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Synthesis of Alkynyl Ketones by Sonogashira Cross-Coupling of Acyl Chlorides with Terminal Alkynes Mediated by Palladium Catalysts Deposited over Donor-Functionalized Silica Gel

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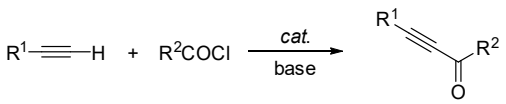
Abstract: Palladium catalysts deposited over silica gel bearing simple amine (≡Si$(CH_2)_3NH_2$) and composite functional amide pendants equipped with various donor groups in the terminal position (≡Si$(CH_2)_3NHC(O)CH_2Y$, Y = SMe, NMe_2 and PPh_2) were prepared and evaluated in Sonogashira-type cross-coupling of acyl chlorides with terminal alkynes to give 1,3-disubstituted prop-2-yn-1-ones. Generally, the catalysts showed good catalytic activity in the reactions of aroyl chlorides with aryl alkynes under relatively mild reaction conditions even without adding a copper co-catalyst. However, their repeated use was compromised by a significant loss of activity after the first catalytic run.

Keywords: deposited catalysts; palladium; functional amides; Sonogashira reaction; alkynyl ketone synthesis

1. Introduction

The first examples of Sonogashira-type cross-coupling of terminal alkynes with acyl chlorides to give alkynyl ketones (Scheme 1) were reported by Crisp and O'Donoghue in 1989 [1], who reacted furoyl chlorides with alkynes in the presence of $[PdCl_2(PhCN)_2]$/CuI and triethylamine to produce alkynyl furanyl ketones. With $[PdCl_2(PPh_3)_2]$/CuI and similar catalysts, this reaction subsequently made it possible to synthesize a number of alkynyl ketones in organic solvents [2,3], in water (when adding sodium dodecyl sulfate as a phase transfer reagent) [4–7] and even in a flow reactor (when using unsupported $Pd(OAc)_2$ as the catalyst) [8].

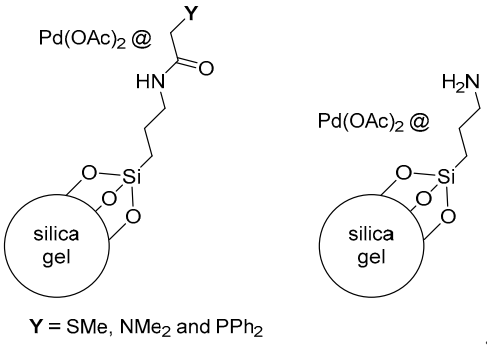


Scheme 1. Sonogashira cross-coupling of alkynes and acyl chlorides resulting in alkynyl ketones.

Alongside the development of homogenous catalysts, various heterogeneous catalytic systems were devised for this cross-coupling reaction. Wang et al. [9] studied the coupling of aromatic chlorides and cinnamoyl chloride with ethynylbenzene mediated by $[PdCl_2(PPh_3)_2]$/CuI deposited on KF-alumina under microwave irradiation. Subsequent reports described the use of conventional Pd/C [10], Pd nanoparticles supported by poly(1,4-phenylene sulfide) [11] or by functionalized polystyrene, PS-CH_2NHC(S)NHN=C(Ph)C(Me)=N-OH (PS = polystyrene) (without a Cu co-catalyst) [12], and applications of $Pd/BaSO_4$ with a $ZnCl_2$ co-catalyst [13,14] in similar reactions.

In 2009, Tsai et al. [15] reported the application of a Pd-bipyridyl complex grafted onto the mesoporous molecular sieve MCM-41.Coupling reactions of various substrates mediated by this catalyst in neat triethylamine, in the presence of CuI and triphenylphosphine, proceeded satisfactorily at low Pd loading (0.002–0.1 mol.%). More recently, Cai et al. [16] used a related Pd catalyst prepared by depositing $Pd(OAc)_2$ over an MCM-41 surface, modified by $\equiv Si(CH_2)_3NHCH_2CH_2NH_2$ groups. At 0.2 mol.% Pd loading, and with 0.2 mol.% CuI as a co-catalyst, this material could be reused ten times with only a marginal loss of activity (reaction in triethylamine at 50 °C). Other authors evaluated the related catalysts obtained from supports bearing phosphine-donor groups, e.g., periodic mesoporous silica with $\equiv CH_2CH_2PPh_2$ substituents [17] and polystyrene modified by the $-CH_2P^+Ph_2CH_2CH_2PPh_2$ Cl^- moieties at the surface [18].

Alkynyl ketones are valuable synthetic building blocks, opening an access to a range of useful compounds, such as intermediates for the synthesis of various heterocycles [19–23], biologically active compounds [24], naturally occurring compounds [25], liquid-crystalline materials [26], and ligands for transition metal ions [27]. In particular, the promising results achieved with deposited catalysts in the cross-coupling of acyl chlorides and alkynes and the wide range of applications of coupling products led us to consider using palladium catalysts deposited over the conventional silica gel bearing donor-substituted amide pendants [28] at the surface (Scheme 2) [29], which were already evaluated in Suzuki-Miyaura biaryl coupling [30]. The results from our study of these catalysts are presented in this contribution, with a particular focus on the reaction scope and a possible influence of the donor moieties within the functional supports that were varied.

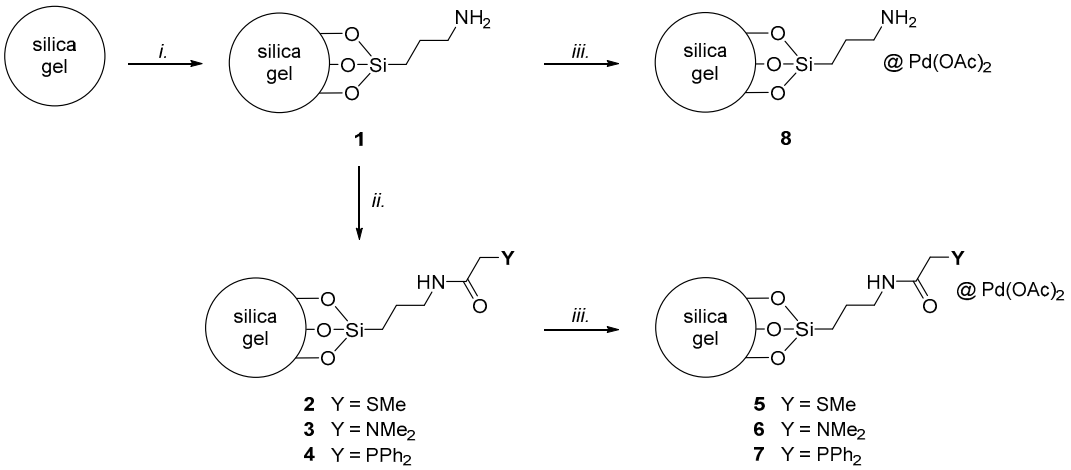


Scheme 2. Deposited catalysts used in this study.

