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A Guide to Sonogashira Cross-Coupling Reactions: The Influence of Substituents in Aryl Bromides, Acetylenes, and Phosphines

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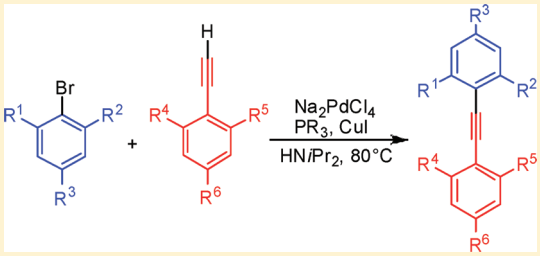
Supporting Information

ABSTRACT: The conversion−time data for 168 different Pd/Cu-catalyzed Sonogashira cross-coupling reactions of five arylacetylenes (phenylacetylene; 1-ethynyl-2-ethylbenzene; 1-ethynyl-2,4,6-R_3-benzene (R = Me, Et, *i*-Pr)) and Me_3SiCCH with seven aryl bromides (three 2-R-bromobenzenes (R = Me, Et, *i*-Pr); 2,6-Me_2-bromobenzene and three 2,4,6-R_3-bromobenzenes (R = Me, Et, *i*-Pr)) with four different phosphines (P-*t*-Bu_3, *t*-Bu_2PCy, *t*-$BuPCy_2$, PCy_3) were determined using quantitative gas chromatography. The stereoelectronic properties of the substituents in the aryl bromides, acetylenes, and phosphines were correlated with the performance in Sonogashira reactions. It was found that the nature of the most active Pd/PR_3 complex for a Sonogashira transformation is primarily determined by the steric bulk of the acetylene; ideal catalysts are: Pd/P-*t*-Bu_3 or Pd/*t*-Bu_2PCy for sterically undemanding phenylacetylene, Pd/*t*-$BuPCy_2$ for 2- and 2,6-substituted arylacetylenes or Me_3SiCCH and Pd/PCy_3 for extremely bulky acetylenes and aryl bromides. Electron-rich and sterically demanding aryl bromides with substituents in the 2- or the 2,6-position require larger amounts of catalyst than 4-substituted aryl bromides. The synthesis of tolanes with bulky groups at one of the two aryl rings is best done by placing the steric bulk at the arylacetylene, which is also the best place for electron-withdrawing substituents.



INTRODUCTION

The Sonogashira coupling of aryl halides and terminal acetylenes remains the most important method for the formation of C(sp^2)−C(sp) bonds.[1] Traditionally palladium complexes, very often in combination with copper(I) salts, are the preferred catalyst for such reactions, despite the fact that in recent years numerous other metals were also claimed to be effective.[1c,2] Closely related approaches leading to the same products involve the reactions of alkynyl halides and arenes ("inverse Sonogashira reaction")[3] or of acetylenes and heterocycles ("direct alkynylation")[4] or the reactions of aryl boronic acids with acetylenes.[5]

The mechanism of the Sonogashira reaction is not understood in detail, also since there can be additional complications due to CuI and the metal coordination of acetylenes.[6] Nonetheless, primarily empirical studies led to a large number of powerful catalyst recipes, which allow the efficient conversion of aryl iodides and bromides using small catalyst loading[7] or aryl chlorides.[8] With an ever larger number of catalysts and reaction conditions published in the literature, it is not easy for the nonspecialist to choose the best reaction conditions for certain substrates. In this respect, answers are needed concerning the factors determining the reactivity of individual substrates in Sonogashira reactions. Several studies focusing on the influence of steric and electronic variables on the individual steps in the catalytic cycles, such as the oxidative addition,[9] transmetalation and reductive elimination, were done, and a few general rules concerning cross-coupling reactions were derived:[10] (i) the oxidative addition in Ar-X is promoted by electron-withdrawing groups at the aryl halide; (ii) steric bulk of phosphines or NHC ligands coordinated to Pd promote the formation of a formally monoligated complex PdL_1, which turns out to be highly active for oxidative addition; (iii) there is a pronounced steric effect in the transmetalation, while the ligand bite angle and the electronic effect are less important; and (iv) reductive elimination tends to be favored by less electron-donating ligands and steric bulk.[11]

These are useful rules. However, for certain substrate−catalyst combinations, it is not always clear which of the various elementary reactions actually control the outcome of a cross-coupling reaction. Substrate−activity relationships or descriptor-based approaches, for which stereoelectronic properties of substrates or ligands are modified in a systematic manner, appear to be useful,[12] to better understand product formation as well as more global approaches.[13] In this respect, Hartwig et al. screened a large number of phosphine ligands to find that the sterically most demanding ligands provide the highest activities in palladium-catalyzed Heck coupling.[14] We have studied in detail substrate−activity relationships for Sonogashira coupling reactions using parallel screening.[15] For sterically undemanding substrates there turns out to be a good correlation between the Sonogashira activity of various palladium−phosphine complexes and the Tolman cone angle of the respective phosphine ligand.[15] Several publications by Organ et al. center around the question of how the steric and electronic environment of NHC ligands influence the performance of the respective (NHC)Pd complex

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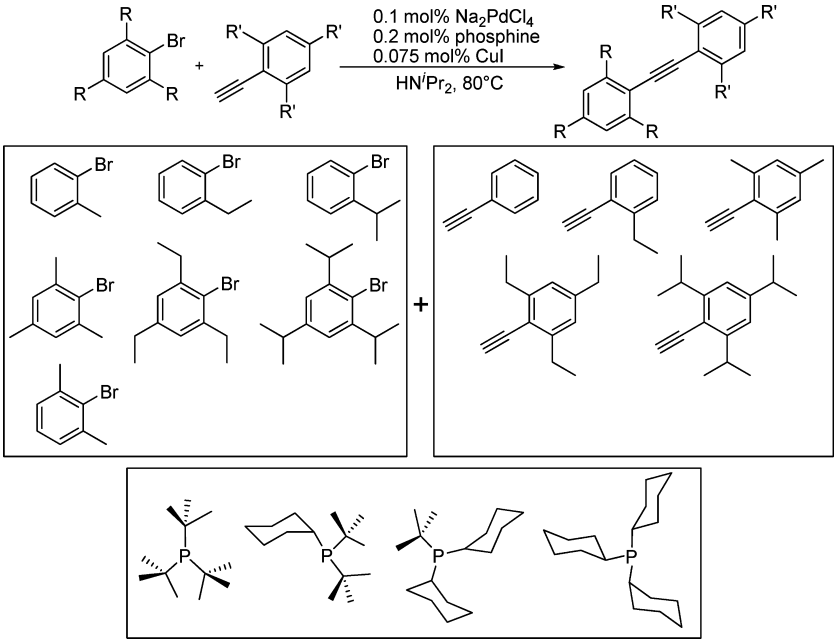
Scheme 1. Representation of 140 Different Sonogashira Cross-Coupling Reactions (7 Aryl Bromides × 5 Acetylenes × 4 Phosphines)



in cross-coupling reactions.[16] Concerning the role of phosphines, Guram et al. showed that within a small series of electronically variable phosphines, the most electron-rich ligand provides the best results in Suzuki–Miyaura reactions.[17] The effect of solvent composition on cross-coupling efficiency was investigated in a systematic manner for the same coupling reaction.[18] Martensson et al. studied the effect of solvent and base in copper-free Sonogashira coupling in a systematic manner.[19]

It is the aim of the present study to elucidate in which manner electronic and steric modifications at aryl bromides, acetylenes, and the ligands influence the outcome of Sonogashira reactions.[20] On the basis of these results, it will be attempted to provide a few general rules for the selection of suitable palladium–phosphine catalyst complexes as well as catalytic procedures for the efficient conversion of various substrate combinations.

