Cy), 25.61 (Cy), 25.53 (Cy), 21.79 (CH₃). HRMS (ESI) *m/z* calcd for C₁₆H₂₂ONa [M + Na]⁺ 253.1568, found 253.1569.

3-Phenyl-1-(thiophen-2-yl)butanone (3m) [48]: Colorless oil (111.5 mg, 97%). ¹H-NMR (400 MHz, CDCl₃) δ(ppm): 7.70–7.69 (m, 1H, thiophenyl), 7.64–7.63 (m, 1H, thiophenyl), 7.36–7.28 (m, 4H, Ph), 7.25–7.23 (m, 1H, Ph), 7.14–7.12 (m, 1H, thiophenyl), 3.56–3.51 (m, 1H, PhCH), 3.24 (dd, *J*₁ = 16.0 Hz, *J*₂ = 6.0 Hz, 1H, CH₂CO), 3.14 (dd, *J*₁ = 15.6 Hz, *J*₂ = 8.4 Hz, 1H, CH₂CO), 1.38 (d, *J* = 6.8 Hz, 3H, CH₃). ¹³C-NMR (100 MHz, CDCl₃) δ(ppm): 191.94 (C=O), 146.18 (C¹_{Ph}), 144.60 (C² thiophenyl), 133.56 (thiophenyl), 131.81 (thiophenyl), 128.49 (C_{Ph}), 128.01 (thiophenyl), 126.78 (C_{Ph}), 126.30 (C⁴_{Ph}), 47.78 (COCH₂), 35.93 (CH), 21.64 (CH₃).

1-Phenylnonanone (3n) [47]: Colorless oil (106.8 mg, 98%). ¹H-NMR (400 MHz, CDCl₃) δ(ppm): 7.97–7.95 (m, 2H, Ph), 7.57–7.53 (m, 1H, Ph), 7.47–7.44 (m, 2H, Ph), 2.96 (t, *J* = 7.6 Hz, 2H, COCH₂), 1.77–1.69 (m, 2H, COCH₂CH₂), 1.39–1.25 (m, 10H, (CH₂)₅), 0.88 (t, *J* = 6.8 Hz, 3H, CH₃). ¹³C-NMR (100 MHz, CDCl₃) δ(ppm): 200.62 (C=O), 137.05 (C¹_{Ph}), 132.83 (C⁴_{Ph}), 128.51 (C_{Ph}), 128.02 (C_{Ph}), 38.61 (COCH₂), 31.81 (CH₂), 29.42 (CH₂), 29.36 (CH₂), 29.15 (CH₂), 24.36 (CH₂), 22.63 (CH₂), 14.08 (CH₃).

4. Conclusions

In summary, we have developed a highly efficient acylative cross-coupling of trialkylboranes with activated amides by using 1,3-bis(2,6-diisopropyl)phenylimidazolylidene and 3-chloropyridine co-supported palladium chloride, the PEPSI catalyst, under mild conditions. Bases appeared to play a key role in the reaction, among which K₂CO₃ performed best in MTBE at room temperature. The reaction proceeded to give alkyl ketones in good to excellent yields, tolerating a variety of functional groups in the amide counterpart. Unlike the high-order arylboron compounds, in which all the aryl groups react effectively, only one of the three primary alkyl groups in trialkylboranes could be used as alkyl source for the acyl alkylation. The trialkylboranes generated in situ by hydroboration of olefins with BH₃ or 9-BBN performed comparably to those separately prepared. This protocol complements ketone synthesis via palladium-catalyzed acylative cross-coupling of amides, providing a feasible access to both monoalkyl and dialkyl ketones.

Supplementary Materials: The following are available online, Figures S1–S28: ¹H and ¹³C-NMR of products 3a–3n, Figure S29 HRMS of 3l.

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Sample Availability: Samples of the compounds are available from the authors.



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