2. Results

2.1. Synthesis of the Catalysts

The deposited catalysts were prepared as reported previously (Scheme 3) [29]. In the first step, freshly calcined, commercial chromatography-grade silica gel (size fraction 63–200 μm) was mixed with (3-aminopropyl)trimethoxysilane in refluxing toluene to afford 3-aminopropylated support **1**. Material **1** was subsequently treated with α-functionalized acetic acids in the presence of peptide coupling agents [31,32], yielding the corresponding amide-functionalized supports **2–4**. In the final step, the resulting materials were treated with palladium(II) acetate in dichloromethane to produce the deposited Pd catalysts **5–7**. As an extension of our previous work, the parent aminopropylated material **1** was also palladated to give material **8** containing only amine functional groups.

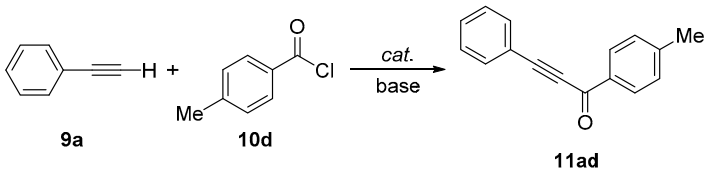


Scheme 3. Preparation of catalysts **5**–**8**. Legend: *i*. (3-aminopropyl)trimethoxysilane in toluene, refluxing; *ii*. amidation with $\mathbf{Y}CH_2CO_2H$ in the presence of peptide coupling agents (1-hydroxybenzotriazole and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDC) or the corresponding hydrochloride (EDC·HCl)); *iii*. treatment with $Pd(OAc)_2$ in dichloromethane.

Materials **1**–**8** were characterized by elemental analysis and infrared (IR) spectroscopy, and the data on **1**–**7** were compared with those on the previously studied catalysts. While the IR spectra of the newly synthesized materials were virtually identical to those previously reported (see ref. [29]), elemental analysis revealed differences, most likely reflecting the amount of residual adsorbed matter (mostly water). Full characterization data are presented in the Experimental Section.

2.2. Catalytic Assessment

Applications of deposited Pd catalysts to Sonogashira-type coupling of terminal alkynes with acyl chlorides (see Introduction) has been studied considerably less than their use in conventional Sonogashira cross-coupling between alkynes and organic halides [33]. Hence, our initial experiments with catalysts **5**–**8** aimed to find the optimal reaction conditions for these catalysts and to compare their performance with regard to influence of the varied functional groups modifying the support's surface. As a model reaction, we chose the coupling between equimolar amounts of ethynylbenzene (**9a**) and 4-methylbenzoyl chloride (**10d**), producing 1-(4-methylphenyl)-3-phenyl-2-propyn-1-one (**11ad**, see Scheme 4). The influence of the solvent and base, which are known to strongly affect these reactions (see references in the Introduction), were evaluated first. The screening experiments were performed with 0.5 mol.% of catalyst **5** and 5 mol.% of CuI in neat amines and in mixtures of triethylamine with an organic solvent as well. When using neat morpholine and pyridine, the coupling reaction did not proceed in any appreciable extent. However, when replacing these bases with *N*-methylmorpholine and *N*,*N*-diisopropylethylamine (Figure 1), the yields determined by gas chromatography (GC yields) of the coupling product **11ad** after 8 h at 50 °C were 2% and 10%, respectively. The best (albeit still rather low) yield of 21% after 8 h was achieved in neat triethylamine.



Scheme 4. Coupling reaction used to screen for reaction conditions.

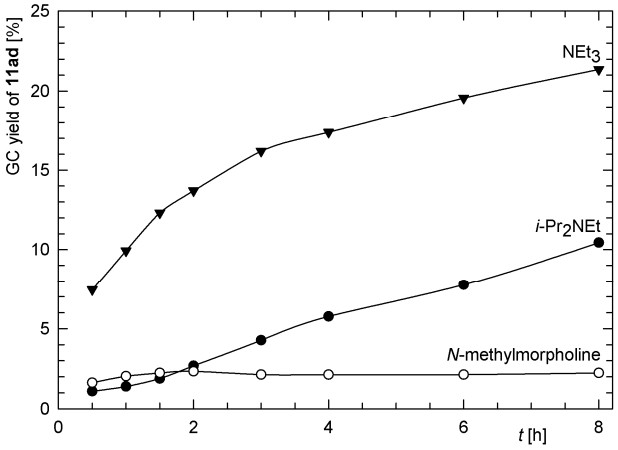


Figure 1. Kinetic profiles for the model coupling reaction performed in neat amines (0.5 mol.% catalyst **5**, 5 mol.% CuI) at 50 °C. Solid lines are added as a visual guide.

Reaction tests performed in organic solvents in the presence of 5 equiv. of triethylamine (Figure 2) revealed a marked acceleration of the coupling reaction in acetonitrile (ca. 60% yield of **11ad** within 3 h at 50 °C). In contrast, reactions in other tested solvents, viz. toluene, 1,4-dioxane, acetone and *N*,*N*-dimethylformamide, proceeded less efficiently, achieving lower yields than the aforementioned reaction in neat triethylamine (below 15% after 8 h; Figure 2); no reaction was observed in methanol.