RESULTS AND DISCUSSION

Setting up the Sonogashira Screens. In order to probe the influence of steric effects on Sonogashira couplings reactions, a large number of such were carried under the conditions reported previously,[7d] using HN-*i*-Pr_2 as solvent and base, Na_2PdCl_4 as the palladium source, CuI as the cocatalyst, and a phosphine.[21] This reaction procedure is highly efficient and is characterized by an excellent selectivity for the formation of the desired tolanes. The steric properties of aryl bromide and arylacetylene substrates and of the catalytically active Pd/phosphine complexes were systematically varied (Scheme 1). All permutations of seven aryl bromides and five arylacetylenes were tested, resulting in the synthesis of 35 different tolanes using four different phosphine–palladium catalysts. The same set of experiments using the seven aryl bromides were also conducted employing trimethylsilylacetylene. The steric properties of the phosphines used (*t*-Bu_3P, *t*-Bu_2PCy, *t*-$BuPCy_2$, PCy_3) were systematically varied by stepwise replacing *tert*-butyl groups by cyclohexyl groups. We decided to use a small set of phosphines, which are closely related and can be changed in a highly systematic manner. Furthermore, we wanted to use simple and easily available phosphines so that others can easily use such ligands for their own experiments. For each of the 168 different Sonogashira coupling reactions, the respective time–conversion data were independently determined twice; each time–conversion plot consists of 10 or 11 individual GC measurements. All data given are the average of two independent determinations. For all of the tolanes studied the individual gas chromatographic response factors were determined to enable the precise quantification of product formation. In order to facilitate reaction screening, a previously established parallel multisubstrate procedure was employed.[15,22] According to this procedure, all seven aryl bromides employed were simultaneously reacted with a single one of the six acetylenes in one reaction vessel.[23] This procedure enables the screening of a large number of reactions in a relatively short time. Furthermore, it ensures identical reaction conditions for each series of aryl bromide coupling and thus allows us to obtain precise and comparable reaction data.

Evaluation of the Individual Sonogashira Screens. As outlined in Schemes 1 and 2 all permutations of the seven aryl bromides and acetylenes (five arylacetylenes and Me_3Si-CCH) with four different Pd/PR_3 complexes were investigated. One multisubstrate screen including the seven aryl bromides was set up for each of the acetylenes. The results for each of those five screens are displayed in Figures 1 and 2 (phenylacetylene), Figures 3 and 4 (1-ethynyl-2-ethylbenzene), Figures 5 and 6 (1-ethynyl-2,4,6-trimethylbenzene), Figures 7 and 8 (1-ethynyl-2,4,6-triethylbenzene), and Figures 9 and 10 (1-ethynyl-2,4,6-triisopropylbenzene). The time–conversion curves for phenylacetylene, 1-ethynyl-2-ethylbenzene, 1-ethynyl-2,4,6-trimethylbenzene, and 1-ethynyl-2,4,6-triethylbenzene were fitted to an exponential function to obtain rate constants.[24] Because of long inhibition periods in the 1-ethynyl-2,4,6-triisopropylbenzene reactions, the data could not be treated in the same manner; instead, the conversion after 210 min is given and used for the evaluation of the reaction efficiency.

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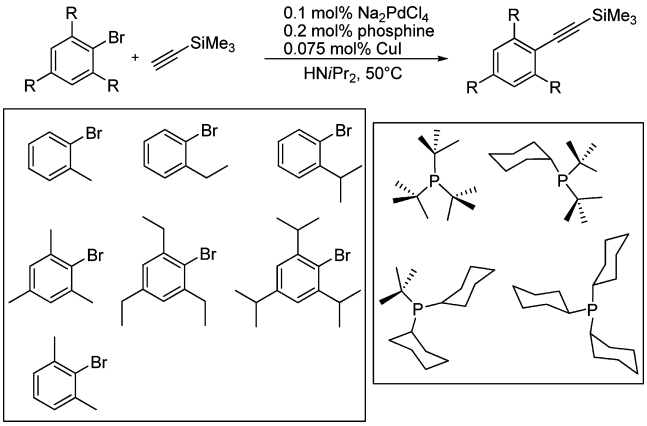
Scheme 2. Representation of 28 Different Sonogashira Cross-Coupling Reactions (7 Aryl Bromides × 4 Phosphines) with Trimethylsilylacetylene



Phenylacetylene. In the reactions with ortho-substituted aryl bromides, Pd/*t*-Bu_2PCy is slightly more efficient than Pd/*t*-Bu_3P (Figures 1 and 2). The latter complex performs better in the coupling of aryl bromides and arylacetylenes with ortho-hydrogen atoms, as reported previously.[15,20] Interestingly, the reactivity of the three 2-alkyl-substituted aryl bromides (2-Me, 2-Et, 2-*i*-Pr) is nearly the same (Figures 1 and 2), while the reactivity of 2,6-substituted aryl bromides is significantly lower. This appears to be due to a combination of steric and electronic effects.

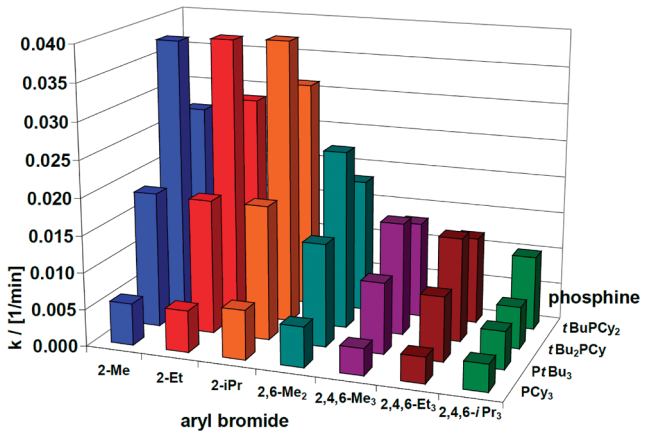


Figure 1. Parallel multisubstrate screen for the reactions of phenylacetylene with seven aryl bromides catalyzed either by 0.1 mol % Pd/*t*-Bu_3P, Pd/*t*-Bu_2PCy, Pd/*t*-$BuPCy_2$ or Pd/PCy_3.

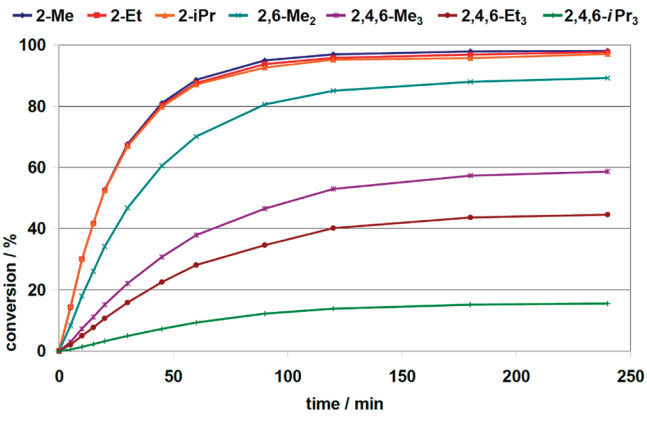


Figure 2. Time conversion curves for the reactions of seven aryl bromides with phenylacetylene catalyzed by 0.1 mol % Pd/*t*-Bu_2PCy.