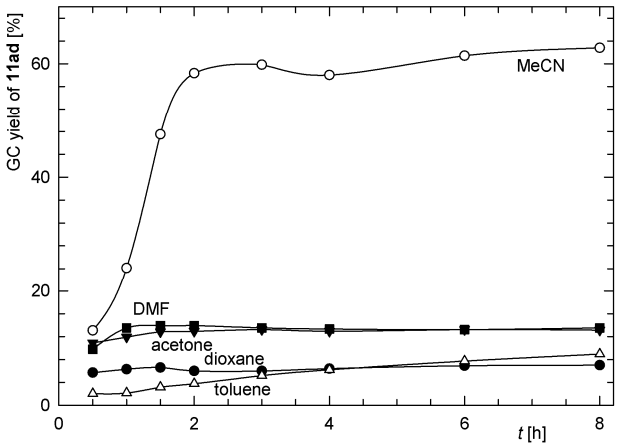


Figure 2. Kinetic profiles for the model coupling reaction performed in organic solvents with added triethylamine (5 equiv. NEt_3, 0.5 mol.% catalyst **5**, 5 mol.% CuI) at 50 °C. Legend: MeCN (○), DMF (■), acetone (▼), dioxane (●), toluene (△). The solid lines connecting the experimental points are a visual guide and do not represent any fit of the data.

A subsequent series of experiments was designed to assess the effect of the CuI additive and relative amounts of the starting materials. Rather surprisingly, the reaction performed in neat triethylamine with 0.5 mol.% of catalyst **5** without adding CuI at 50 °C ensued in a higher yield of the coupling product than the similar reaction in the presence of the CuI co-catalyst (5 mol.%; 39% vs. 21%). Consistently, when using acetonitrile as the solvent (with added NEt_3, 5 equiv.), the reaction without CuI produced **11ad** in a 78% yield after 8 h, which is a higher yield than that of the reaction performed in the absence of CuI (63%). Subsequently, we determined whether the coupling reaction is affected by the amount of acyl chloride when gradually increasing the amount of 4-toulyl chloride (**10d**) up to 1.5 equiv. As shown in Figure 3, the yield of **11ad** significantly increased with the amount of acyl chloride. With only 1.3 equiv. of **10d**, the GC yields of the coupling product were already virtually quantitative within 1 h of the reaction time.

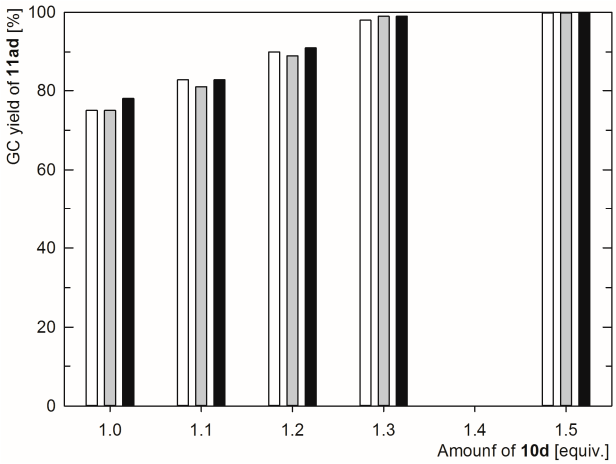


Figure 3. Variation in the gas chromatography (GC) yields of **11ad** observed when changing the amount of acyl chloride in the reaction mixture. Conditions: catalyst **5** (0.5 mol.%), alkyne **9a** (1 equiv.), triethylamine (5 equiv.), dodecane (1 equiv.; internal standard) in acetonitrile solvent at 50 °C. Reaction time: 1 h (white bars), 3 h (grey bars), and 8 h (black bars).

Using 1.5 equiv. of **10d**, we subsequently tried to reduce the catalyst loading. Under these conditions, the reaction proceeded satisfactorily, even in the presence of 0.1 and 0.2 mol.% of the selected model catalyst **5** and at short reaction times, as shown in Figure 4, which compares the GC yields of the coupling product **11ad** achieved over different periods of time. When decreasing the reaction temperature, however, the yield of the coupling product dramatically decreased (100% at 50 °C, 67% at 40 °C and ≈14% at 30 °C after 30 min of the reaction with catalyst **5** and 0.5 mol.% Pd in the reaction mixture).

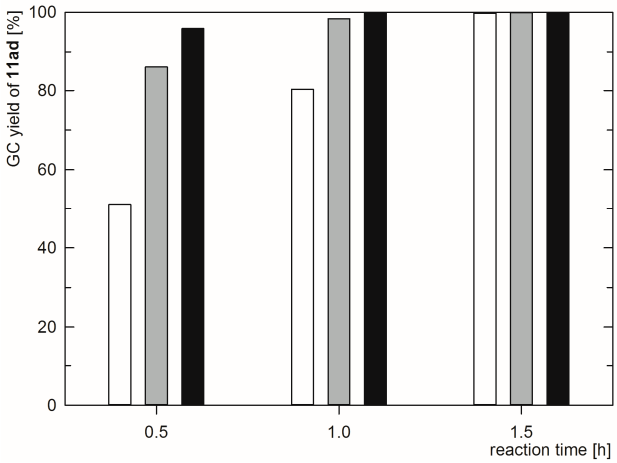


Figure 4. Variation in the GC yields of **11ad** observed upon changing the amount of catalyst **5**. Catalyst loading: 0.1 mol.% (white bars), 0.2 mol.% (grey bars), and 0.5 mol.% (black bars). Conditions: alkyne **9a** (1 equiv.), acyl chloride **10d** (1.5 equiv.), triethylamine (5 equiv.), dodecane (1 equiv.; internal standard) in acetonitrile solvent at 50 °C.

Lastly, we compared all prepared catalysts and palladium(II) acetate under rather harsh reaction conditions (0.1 mol.% Pd, 30 °C reaction temperature). Regrettably, the kinetic profiles presented in Figure 5 clearly indicate that unsupported palladium(II) acetate outperforms all deposited catalysts. Among the deposited catalysts, the lowest efficiency exerted catalyst **7** bearing phosphine groups, whereas the performance of catalysts bearing the S- and N-donor groups (**5** and **6**) was quite similar and slightly better than that of catalyst **8** obtained from the amine-functionalized support.

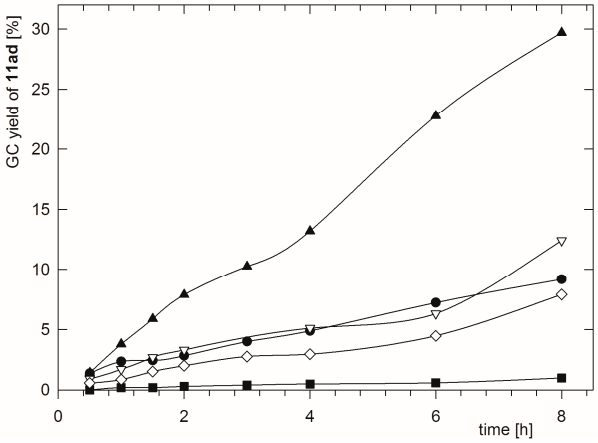


Figure 5. Kinetic profiles for the model coupling reaction performed in the presence of different catalysts: $Pd(OAc)_2$ (▲), catalyst **5** (●), catalyst **6** (▽), catalyst **7** (■), and catalyst **8** (◇). Conditions: 0.1 mol.% Pd, alkyne **9a** (1 equiv.), acyl chloride **10d** (1.5 equiv.), triethylamine (5 equiv.), dodecane (1 equiv.; internal standard) in acetonitrile solvent at 30 °C. The solid lines connecting the experimental points serve as a visual guide and do not represent any fit of the data.