1-Ethynyl-2-ethylbenzene. With this acetylene, Pd/*t*-$BuPCy_2$ is performing better than Pd/*t*-Bu_2PCy for all aryl bromides tested. Obviously the influence of acetylene bulk on the Sonogashira coupling (in the choice of the "best" phosphine ligand) is more important than that of aryl bromide bulk. The increased bulk of 1-ethynyl-2-ethylbenzene relative to phenylacetylene leads to a change in the choice of the "best" phosphine ligand. For larger acetylenes, a smaller phosphine is the better choice. An interesting change in the Sonogashira reactivity is observed when 1-ethynyl-2-ethylbenzene is used (Figures 3 and 4). Coupling reactions employing this large

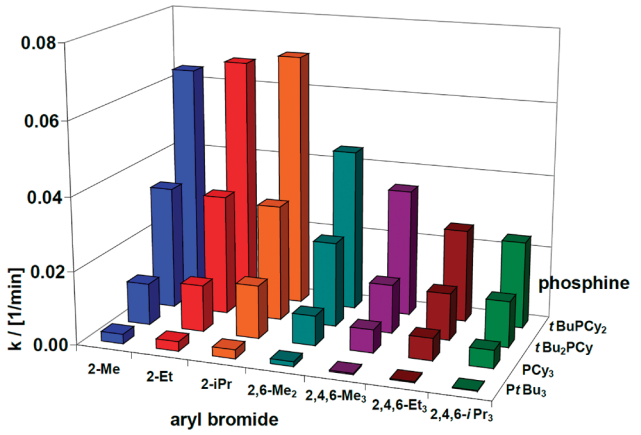


Figure 3. Parallel multisubstrate screen for the reactions of 1-ethynyl-2-ethylbenzene with seven aryl bromides catalyzed either by 0.1 mol % Pd/*t*-Bu_3P, Pd/*t*-Bu_2PCy, Pd/*t*-$BuPCy_2$, or Pd/PCy_3.

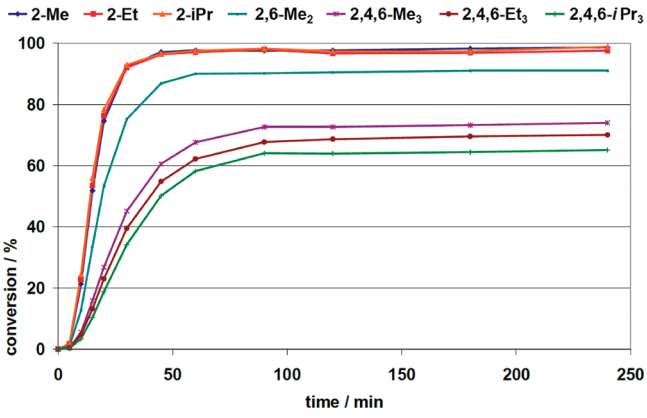


Figure 4. Time conversion curves for the reactions of seven aryl bromides with 1-ethynyl-2-ethylbenzene catalyzed by 0.1 mol % Pd/*t*-$BuPCy_2$.

substrate occur faster than analogous reactions using the smaller phenylacetylene. This unexpected steric effect[25] might result from a hindered side-on coordination of the acetylene to the active palladium species, which is known to be detrimental to the activity of the catalyst in the Sonogashira coupling.[6b]

1-Ethynyl-2,4,6-trimethylbenzene. The reactivity trends observed for 1-ethynyl-2-ethylbenzene are more pronounced for reactions of 1-ethynyl-2,4,6-trimethylbenzene (Figures 5 and 6). The reaction rate is even faster than for conversions of

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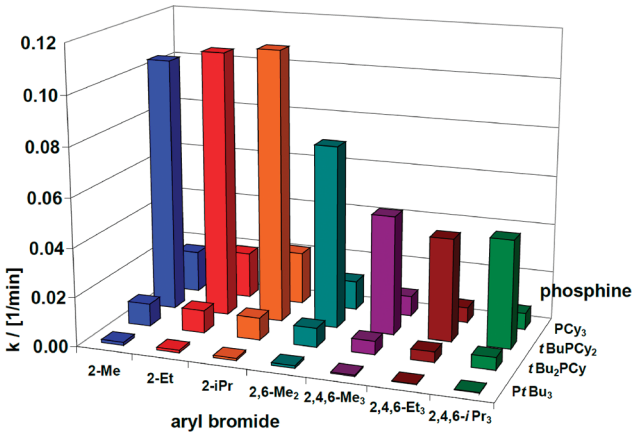

Figure 5. Parallel multisubstrate screen for the reactions of 1-ethynyl-2,4,6-trimethylbenzene with seven aryl bromides catalyzed either by 0.1 mol % of Pd/*t*-Bu_3P, Pd/*t*-Bu_2PCy, Pd/*t*-$BuPCy_2$, or Pd/PCy_3.

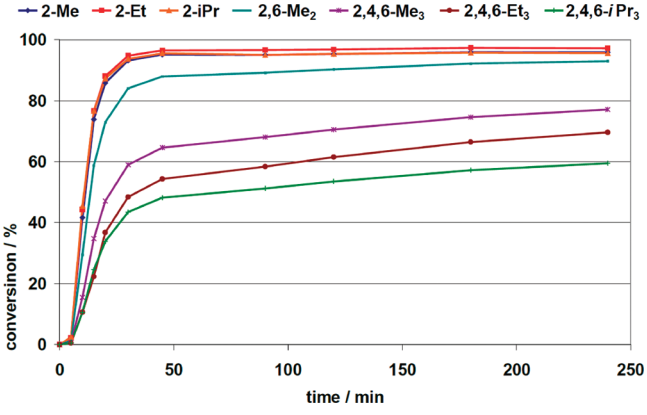

Figure 6. Time−conversion curves for the reactions of seven aryl bromides with 1-ethynyl-2,4,6-trimethylbenzene acetylene catalyzed by 0.1 mol % Pd/*t*-$BuPCy_2$.

the two less bulky arylacetylenes. The Pd complex of the less bulky phosphine *t*-$BuPCy_2$ performs much better than Pd/*t*-Bu_2PCy.

1-Ethynyl-2,4,6-triethylbenzene. The Sonogashira reactions of 1-ethynyl-2,4,6-triethylbenzene are still faster than those of phenylacetylene but slower than those of 1-ethynyl-2,4,6-trimethylbenzene (Figures 7 and 8). The diminished inhibition of the active center enhances the Sonogashira rates, while the increasing bulk begins to slow down the reaction. For this substrate, Pd/*t*-$BuPCy_2$ turns out to be the most efficient catalyst for the Sonogashira transformations.

1-Ethynyl-2,4,6-triisopropylbenzene. The reactions of very bulky 1-ethynyl-2,4,6-triisopropylbenzene with aryl bromides (Figures 9 and 10) are characterized by a significant inhibition period; no substrate conversion was observed during the first ca. 20 min of the reaction. The solution of Na_2PdCl_4 in HN-*i*-Pr_2 is characterized by a pale yellow color, which persists after addition of the respective aryl bromide. Upon addition of the acetylene, a slow change to a dark yellow or orange color is observed. This color persists throughout the coupling reaction. It is generally believed that for the Sonogashira reaction, the conversion of the inactive Pd^{2+} salt into the active Pd^0 species occurs via the formation of a $L_nPd(CCR)_2$ complex, followed by the reductive elimination of the respective butadiyne. The initial absence of reactivity and of the typical red color of the

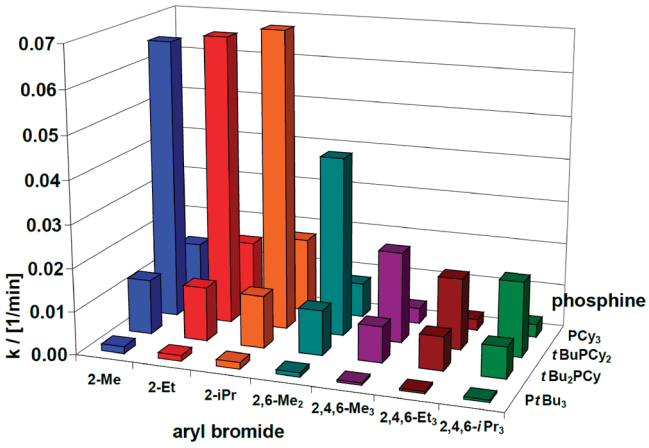

Figure 7. Parallel multisubstrate screen for the reactions of 1-ethynyl-2,4,6-triethylbenzene with seven aryl bromides catalyzed either by 0.1 mol % of Pd/*t*-Bu_3P, Pd/*t*-Bu_2PCy, Pd/*t*-$BuPCy_2$, or Pd/PCy_3.