Recycled catalysts **5–8** significantly lost their activity (Figure 6), presumably due to leaching of the deposited metal and to overall catalyst deactivation (the amount of Pd leached out during the first run was only 1%–4% of the initial amount). Notably, CuI (5 mol.%) addition to the reaction mixture increased the stability of the catalysts and even led to an activation of the phosphine-functionalized catalyst **7**, whereas the amount of leached-out Pd remained approximately the same (2–4% during the first run; see the Supporting Information, Table S1). However, the yields of **11ad** obtained with recycled deposited catalysts **5–8**/CuI were still considerably lower than the yields achieved during the first runs and further decreased upon catalyst reuse.

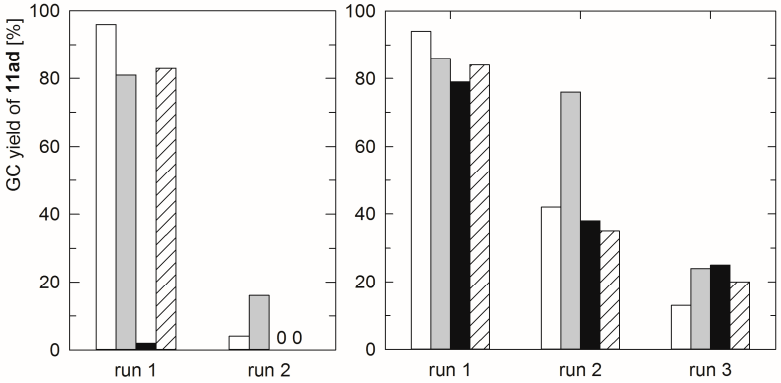


Figure 6. Results of catalytic experiments with fresh and reused catalysts without (left) and with (right) added CuI (5 mol.%): catalyst **5** (white bars), catalyst **6** (grey bars), catalyst **7** (black bars), and catalyst **8** (hatched bars). Conditions: 0.1 mol.% Pd, alkyne **9a** (1 equiv.), acyl chloride **10d** (1.5 equiv.), triethylamine (5 equiv.), dodecane (1 equiv.; internal standard) in acetonitrile at 50 °C for 2 h.

Using catalyst **5** (0.5 mol.% Pd), we also performed reaction scope tests, which are summarized in Table 1. Initially, we focused on the reactions of ethynylbenzene (**9a**) with substituted benzoyl chlorides. In the case of methyl-substituted acyl chlorides, the yields of the coupling products increased with the decrease in steric hindrance. Similar reactions with isomeric nitrobenzoyl chlorides proceeded generally less efficiently and required longer reaction times to achieve isolated yields of the coupling products higher than 50%; the reaction of **9a** with 2-nitrobenzoyl chloride, the most sterically crowded and deactivated acyl chloride, did not proceed. For the acyl chlorides, the substituents with a positive

inductive (+*I*) or a mesomeric (+*M*) effect (4-Me, 4-Cl and 4-MeO) apparently facilitated the reaction (isolated yields 85% or higher), whereas the nitro group, with a strong −*M* effect, hampered the cross-coupling. Conversely, the outcome of the coupling reactions between benzoyl chloride (**10a**) and substituted phenylacetylenes (4-Me, 4-MeO and 4-CF_3) all proceeded with high isolated yields, in line with the long distance between the substituents in position 4 of the benzene ring and the reaction site, which inevitably minimizes their influence.

Table 1. Summary of the reaction scope tests [a].

Alkyne	Acyl Chloride	Product	Yield (%) [b]
PhC≡CH (**9a**)	2-MeC_6H_4COCl (**10b**)	**11ab**	66
PhC≡CH (**9a**)	3-MeC_6H_4COCl (**10c**)	**11ac**	75
PhC≡CH (**9a**)	4-MeC_6H_4COCl (**10d**)	**11ad**	85
PhC≡CH (**9a**)	2-$NO_2C_6H_4COCl$ (**10e**)	**11ae**	n.d. [d,e]
PhC≡CH (**9a**)	3-$NO_2C_6H_4COCl$ (**10f**)	**11af**	75 [d]
PhC≡CH (**9a**)	4-$NO_2C_6H_4COCl$ (**10g**)	**11ag**	60 [d]
PhC≡CH (**9a**)	4-$MeOC_6H_4COCl$ (**10h**)	**11ah**	87
PhC≡CH (**9a**)	4-ClC_6H_4COCl (**10i**)	**11ai**	93
4-MeC_6H_4C≡CH (**9b**)	PhCOCl (**10a**)	**11ba**	95
4-$MeOC_6H_4C$≡CH (**9e**)	PhCOCl (**10a**)	**11ea**	85
4-$CF_3C_6H_4C$≡CH (**9j**)	PhCOCl (**10a**)	**11ja**	85
PhC≡CH (**9a**)	(*E*)-PhCH=CHCOCl (**10k**)	**11ak**	87
PhC≡CH (**9a**)	$PhCH_2CH_2COCl$ (**10l**)	**11al**	n.d. [e]
PhC≡CH (**9a**)	*t*-BuCOCl (**10m**)	**11am**	51
PhC≡CH (**9a**)	(2-furanyl)COCl (**10n**)	**11an**	50
PhC≡CH (**9a**)	(2-thienyl)COCl (**10o**)	**11ao**	25 [d]
FcC≡CH (**9m**) [c]	PhCOCl (**10p**)	**11pa**	43 [f]

[a] Conditions: alkyne (1.0 mmol), acyl chloride (1.5 mmol) and triethylamine (5 mmol) were mixed in the presence of catalyst **5** (0.5 mol.% Pd) in acetonitrile (5 mL) at 50 °C for 2 h. [b] Isolated yield after column chromatography. An average of two independent runs is given. [c] Fc = ferrocenyl. [d] Reaction time was extended to 24 h. [e] n.d. = the product was not detected. [f] The reaction was performed with 1.0 mmol of acyl chloride, and the reaction time was extended to 4 h.