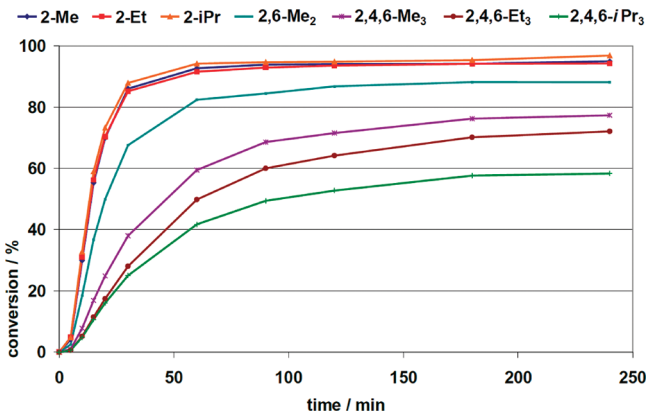

Figure 8. Time−conversion curves for the reactions of seven aryl bromides with 1-ethynyl-2,4,6-triethylbenzene catalyzed by 0.1 mol % of Pd/*t*-$BuPCy_2$.

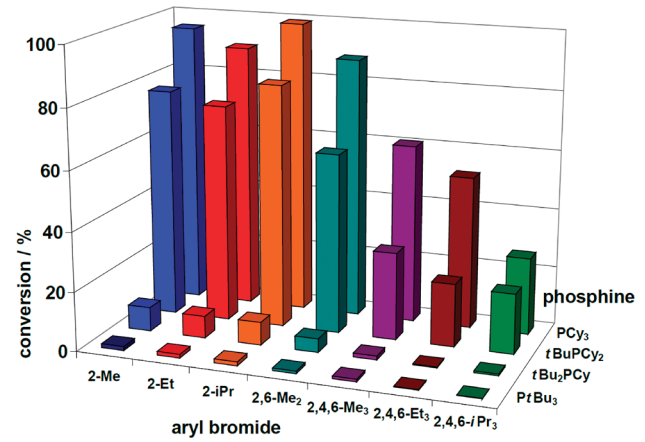

Figure 9. Parallel multisubstrate screen for the reactions of 1-ethynyl-2,4,6-triisopropylbenzene with seven aryl bromides catalyzed either by 0.1 mol % Pd/*t*-Bu_3P, Pd/*t*-Bu_2PCy, Pd/*t*-$BuPCy_2$ or Pd/PCy_3 (conversion after 210 min).

reaction mixture points to the absence of catalytically active Pd(0).[26] This can be explained for sterically highly demanding acetylenes, such as 1-ethynyl-2,4,6-triisopropylbenzene, by a more difficult formation of the respective $L_nPd(CCAr)_2$ complexes.

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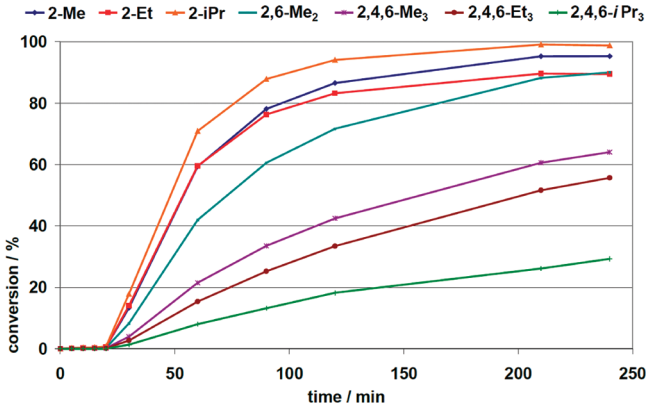

Figure 10. Time conversion curves for the reactions of seven aryl bromides with 1-ethynyl-2,4,6-triisopropylbenzene catalyzed by 0.1 mol % Pd/PCy_3.

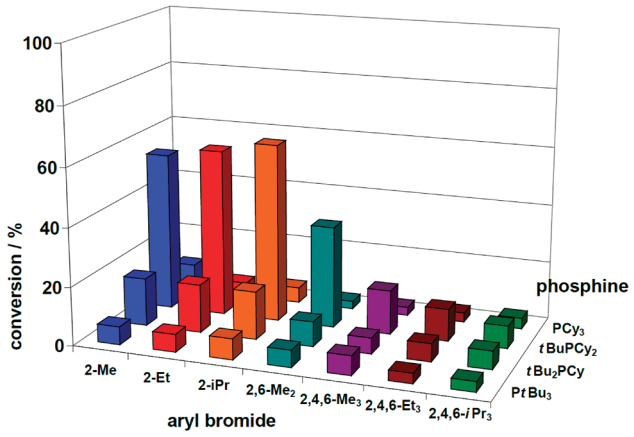

Figure 11. Parallel multisubstrate screen for the reactions of trimethylsilylacetylene with seven aryl bromides catalyzed either by 0.1 mol % of $Pd/t\text{-}Bu_3P$, $Pd/t\text{-}Bu_2PCy$, $Pd/t\text{-}BuPCy_2$, or Pd/PCy_3 (conversion after 240 min).

Concerning the choice of the "best" phosphine, the pronounced bulk in 1-ethynyl-2,4,6-triisopropylbenzene leads to a preference for an even smaller phosphine and Pd/PCy_3 constitutes the most active catalyst. Qualitatively speaking, the sum of the steric bulk of the respective acetylene and of the phosphine appear to be constant: small acetylenes require large phosphines ($t\text{-}Bu_3P$ or $t\text{-}Bu_2PCy$), medium-sized acetylenes (1-ethynyl-2,4,6-triethylbenzene) require smaller phosphines ($t\text{-}BuPCy_2$), and the largest acetylenes perform best with the small phosphines (PCy_3). The most prominent byproduct of Sonogashira reactions reported here is the respective enyne resulting from the dimerization of two acetylenes, while the respective butadiyne resulting from an oxidative coupling of two acetylenes is negligible. The amount of formed dimerization product depends on the nature of the phosphine; with $Pd/Pt\text{-}Bu_3$ and $Pd/t\text{-}Bu_2PCy$ it is negligible, with $Pd/t\text{-}Bu_2PCy$ up to 5% and with Pd/PCy_3 up to 10% are formed.

Trimethylsilylacetylene. Me_3SiCCH is a very important substrate in Sonogashira reactions, which is often used as a monofunctional surrogate for acetylene, since following the cross coupling reaction the $-SiMe_3$ group can be cleaved off easily.[1d,27] The pronounced steric bulk of this protective group prompted us study, which of the phosphine/Pd complexes tested here, is best suited for this substrate. This was done according to the general protocol (scheme 2).[28] Initially, the observed product formation appeared to be modest, despite excellent substrate reactivity. This is not due to incomplete conversion of the reactants but is an artifact of the strongly basic post-reaction treatment, which primarily has to ensure rapid quenching of the catalyst. In the course of sample preparation (see the Experimental Section) for chromatographic product analysis, the $-SiMe_3$ group is partially cleaved off and the respective $Ar\text{-}CCSiMe_3$ and Ar-CCH are both observed in the gas chromatograms. This is why in contrast to the other arylacetylene reactions the data evaluation is based on the decrease in the aryl bromide concentration. Nonetheless, the difference in the reactivity of the four Pd/phosphine complexes tested is pronounced (Figure 11). $Pd/t\text{-}BuPCy_2$ is the most powerful catalyst for the Sonogashira coupling of Me_3SiCCH.[29]

Guidelines for Sonogashira Coupling Reactions. On the basis of the results of the extensive screening studies described above, it is possible to recommend certain Pd/phosphine catalyst complexes, which display the highest catalytic activity for certain Sonogashira substrates (Table 1). The amount of catalyst given should be considered as approximate values. The loading given in Table 1 is based on reactions with simple alkyl groups and may well be higher for other substrates with problematic substituents. The choice of the best phosphine is primarily guided by the nature of the respective acetylene and depends only to a smaller extent on the bulk of the aryl bromide substituents. In short: The higher the steric bulk of the arylacetylene, the lower is the bulk of the phosphine ligands (in the series $P\text{-}t\text{-}Bu_3$ to PCy_3) needed for the most efficient Sonogashira transformation. Electron-rich and sterically demanding aryl bromides require a considerably higher catalyst loading than for example bromobenzene.