The coupling of **9a** with cinnamoyl chloride also proceeded satisfactorily, producing **11ak** in an 87% isolated yield. In contrast, 3-phenylpropanoyl chloride (as a representative of aliphatic acyl chlorides bearing an sp^3 substituent at the acyl group) did not produce any coupling product under analogous conditions. Conversely, pivaloyl chloride was converted into **11am** with an acceptable 51% isolated yield. A similar yield was obtained with 2-furoyl chloride, whereas the reaction with 2-thiophenecarbonyl chloride had a lower yield. The ethynylferrocene/benzoyl chloride pair also displayed a rather sluggish reaction, associated with side processes that were partly suppressed by lowering the amount of the acyl chloride.

In addition to spectroscopic characterization, the structure of **11af** was determined by single-crystal X-ray diffraction analysis. Figure 7 shows the corresponding molecular structure along with selected interatomic distances and angles.

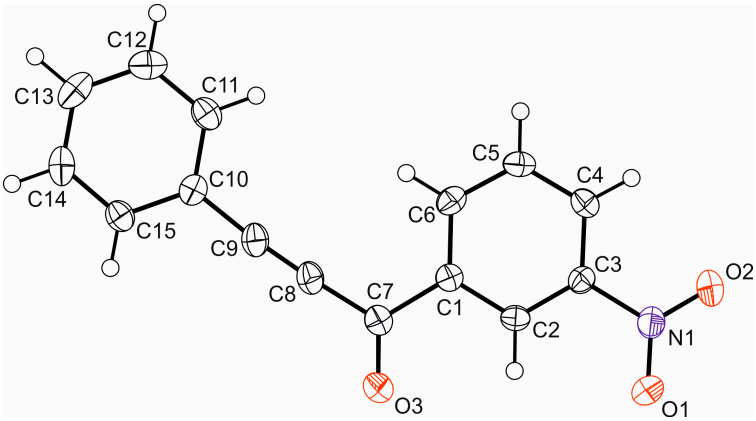


Figure 7. PLATON [34] plot of the molecular structure of **11af** showing the atomic labels and displacement ellipsoids at 50% probability level. Selected distances and angles (in Å and deg): N1=O1 1.224(4), N1=O2 1.229(3), C3-N1 1.468(4), C7=O3 1.223(4), C1-C7 1.492(4), C7-C8 1.447(4), C8-C9 1.205(4), C9-C10 1.433(4); O1=N1=O2 123.4(2), C1-C7-C8 116.7(3), O3=C7-C1/C8 121.6(2)/121.7(2), C7-C8-C9 177.0(3), C8-C9C-10 175.5(3).

The compound crystallizes with the symmetry of the triclinic space group *P*–1 and with one molecule in the asymmetric unit. Parameters describing the molecular geometry of **11af** are unexceptional and in line with the corresponding parameters reported for 1-(4-nitrophenyl)- 3-phenylprop-2-yn-1-one (4-$O_2NC_6H_4C(O)C{\equiv}CPh$) [2,35] and 3-(4-methoxyphenyl)-1-phenylprop-2-yn-1-one ($PhC(O)C{\equiv}CC_6H_4OMe$-4) [36]. The planes of the benzene rings C(1-6) and C(10-15) in **11af** are essentially coplanar (dihedral angle: 0.4(1)°), and even the nitro group is twisted by only 4.1(3)° with respect to its bonding benzene ring. In the crystal, the individual molecules assemble into columnar stacks of inversion-related molecules (Figure 8) via offset π···π stacking interactions of their parallel aromatic rings. These stacks, oriented along the crystallographic *b* axis, are further interconnected in the direction of the crystallographic *a* axis by the C11-H11···O3 soft hydrogen bonds (C11···O3 = 3.327(3) Å, angle at H11 = 158°).

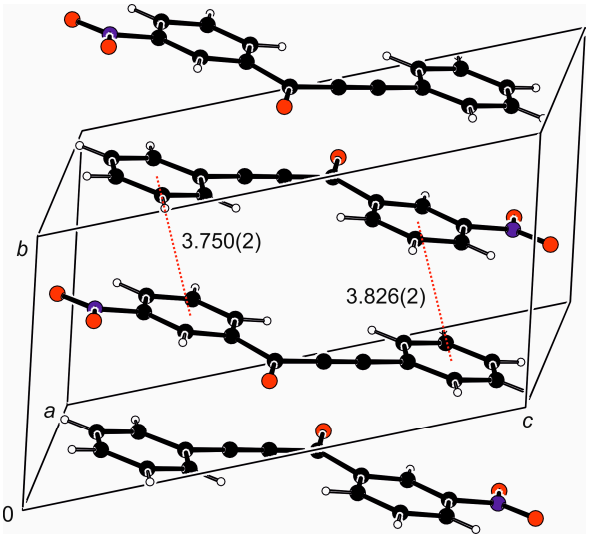


Figure 8. Section of the columnar stacks in the structure of **11af**. The π···π interactions of the parallel benzene rings are indicated by red dotted lines, and the centroid···centroid separation is given in Å.

3. Experimental

3.1. Methods and Materials

Infrared spectra were recorded in diffuse reflectance mode using a Fourier-transform infrared spectrometer FTIR Nicolet 6700 (Thermo Fisher Scientific, Waltham, MA, USA; (scan range 400–4000 cm^{-1}, 64 scans, 4 cm^{-1} resolution). The samples analyzed in this study were diluted with KBr (grade for spectroscopy) before the measurement. Nuclear magnetic resonance (NMR) spectra were recorded at 25 °C on a Varian UNITY Inova 400 spectrometer (Palo Alto, CA, USA) operating at 399.95, 100.58 and 376.29 MHz for ^{1}H, ^{13}C and ^{19}F, respectively. Chemical shifts (δ in ppm) are expressed relative to internal tetramethylsilane (^{1}H and ^{13}C) and to external neat $CFCl_3$ (^{19}F). GC analyses were performed with an Agilent 6850 gas chromatograph (Santa Clara, CA, USA) equipped with a DB-5 column (0.18 mm diameter, 50 m length).