In order to utilize the knowledge obtained in the present study for practical Sonogashira transformations, optimized procedures for various substituted arylacetylenes and substituted aryl bromides are also given in the Experimental Section.

Electronic Effect in Arylacetylenes. Electron-withdrawing substituents at the aryl halides accelerate cross-coupling reactions.[11b] The effect of such groups in the acetylenes on the Sonogashira coupling is less well studied. Martensson et al. suggested for copper-free Sonogashira reactions that different mechanisms are followed, depending on the electronic nature of the acetylene.[30] We tested the Sonogashira coupling of four substituted phenylacetylenes with electron-withdrawing and -donating substituents (Scheme 3).

The respective time−conversion data are plotted in Figure 12. The arylacetylene with the least electron-donating 4-R = CF_3 is rapidly converted into the respective tolane, producing the best chemical yields. With progressively stronger donating 4-R groups the reaction is more sluggish at the beginning and the conversion of the respective phenylacetylene is less efficient. The deprotonation of the acetylene may be a critical step at the beginning of the cross-coupling reaction. However, the use of other bases (Cs_2CO_3, LiN-$i\text{-}Pr_2$, KO-t-Bu, Na-amylate) did not lead to enhanced product formation. Interestingly, a combined experimental/theoretical study by Álvares, Maseras, Espinet et al. has shown that the coordination of acceptor olefins to Pd enhances the reductive elimination, while at the same time the oxidative addition is slowed down. Clearly a compromise between the two effects should be reached, but for aryl bromide cross coupling the oxidative addition tends to be less important, so this might well be an explanation for the observed effects with acetylenes.[31]

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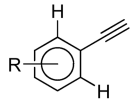
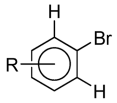
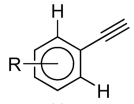
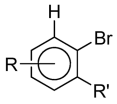
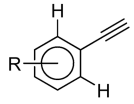
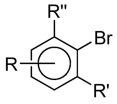
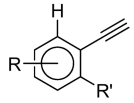
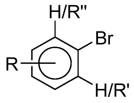
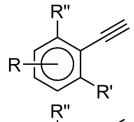
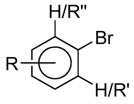
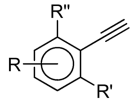
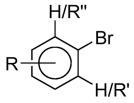
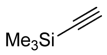
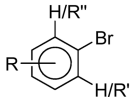
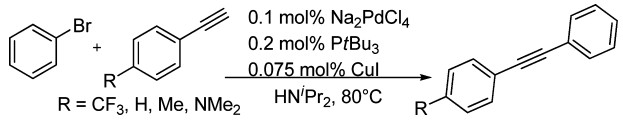
Table 1. Suitable Conditions for Pd-Catalyzed Sonogashira Coupling of Arylacetylenes or Me_3SiCCH with Aryl Bromides (R′, R″ ≠ H)[a]

aryl acetylene	aryl bromide	phosphine	[Pd]	time
		$PtBu_3$	0.1 mol%	2 h
		tBu_2PCy	0.25 mol%	2 h
		$tBuPCy_2$	0.25 mol%	6 h
		$tBuPCy_2$	0.25 mol%	2 h
		$tBuPCy_2$	0.5 mol%	4 h
 very bulky R′, R″		PCy_3	0.5 mol%	6 h
		$tBuPCy_2$	0.5 mol%	8 h

[a]Ratio of $Na_2PdCl_4/PR_3/CuI$ = 4:8:3; solvent/base: $HNi\text{-}Pr_2$, T = 80 °C, PR_3 used as $PR_3{\cdot}HBF_4$.

Scheme 3. Sonogashira Coupling Reactions with Electronically Variable Acetylenes



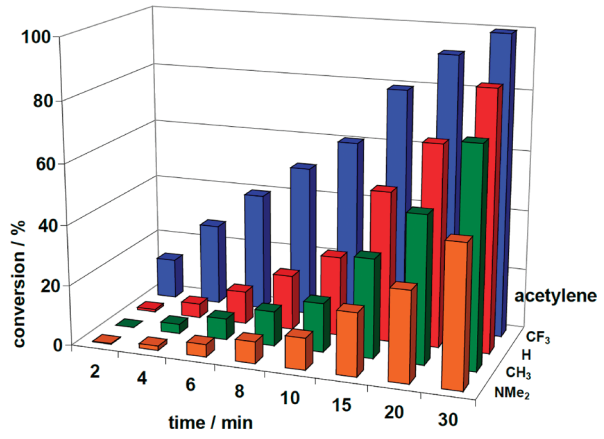
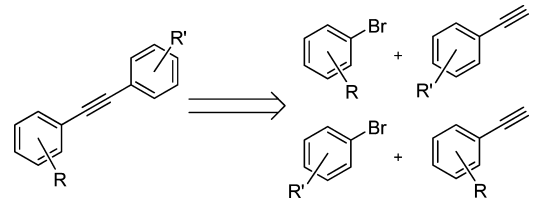


Figure 12. Sonogashira coupling of bromobenzene with arylacetylenes with ewg and edg substituents catalyzed by 0.1 mol % of Pd/P*t*-Bu_3.

Alternative Tolane Synthesis: Steric and Electronic Effects. In principle, the synthesis of unsymmetrical tolanes is possible by employing two different approaches (Scheme 4). From a synthetic point of view it is important to ask which of

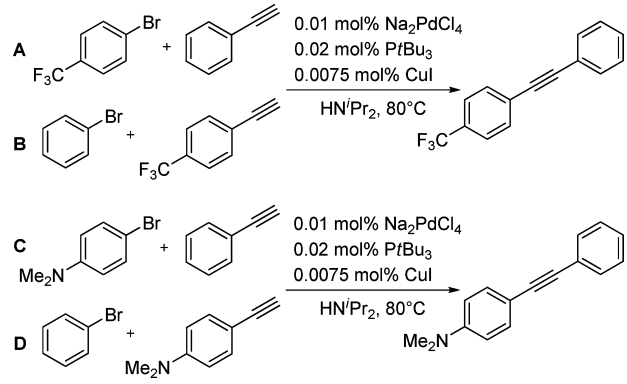
Scheme 4. Potential Sonogashira Routes to Tolanes



the two leads to better yields when R or R′ are sterically demanding or undemanding or when R or R′ possess electron-releasing or -donating character.

We first studied which of the two pairs of reactions (Scheme 5) leading to the same product is influenced more strongly by

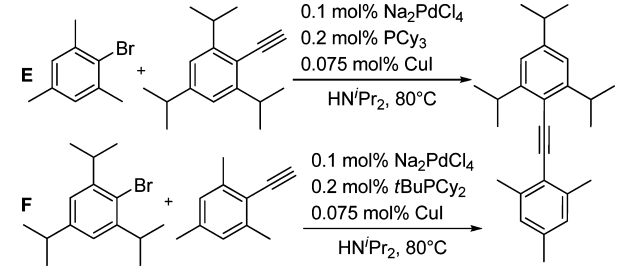
Scheme 5. Electronic Modifications of Substrates for Sonogashira Coupling



electronic effects. Electron-withdrawing groups are known to increase the reactivity of both substrates. Our experiments show that this acceleration is more pronounced for electron-withdrawing groups located at the arylacetylene. Reactions B (Scheme 5) reaches 85% conversion already after 240 min and reaction A only 18%; nonetheless, after 1200 min both reactions stall at ca. 90% conversion. For reactions C 97% yield is observed after 1440 min and with reaction D only 73%.

Next, the effect of steric bulk was tested in reactions outlined in Scheme 6. Steric bulk next to the bromo

Scheme 6. Synthesis of Tolanes with Bulky Substituents



substituents is more detrimental for the cross-coupling reaction than steric bulk at the acetylene. The conversion for reaction E is 90% after 20 h, while it is only 66% for reaction F after the same time period, when using different, but the "best", phosphines for the respective transformations. Again the choice of the phosphine determines the reactivity differences and under the best possible reaction condition (in the subset of reaction parameters

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tested here) the effect of steric bulk on the reaction is less pronounced in the arylacetylene.

Phosphines: Steric and Electronic Effects. Finally, the effect of variable electron donation on the catalytic activity of the respective palladium phosphine complexes was tested, using two different phosphines *t*-$Bu_2P(C_6H_4$-R) [17a] with R = 4-CF_3, 4-NMe_2. As expected, the time−conversion curves (Figure 13)

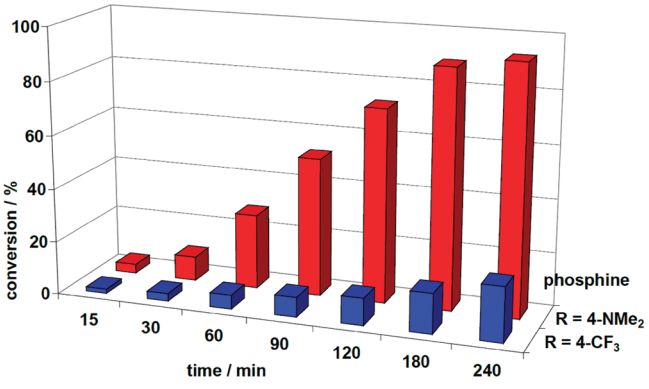

Figure 13. Electronic modification of the phosphine *t*-$Bu_2P(C_6H_4$-R) R = 4-CF_3 or 4-NMe_2 using 0.01 mol % of Pd/*t*-$Bu_2P(C_6H_4$-R) in the reaction of 4-tolyl bromide and mesitylacetylene.

for two Sonogashira reactions provide clear evidence for the higher reactivity of the more electron-rich phosphine.

CONCLUSIONS

Based on the screening of nearly 200 different Sonogashira reactions with systematically varied aryl bromides, arylacetylenes and Me_3SiCCH and phosphine ligands, a set of simple rules aiding such cross coupling reactions and the choice of the "ideal" substrate/catalyst combinations are reported. In general, the steric bulk of the phenylacetylene is the most important factor determining the choice of the "ideal" Pd/phosphine catalyst.

Electronic Effects of the Aryl Bromide Substituents. Electron-withdrawing groups at the aryl bromides accelerate the rate of the Sonogashira coupling. Such an electronic effect is more important than moderate steric bulk at the aryl bromide.

Steric Effects of the Aryl Bromide Substituents. The effect of steric bulk in 2-substituted aryl bromides on the rate of Sonogashira reactions is modest. For 2,6-substituted aryl bromides the steric effect is much more pronounced.

Electronic Effects of the Acetylene Substituents. Electron-withdrawing groups on the acetylene lead to an increase in the rate of the Sonogashira coupling. This rate acceleration is more pronounced for arylacetylenes than for aryl bromides with electron withdrawing substituents.

Steric Effects of the Acetylene Substituents. Moderate steric bulk at the arylacetylene is beneficial and leads to a significant increase in the rate of the Sonogashira reaction compared to phenylacetylene. However, this is only true, when the increase in the steric bulk of the acetylene is compensated by using progressively smaller phosphine ligands. There exists an ideal combination of steric bulk at the acetylene and the phosphine. Consequently, the nature of the acetylene determines the choice of the ideal phosphine for a Sonogashira coupling reaction. Bulky acetylenes require small phosphines, smaller acetylenes require larger phosphines. An unsymmetrical tolane with sterically demanding groups on one aryl ring is best synthesized by attaching bulky and/or electron-withdrawing groups on the arylacetylene.

Effects on the Initiation Period. The use of increasingly bulky acetylenes leads to significant initiation periods in the Sonogashira reaction. The formation of catalytically active Pd(0) complexes appears to rely primarily on the nature of the acetylene.

Choosing the Best Phosphine Ligand. The detailed investigation of substrate reactivity provides guidelines for efficient Sonogashira coupling reactions (Table 1): (a) reactions of arylacetylenes (no ortho-substituents other than H) with aryl bromides (no ortho-substituents other than H) are best done with a Pd/*t*-Bu_3P catalyst; (b) reactions of arylacetylenes (no ortho-substituents other than H) with aryl bromides (bulky ortho-substituents) are best done with Pd/*t*-Bu_2PCy or with Pd/*t*-$BuPCy_2$; (c) reactions of 2-substituted arylacetylenes and aryl bromides are best done with Pd/*t*-$BuPCy_2$; (d) reactions of 2,6-disubstituted arylacetylenes and aryl bromides are best done with Pd/*t*-$BuPCy_2$; (e) reactions of 2,6-disubstituted arylacetylenes (very bulky ortho-substituents) and aryl bromides are best done with Pd/PCy_3; (f) reactions of Me_3SiCCH with aryl bromides are best done with Pd/*t*-$BuPCy_2$.

EXPERIMENTAL SECTION

General Experimental Methods. All chemicals were purchased as reagent grade and used without further purification unless otherwise noted. All reactions were performed under an atmosphere of argon using the standard Schlenk technique. Solvents for syntheses were dried using a column purification system. HN-*i*-Pr_2 was dried using CaH_2, distilled prior to use, and degassed three times using a "freeze and thaw" technique. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded at 300 MHz (^{1}H), 75 MHz (^{13}C), and 121 MHz (^{31}P) or at 500 MHz (^{1}H), 126 MHz (^{13}C), and 202 MHz (^{31}P), respectively. Chemical shifts are given in parts per million (ppm) on the delta scale (δ) and are referred either to tetramethylsilane (^{1}H-; ^{13}C NMR = 0 ppm) or the residual solvent peak. ^{31}P NMR was referred to H_3PO_4 (65% aq. = 0 ppm). Thin layer chromatography (TLC) was performed using silica gel 60 F 254 (0.2 mm) on alumina plates. For preparative chromatography silica gel 60 (0.063−0.20 mesh) was used.

2-Bromotoluene, 1-bromo-2-ethylbenzene, 1-bromo-2-isopropylbenzene, and 2-bromo-*m*-xylene as well as 1-bromomesitylene were available from commercial sources. 1-Bromo-2,4,6-triethylbenzene and 1-bromo-2,4,6-triisopropylbenzene were prepared according to literature procedures.[32] The phosphines used were purchased and converted into the respective phosphonium tetrafluoroborates with $HBF_4{\cdot}Et_2O$.

Gas Chromatography. A chromatograph with a split/splitless injector system and FID was used. Chromatographic separation was performed by using a 15 m × 0.25 mm Varian CP-Sil 8 CB column (d_f = 1.0 μm) and nitrogen used as carrier gas at a flow rate of 0.35 mL·min^{-1}. All injections were carried out in the split flow mode with a split ratio of 20:1. The injector was maintained at a temperature of 300 °C and the detector at 350 °C. Quantification was accomplished by using dibenzofuran and mesitylene as internal standards, the concentration of the standard was equal to each of the substrates in the screening reactions. Details concerning chromatographic separation (temperature programming, retention times) of the reactants as well as the products are given below.

GC Temperature Programming for Compound Separation. In the Me_3SiCCH screen the following program was used: 100 °C for 1 min, heating to 262 °C at a rate of 15 °C min^{-1}, hold 0 min and finally heating to 310 °C at a rate of 35 °C min^{-1}, hold isotherm for 0 min (total runtime is 13.17 min). In the phenylacetylene screen the following program was used: 100 °C for 1 min, heating to 262 °C at a rate of 15 °C min^{-1}, hold 0 min and finally heating to 310 °C at a rate of 35 °C min^{-1}, hold isotherm for 3 min (total runtime is 16.17 min).