Elemental composition of the deposited catalysts was determined using the standard combustion method and a PerkinElmer PE 2400 CHN analyzer (Waltham, MA, USA). The content of palladium in solid samples and in the reaction mixtures was determined by inductively coupled plasma optical emission spectroscopy (ICP-OES) on an IRIS Interpid II instrument (Thermo Electron, Waltham, MA, USA) with axial plasma and ultrasonic CETAC nebulizer U-5000AT+. The samples were dissolved in a mixture of HF with HNO_3 (3:2, suprapure from Merck; Kenilworth, NJ, USA) at 50 °C for 15 min and evaporated. The residue was diluted with redistilled water for ^{105}Pd (the wavelength used for the spectrophotometric analysis was 324.270 nm).

Dichloromethane was dried over potassium carbonate and distilled under argon. Other solvents were dried over activated 3 Å molecular sieves. Triethylamine was dried over sodium metal and distilled. Other chemicals were used as obtained from commercial sources (Sigma-Aldrich, St. Louis, MO, USA). Materials **2–7** were prepared as previously described [29]. The analytical data determined for the newly prepared samples are as follows. The IR spectra were identical to those of the authentic samples.

Elemental analysis for **2**: C 6.3, N 1.1, S 0.95 $mmol \cdot g^{-1}$. Elemental analysis for **3**: C 7.0, N 1.9 $mmol \cdot g^{-1}$. Elemental analysis for **4**: C 11.3, N 1.1, P 0.77 $mmol \cdot g^{-1}$. Elemental analysis for **5**: C 7.0, N 0.97, S 0.52, Pd 0.64 $mmol \cdot g^{-1}$. Elemental analysis for **6**: C 7.6, N 1.7, Pd 0.62 $mmol \cdot g^{-1}$. Elemental analysis for **7**: C 11.3, N 1.1, P 0.21, Pd 0.43 $mmol \cdot g^{-1}$.

Catalyst **8** was prepared similarly by direct palladation of material **1**. Thus, palladium(II) acetate (0.449 g, 2.0 mmol) dissolved in dry dichloromethane (10 mL) was added to a suspension of support **1** (2.0 g) [29] in the same solvent (50 mL). After stirring the resulting mixture at room temperature for 1 h, the solid was filtered off and washed with dichloromethane until the washings were colorless. Then, the filter cake was washed a few more times (2-3×) and left to dry in the air.

Characterization data for **8**. IR (DRIFTS): 3648 w, 3243 br w, 1567 m, 1430 w, 1388 w, 1330 vw, 1080 s (Si-O-Si asymetric stretch), 944 vw, 794 m (Si-O-Si symetric stretch), 688 w, 462 (Si-O-Si bending) cm^{-1}. Elemental analysis: C 6.1, N 1.1, Pd 0.58 $mmol \cdot g^{-1}$.

3.2. Description of the Screening Experiments

A Schlenk tube was successively charged with the catalyst (typically 0.1–0.5 mol.% Pd), CuI (9.5 mg, 5 mol.%; if appropriate), phenylacetylene (102 mg, 1.0 mmol), 4-toluoyl chloride (230 mg, 1.5 mmol) and dodecane (internal standard; 170 mg, 1.0 mmol). The reaction vessel was flushed with nitrogen and sealed. The solvent was introduced (5 mL of pure solvent or 5 mL of a solvent with 697 μL (5 mmol) of triethylamine), and the reaction flask was transferred to a Heidolph Synthesis I parallel reactor pre-heated to the required temperature. Aliquots of the reaction mixture were periodically collected, diluted with saturated aqueous $NaHCO_3$ and centrifuged at 4000 rpm for 5 min. The organic phase was analyzed by gas chromatography.

During recyclation experiments, the reaction mixture obtained after 2 h at 50 °C was diluted with acetone (5 mL) and cooled on ice. A small amount of the liquid phase was separated and used to determine the conversion. The solids were filtered off, washed successively with acetone,

methanol (removal of triethylammonium chloride) and acetone again. The filtrate and washings were combined and used to quantify the amount of leached-out metal. The recovered solid was used in the next catalytic experiments.

3.3. Preparative Experiments

A Schlenk tube was charged with the respective alkyne (1.0 mmol) and acyl chloride (1.5 mmol; only 1.0 mmol of the acyl chloride was used in the reaction of ethynylferrocene with benzoyl chloride to avoid decomposition). After flushing the reaction vessel with argon, catalyst **5** (0.5 mol.% Pd) was introduced, followed by dry acetonitrile (5 mL) and anhydrous triethylamine (0.7 mL, ca. 5 mmol). The reaction mixture was stirred at 50 °C for 2 h, diluted with ethyl acetate (10 mL) and cooled on ice. The cold reaction mixture was filtered, and the solid residue was washed with ethyl acetate. The combined organic washings were evaporated under vacuum, leaving a crude reaction product, which was taken up with 1,4-dioxane. Solid $NaHCO_3$ was added (≈0.1 g), and the resulting mixture was stirred at room temperature for 1–7 days to hydrolyze unreacted acyl chloride. The hydrolyzed reaction mixture was evaporated, and the residue was extracted with ethyl acetate. Organic washings were dried over anhydrous $MgSO_4$ and evaporated. Analytically pure coupling products were isolated by column chromatography over silica gel using ethyl acetate-hexane (1:10 or 1:20) as the eluent (dichloromethane was used in the case of **11ag**).

3.4. Analytical Data of the Cross-Coupling Products

1-(2-Tolyl)-3-phenylprop-2-yn-1-one (**11ab**) [37]. ^{1}H NMR ($CDCl_3$): δ 2.68 (s, 3 H, CH_3), 7.26–7.29 (m, 1 H, aromatics), 7.33–7.49 (m, 5 H, aromatics), 7.64–7.67 (m, 2 H, aromatics), 8.28–8.32 (m, 1 H, aromatics). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 21.9 (CH_3), 88.4 and 91.8 (C≡C), 120.4, 125.9, 128.6, 130.6, 132.2, 132.90, 132.93, 133.2, 135.8, 140.5 (aromatics), 179.8 (C=O).

1-(3-Tolyl)-3-phenylprop-2-yn-1-one (**11ac**) [37]. ^{1}H NMR ($CDCl_3$): δ 2.45 (bq, 3 H, J_{HH} = 0.7 Hz, CH_3), 7.41-7.51 (m, 5 H, aromatics), 7.67–7.71 (m, 2 H, aromatics), 8.01–8.06 (m, 2 H, aromatics). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 21.3 (CH_3), 87.0 and 92.9 (C≡C), 120.2, 127.1, 128.5, 128.7, 129.8, 130.7, 133.1, 135.0, 136.9 and 138.5 (aromatics), 178.2 (C=O).