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In the mesitylacetylene screen the final isotherm was extended to 6 min (total runtime is 19.17 min), in the 1-ethynyl-2,4,6-triethylbenzene screen to 9 min (total runtime is 22.17 min) and in the 1-ethynyl-2,4,6-triisopropylbenzene screen to 12 min (total runtime is 25.17 min). In the 1-ethynyl-2-ethylbenzene screen the following program was used: 150 °C for 0 min, heating to 200 °C at a rate of 10 °C min^{-1}, hold 5 min, heating to 262 °C at a rate of 10 °C min^{-1}, hold 5 min and finally heating to 310 °C at a rate of 35 °C min^{-1}, hold isotherm for 4 min (total runtime is 21.90 min).

Sonogashira Coupling Reactions. *Catalyst Stock Solution.* Na_2PdCl_4 (17.7 mg; 60 μmol), CuI (8.6 mg; 45 μmol) and the respective trialkylphosphonium tetrafluoroborate salt (120 μmol) were placed in an oven-dried Schlenk tube, evacuated, and backfilled with argon three times. Subsequently, HN-*i*-Pr_2 (15 mL) was added and the resulting mixture stirred at 40 °C for 60 min. After the mixture was cooled to room temperature, the formed salt was filtered off. The resulting solution had a concentration of 4 μmol Pd/mL. Two hundred and fifty microliters of this solution correspond to a catalyst loading (Pd/phosphine/CuI = 4:8:3) of 0.1 mol % in the screening reactions with a total aryl bromide loading of 1 mmol.

Aryl Bromide Stock Solution. Aryl bromides were weighed with the appropriate amount of the internal GC-standard and subsequently filled up with HN-*i*-Pr_2 to reach the desired concentration. The concentration for the aryl bromide stock solution was 1 mmol/mL for the sum of all components and $(n(components)\ M)^{-1}$ for dibenzofuran as internal GC standard.

Sonogashira Screening Reactions. A mixture of the aryl bromide stock solution (1000 μL, 1 mmol) and the respective catalyst stock solution (250 μL, 1 μmol, 0.1 mol %) in HN-*i*-Pr_2 (5000 μL) was degassed using a "freeze and thaw" technique and then heated to 80 °C under vigorous stirring for 10 min. Initiation of the reaction is done by the addition of 1.05 mmol (1.05 equivs) of the respective alkyne. The precipitation of H_2N-*i*-Pr_2Br indicates the start of the reaction, and GC samples were taken at given times.

Sonogashira Reactions of Substituted Acetylenes with Aryl Bromides (General Procedure). Na_2PdCl_4 (7.1 mg, 0.025 mmol), 0.05 mmol of the respective phosphonium salt, and CuI (3.6 mg, 0.019 mmol) were weighed in an oven-dried two-necked Schlenk-flask equipped with a reflux condenser. HN-*i*-Pr_2 (50 mL) was transferred to the flask via cannula. The respective *ortho*-alkylated aryl bromide (10 mmol) was transferred to the flask with a syringe and the mixture carefully degassed via "freeze and thaw" technique. After being warmed to rt, the mixture was warmed and stirred at 80 °C for 10 min and 1.05 equiv of the respective acetylene added via syringe. The precipitation of H_2N-*i*-Pr_2Br and a darkening of the reaction mixture indicated the onset of the reaction, and stirring was continued for the appropriate time (see Table 1). After the mixture was cooled to room temperature, the precipitate was separated via suction filtration (glass frit G4) and washed twice with HN*i*-Pr_2. The volatiles are evaporated in vacuo. The residue is purified by column chromatography using cyclohexane/ethyl acetate mixtures as the eluent.

Following this general procedure, the respective coupling products were obtained in yields of 70−98% yield (Supporting Information). Table 1 shows the recommended acetylene/phosphine combinations and catalyst loadings for certain substrate combinations, which were applied for the products reported here.

Data for previously unknown Sonogashira products are listed below:

1,3,5-Triethyl-2-(phenylethynyl)benzene. This compound was isolated from the reaction of 1-bromo-2,4,6-triethylbenzene with phenylacetylene (0.25 mol % Pd/*t*-BuPCy_2) according to the general procedure as a colorless oil (yield 69%, 362 mg): ^{1}H NMR ($CDCl_3$) δ 7.57−7.54 (m, 2H), 7.40−7.31 (m, 3H), 6.96 (s, 2H), 2.91 (q, *J* = 7.6 Hz, 4H), 2.66 (q, *J* = 7.6 Hz, 2H), 1.34 (t, *J* = 7.6 Hz, 6H), 1.28 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 146.7, 144.7, 131.4, 128.5, 128.0, 125.2, 124.3, 118.9, 96.3, 87.1, 29.1, 28.3, 15.6, 15.1; HRMS (EI) for $C_{20}H_{22}$ (M^+) calcd 262.1721, found 262.17034.

1,3,5-Trimethyl-2-[(2-methylphenyl)ethynyl]benzene. This compound was isolated from the reaction of 2-bromotoluene with mesitylacetylene (0.5 mol % Pd/*t*-BuPCy_2) according to the general procedure as a white solid (yield: 93%, 651 mg): ^{1}H NMR ($CDCl_3$) δ 7.55 (d/d, *J* = 6.8/1.5 Hz, 1H), 7.29 − 7.18 (m, 3H), 6.94 (d, *J* = 0.6 Hz, 2H), 2.57 (s, 3H), 2.53 (s, 6H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 140.2, 139.8, 137.8, 131.9, 129.6, 128.1, 127.8, 125.7, 124.0, 120.5, 96.3, 91.5, 21.5, 21.3, 21.2; HRMS (EI) for $C_{18}H_{18}$ (M^+) calcd 234.1408, found 234.13989; mp 38−39 °C.

1,3,5-Trimethyl-2-[(2-ethylphenyl)ethynyl]benzene. This compound was isolated from the reaction of 1-bromo-2-ethylbenzene with mesitylacetylene (0.5 mol % Pd/*t*-BuPCy_2) according to the general procedure as a colorless oil (yield 85%, 422 mg): ^{1}H NMR ($CDCl_3$) δ 7.52−7.49 (d/t, *J* = 7.5/1.0 Hz, 1H), 7.27−7.13 (m, 3H), 6.89 (d, *J* = 0.6 Hz, 2H), 2.90 (q, *J* = 7.6 Hz, 2H), 2.48 (s, 6H), 2.28 (s, 3H), 1.29 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 145.8, 140.2, 137.8, 132.3, 128.3, 128.2, 127.8, 125.8, 123.3, 120.5, 96.0, 91.0, 28.1, 21.5, 21.2, 15.2; HRMS (EI) for $C_{19}H_{20}$ (M^+) calcd 248.1565, found 248.15365.

1,3,5-Trimethyl-2-[(2-isopropylphenyl)ethynyl]benzene. This compound was isolated from the reaction of 1-bromo-2-isopropylbenzene with mesitylacetylene (0.5 mol % Pd/*t*-BuPCy_2) according to the general procedure as a colorless oil (yield 94%, 491 mg): ^{1}H NMR ($CDCl_3$) δ 7.58−7.54 (m, 1H), 7.36−7.29 (m, 2H), 7.23−7.17 (m, 1H), 6.94 (d, *J* = 0.6 Hz, 2H), 3.66 (sept, *J* = 6.9 Hz, 1H), 2.53 (s, 6H), 2.33 (s, 3H), 1.35 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 150.1, 140.2, 137.8, 132.5, 128.5, 127.8, 125.7, 125.0, 123.0, 120.5, 96.1, 91.3, 31.8, 23.3, 21.5, 21.2; HRMS (EI) for $C_{20}H_{22}$ (M^+) calcd 262.1721, found 262.16913.