1-(4-Tolyl)-3-phenylprop-2-yn-1-one (**11ad**) [37]. ^{1}H NMR ($CDCl_3$): δ 2.45 (s, 3 H, CH_3), 7.29–7.33 (m, 2 H, aromatics), 7.40–7.45 (m, 2 H, aromatics), 7.46–7.51 (m, 1 H, aromatics), 7.67–7.71 (m, 2 H, aromatics), 8.10–8.14 (m, 2 H, aromatics). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 21.9 (CH_3), 87.0 and 92.6 (C≡C), 120.3, 128.7, 129.4, 129.7, 130.7, 133.0, 134.6 and 145.2 (aromatics), 177.3 (C=O).

1-(3-Nitrophenyl)-3-phenylprop-2-yn-1-one (**11af**) [8]. ^{1}H NMR ($CDCl_3$): δ 7.46 (m, 2 H, aromatics), 7.54 (m, 1 H, aromatics), 7.74 (m, 3 H, aromatics), 8.49 (ddd, J_{HH} = 8.2, 2.3, 1.1 Hz, 1 H, aromatics), 8.53 (dt, J_{HH} = 7.8, 1.4 Hz, 1 H, aromatics), 9.06 (t, J_{HH} = 1.9 Hz, 1 H, aromatics). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 86.2 and 95.3 (C≡C), 119.4, 124.6, 128.2, 128.9, 129.9, 131.5, 133.4, 134.6, 138.1, 148.5 (aromatics), 175.4 (s, C=O). Crystal used for structure determination was grown from chloroform/hexane.

1-(4-Nitrophenyl)-3-phenylprop-2-yn-1-one (**11ag**) [38]. ^{1}H NMR ($CDCl_3$): δ 7.43 and 7.49 (m, 2 H, aromatics), 7.51–7.57 (m, 1 H, aromatics), 7.69–7.74 (m, 2 H, aromatics), 8.38 (m, 4 H, aromatics). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 86.5 and 95.4 (C≡C), 119.4, 123.9, 128.9, 130.5, 131.5, 133.3, 141.0 and 150.9 (aromatics), 175.9 (C=O).

1-(4-Anisyl)-3-phenylprop-2-yn-1-one (**11ah**) [37]. ^{1}H NMR ($CDCl_3$): δ 3.90 (s, 3 H, CH_3O), 6.97–7.01 (m, 2 H, aromatics), 7.39–7.50 (m, 3 H, aromatics), 7.66–7.70 (m, 2 H, aromatics), 8.18–8.22 (m, 2 H, aromatics). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 55.6 (CH_3), 86.9 and 92.3 (C≡C), 113.9, 120.4, 128.7, 130.3, 130.6, 132.0, 133.0 and 164.5 (aromatics), 176.7 (C=O).

1-(4-Chlorophenyl)-3-phenylprop-2-yn-1-one (**11ai**) [37]. ^{1}H NMR ($CDCl_3$): δ 7.40–7.46 (m, 2 H, aromatics), 7.47-7.52 (m, 3 H, aromatics), 7.67–7.70 (m, 2 H, aromatics), 8.14-8.18 (m, 2 H, aromatics). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 86.6 and 93.6 (C≡C), 119.9, 128.8, 129.0, 130.9, 131.0, 133.1, 135.3 and 140,7 (aromatics), 176.7 (C=O).

3-(4-Tolyl)-1-phenylprop-2-yn-1-one (**11ba**) [38]. ^{1}H NMR ($CDCl_3$): δ 2.41 (s, 3 H, CH_3), 7.21–7.25 (m, 2 H, aromatics), 7.49-7.54 (m, 2 H, aromatics), 7.57–7.65 (m, 3 H, aromatics), 8.20–8.24 (m, 2 H, aromatics). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 21.8 (CH_3), 86.8 and 93.8 (C≡C), 117.0, 128.6, 129.5, 129.6, 133.1, 134.0, 137.0 and 141,6 (aromatics), 178.1 (C=O).

3-(4-Anisyl)-1-phenylprop-2-yn-1-one (**11ea**) [38]. ^{1}H NMR ($CDCl_3$): δ 3.86 (s, 3 H, CH_3O), 6.91–6.96 (m, 2 H, aromatics), 7.49–7.54 (m, 2 H, aromatics), 7.60–7.67 (m, 3 H, aromatics), 8.20–8.24 (m, 2 H, aromatics). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 55.5 (CH_3), 86.9 and 94.3 (C≡C), 111.9, 114.4, 128.6, 129.5, 133.9, 135.2, 137.1 and 161.8 (aromatics), 178.1 (C=O).

3-[4-(Trifluoromethyl)phenyl]-1-phenylprop-2-yn-1-one (**11ja**) [39]. ^{1}H NMR ($CDCl_3$): δ 7.51–7.56 (m, 2 H, aromatics), 7.64–7.71 (m, 3 H, aromatics), 7.78–7.81 (m, 2 H, aromatics), 8.20–8.23 (m, 2 H, aromatics). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 88.1 and 90.5 (C≡C), 123.6 (q, $^{1}J_{FC}$ = 273 Hz, CF_3), 124.0, 125.6 (q, $^{3}J_{FC}$ = 4 Hz), 128.8, 129.6, 132.3 (q, $^{2}J_{FC}$ = 33 Hz), 133.2, 134.5 and 136.6 (aromatics), 177.7 (C=O) ^{19}F NMR ($CDCl_3$): δ − 63.4 (s).

1-(2-Phenylvinyl)-3-phenylprop-2-yn-1-one (**11ak**) [39]. ^{1}H NMR ($CDCl_3$): δ 6.88 (d, $^{3}J_{HH}$ = 16.1 Hz, 1 H, CH=), 7.39–7.50 (m, 5 H, aromatics), 7.58–7.68 (m, 4 H, aromatics), 7.91 (d, $^{3}J_{HH}$ = 16,1 Hz, 1 H, CH=). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 86.6 and 91.5 (C≡C), 120.2, 128.6, 128.7, 128.7, 129.1, 130.6, 131.2, 133.0, 134.1 and 148.3 (CH=CH and aromatics), 178.2 (C=O).

1-(*t*-Butyl)-3-phenylprop-2-yn-1-one (**11am**) [40]. ^{1}H NMR ($CDCl_3$): δ 1.28 (s, 9 H, CH_3), 7.36–7.41 (m, 2 H, aromatics), 7.43–7.48 (m, 1 H, aromatics), 7.56–7.60 (m, 2 H, aromatics). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 26.1 (CH_3), 44.9 ((CH_3)$_3$*C*), 86.0 and 92.2 (C≡C), 120.3, 128.6, 130.6 and 133.0 (aromatics), 194.3 (C=O).

1-(2-Furanyl)-3-phenylprop-2-yn-1-one (**11an**) [41]. ^{1}H NMR ($CDCl_3$): δ 6.61 (dd, $^{3}J_{HH}$ = 3.6 Hz, $^{3}J_{HH}$ = 1.71 Hz, 1 H, furanyl), 7.39–7.51 (m, 4 H, furanyl and aromatics), 7.63–7.67 (m, 2 H, aromatics), 7.70 (dd, $^{3}J_{HH}$ = 1.7 Hz, $^{4}J_{HH}$ = 0.9 Hz, 1 H, furanyl). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 86.2 and 91.0 (C≡C), 112.7, 119.9, 120.9, 128.7, 130.9, 133.1, 148.1, 153.2 (aromatics and furanyl), 164.8 (C=O).

1-(2-Thienyl)-3-phenylprop-2-yn-1-one (**11ao**) [39]. ^{1}H NMR ($CDCl_3$): δ 7.19 (dd, $^{3}J_{HH}$ = 4.92 Hz, $^{3}J_{HH}$ = 3.8 Hz, 1 H, thienyl), 7.39–7.51 (m, 3 H, aromatics), 7.65–7.69 (m, 2 H, aromatics), 7.73 (dd, $^{3}J_{HH}$ = 4.9 Hz, $^{4}J_{HH}$ = 1.2 Hz, 1 H, thienyl), 8.01 (dd, $^{3}J_{HH}$ = 3.8 Hz, $^{4}J_{HH}$ = 1.2 Hz, 1 H, thienyl). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 86.5 and 91.7 (C≡C), 120.0, 128.4, 128.7, 130.9, 133.1, 135.1, 135.3 a 145.0 (thienyl and aromatics), 169.8 (C=O).

3-Ferrocenyl-1-phenylprop-2-yn-1-one (**11pa**) [42]. ^{1}H NMR ($CDCl_3$): δ 4.29 (s, 5 H, C_5H_5), 4.43 (virtual t, $^{3}J_{HH}$ = 1.9 Hz, 2 H, C_5H_4), 4.69 (vt, $^{3}J_{HH}$ = 1.9 Hz, 2 H, C_5H_4), 7.49–7.55 (m, 2 H, aromatics), 7.59–7.65 (m, 1 H, aromatics), 8.17–8,21 (m, 2 H, aromatics). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 60.3, 70.5, 70.8 and 73.2 (ferrocene), 85.5 and 96.6 (C≡C), 128.5, 129.4, 133.7, 137.2 (aromatics), 177.6 (C=O).

3.5. Structure Determination

Crystal data for **11af**: $C_{15}H_9NO_3$, M = 251.23 g·mol^{-1}, light yellow plate, 0.10 × 0.32 × 0.55 mm^3, triclinic, space group p − 1 (no. 2), a = 6.8003(6) Å, b = 7.1934(7) Å, c = 13.471(1) Å; α = 75.075(4)°, β = 79.161(3)°, γ = 69.530(3)°, V = 593.0(1) Å^3, Z = 2, D_{calc} = 1.407 g·mL^{-1}.

Full-set diffraction data were collected with an Apex 2 (Bruker, Billerica, MA, USA) diffractometer equipped with a Cryostream Cooler (Oxford Cryosystems, Oxford, UK) at 150(2) K using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). The data were corrected for absorption (μ = 0.10 mm^{-1}) using a multi-scan routine incorporated in the diffractometer software. A total of 5295 diffractions was recorded (θ_{max} = 26°, data completeness = 99.3%), of which 2309 were unique (R_{int} = 2.50%) and 1652 were observed according to the $I > 2\sigma(I)$ criterion.

The structure was solved using direct methods (SHELXS-97 [43]) and refined by a full-matrix least-squares routine based on F^2 (SHELXL-2017 [44]). The non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were included in their theoretical positions and refined as riding atoms with U_{iso}(H) assigned to 1.2U_{eq}(C). The refinement converged (Δ/σ = 0.000, 172 parameters) to R = 5.77% for the observed, and R = 8.42%, wR = 15.8% for all diffractions. The final

difference map revealed no peaks of chemical significance ($\Delta\rho_{max}$ = 0.22, $\Delta\rho_{min}$ = −0.23 e Å^{-3}). CCDC deposition no. 2015269.

4. Conclusions

In summary, we have described the catalytic applications of palladium catalysts deposited over silica gel bearing composite amide-donor functional moieties at the surface in the Sonogashira-type cross-coupling of acyl chlorides with terminal alkynes producing synthetically useful 1,3-disubstituted prop-2-yn-1-ones. The collected data suggest a generally good catalytic performance of these heterogeneous catalysts alone (i.e., without a co-catalyst) in the reactions of aromatic acyl chlorides with aryl alkynes under relatively mild reaction conditions. Nevertheless, a careful optimization is required for achieving good catalytic results, as the catalytic properties are significantly affected by the reaction conditions (solvent and base) and depend on the nature of the functional pendant at the support's surface. Of the tested catalysts, the poorest performance surprisingly exerted catalyst **7** bearing the phosphine moieties, which contrasts with the general notion that phosphine ligands give rise to active cross-coupling catalysts. When recycled, however, the studied catalysts lost their catalytic activity and, therefore, could not be efficiently reused. Very likely, the catalysts serve as a source of catalytically active Pd species that efficiently mediate the cross-coupling reaction but are not redeposited without deactivation.

Supplementary Materials: The following are available online at http://www.mdpi.com/2073-4344/10/10/1186/s1, Table S1: Yields of the coupling product **11ad** and the amount of leached-out Pd in the recycling experiments.

Author Contributions: P.Š. conceived the study and, in collaboration with M.S. and F.H., interpreted the collected data and wrote this article; M.S. and F.H. performed all syntheses and catalytic tests; all authors contributed to the characterization of the coupling products. All authors have read and agreed to the published version of the manuscript.

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