2-((2,6-Dimethylphenyl)ethynyl)-1,3,5-trimethylbenzene. This compound was isolated from the reaction of 2-bromo-*m*-xylene with mesitylacetylene (0.5 mol % Pd/*t*-BuPCy_2) according to the general procedure as a white solid (yield 81%, 402 mg): ^{1}H NMR ($CDCl_3$) δ 7.18−7.10 (m, 3H), 6.95 (d, *J* = 0.6 Hz, 2H), 2.58 (s, 6H), 2.55(s, 6H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 140.1, 137.8, 127.8, 127.6, 126.9, 124.0, 120.8, 96.2, 95.2, 21.8, 21.6, 21.5; HRMS (EI) for $C_{19}H_{20}$ (M^+) calcd 248.1565, found 248.15380; mp 89−90 °C.

1,3,5-Triethyl-2-[(2,4,6-trimethylphenyl)ethynyl]benzene. This compound was isolated from the reaction of 1-bromo-2,4,6-triethylbenzene with mesitylacetylene (0.5 mol % Pd/*t*-BuPCy_2) according to the general procedure as a white solid (yield 82%, 749 mg): ^{1}H NMR ($CDCl_3$) δ 6.99 (s, 2H), 6.95 (d, *J* = 0.6 Hz, 2H), 2.96 (q, *J* = 7.6 Hz, 4H), 2.67 (q, *J* = 7.6 Hz, 2H), 2.54 (s, 6H), 2.34 (s, 3H), 1.34 (t, *J* = 7.6 Hz, 6H), 1.29 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 146.4, 144.4, 140.1, 137.6, 127.8, 125.2, 121.1, 119.7, 94.7, 94.27, 29.1, 28.5, 21.4, 15.6, 15.4; HRMS (EI) for $C_{23}H_{28}$ (M^+) calcd 304.2191, found 304.21780; mp 76−77 °C.

1,3,5-Triisopropyl-2-[(2,4,6-trimethylphenyl)ethynyl]benzene. This compound was isolated from the reaction of 1-bromo-2,4,6-triisopropylbenzene with mesitylacetylene (0.5 mol % Pd/*t*-BuPCy_2) according to the general procedure as a white solid (yield: 75%, 778 mg). The isolated yield is significantly lower than in the multisubstrate screen, since the enyne byproduct is difficult to separate by chromatography: ^{1}H NMR ($CDCl_3$) δ 7.06 (s, 2H), 6.94 (d, *J* = 0.5 Hz, 2H), 3.74 (sept, *J* = 6.9 Hz, 2H), 2.95 (sept, *J* = 6.9 Hz, 1H), 2.53 (s, 6H), 2.33 (s, 3H), 1.34 (d, *J* = 6.9 Hz, 12H), 1.30 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 150.5, 149.1, 140.1, 137.6, 127.9, 121.1, 120.4, 119.4, 94.8, 94.5, 34.7, 32.0, 24.1, 23.6, 21.4; HRMS (EI) for $C_{26}H_{34}$ (M^+) calcd 346.266, found 346.26818; mp 84−85 °C.

2-[(2-Ethylphenyl)ethynyl]-1,3-dimethylbenzene. This compound was isolated from the reaction of 2-bromo-*m*-xylene with 1-ethyl-2-ethynylbenzene (0.25 mol % Pd/*t*-BuPCy_2) according to the general procedure as a slight yellow oil (yield: 90%, 420 mg): ^{1}H NMR ($CDCl_3$) δ 7.56−7.53 (m, 1H), 7.28−7.06 (m, 6H), 2.93 (q, *J* = 7.6 Hz, 2H), 2.54 (s, 6H), 1.31 (d, *J* = 7.6 Hz, 3H), 1.26 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 145.9, 140.3, 132.4, 128.5, 128.2, 127.8, 126.9, 125.8, 123.5, 123.1, 96.8, 90.7, 28.1, 21.4, 15.3; HRMS (EI) for $C_{18}H_{18}$ (M^+) calcd 234.1408, found 234.14032.

2-((2,6-Dimethylphenyl)ethynyl)-1,3,5-triisopropylbenzene. This compound was isolated from the reaction of 2-bromo-*m*-xylene with 1-ethynyl-2,4,6-triisopropylbenzene (0.5 mol % Pd/PCy_3) according to the general procedure as a slight yellow oil (yield: 70%, 491 mg). The isolated yield is significantly lower than in the multisubstrate

screen, since the enyne byproduct is difficult to separate by chromatography: ^{1}H NMR ($CDCl_3$) δ 7.18−7.09 (m, 3H), 7.07 (s, 2H), 3.75 (sept, J = 6.8 Hz, 2H), 2.95 (sept, J = 6.9 Hz, 1H), 2.57 (s, 6H), 1.35 (d, J = 6.8 Hz, 12H), 1.31 (d, J = 6.9 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 150.6, 149.3, 140.2, 127.6, 127.0, 124.1, 120.4, 119.2, 95.3, 94.6, 34.7, 32.0, 24.1, 23.7, 21.5; HRMS (EI) for $C_{25}H_{32}$ (M^+) calcd 332.2504, found 332.25207.

Trimethyl[(2,4,6-triisopropylphenyl)ethynyl]silane. This compound was isolated from the reaction of 1-Bromo-2,4,6-triisopropylbenzene with trimethylsilylacetylene (0.5 mol % Pd/*t*-BuPCy$_2$) according to the general procedure as pale yellow crystals (yield: 72%, 4.47 g): ^{1}H NMR ($CDCl_3$) δ 6.97 (s, 2H), 3.52 (sept, J = 6.8 Hz, 2H), 2.89 (sept, J = 6.9 Hz, 1H), 1.28 (d, J = 6.8 Hz, 12H), 1.26 (d, J = 6.9 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 151.2, 149.4, 120.3, 118.7, 102.9, 101.9, 34.7, 31.9, 24.1, 23.3, 0.2; HRMS (EI) for $C_{20}H_{32}Si$ (M^+) calcd 300.2273, found 300.22474; mp 58−59 °C.

Synthesis of Known Arylacetylenes Synthesized According to the General Procedure. *1-Methyl-2-(phenylethynyl)-benzene.*[7d] This compound was isolated from the reaction of 2-bromotoluene with phenylacetylene (0.25 mol % Pd/*t*-Bu$_2$PCy) according to the general procedure as yellow oil, which solidified on standing (yield 97%). **1-Ethyl-2-(phenylethynyl)benzene.**[33] This compound was isolated from the reaction of 1-bromo-2-ethylbenzene with phenylacetylene (0.25 mol % Pd/*t*-Bu$_2$PCy) according to the general procedure as colorless oil (yield 87%). **1-Isopropyl-2-(phenylethynyl)benzene.**[34] This compound was isolated from the reaction of 1-bromo-2-isopropylbenzene with phenylacetylene (0.25 mol % Pd/*t*-Bu$_2$PCy) according to the general procedure as colorless oil (yield 91%).[7d] This compound was isolated from the reaction of 2-bromo-*m*-xylene with phenylacetylene (0.25 mol % Pd/*t*-BuPCy$_2$) according to the general procedure as colorless oil (yield 86%). **1,3,5-Trimethyl-2-(phenylethynyl)benzene.**[35] This compound was isolated from the reaction of 2-bromomesitylene with phenylacetylene (0.25 mol % Pd/*t*-BuPCy$_2$) according to the general procedure as a white solid (yield 74%). **1,3,5-Triisopropyl-2-(phenylethynyl)-benzene.**[36] This compound was isolated from the reaction of 1-bromo-2,4,6-triisopropylbenzene with phenylacetylene (0.25 mol % Pd/*t*-BuPCy$_2$) according to the general procedure as a colorless oil (yield 69%). The isolated yield is lower than GC conversion, since the enyne byproduct is difficult to separate by chromatography. **1,1′-Ethyne-1,2-diylbis(2,4,6-trimethylbenzene).**[37] This compound was isolated from the reaction of 2-bromomesitylene with mesitylacetylene (0.5 mol % Pd/*t*-BuPCy$_2$) according to the general procedure as a white solid (yield 83%). **Trimethyl(*o*-tolylethynyl)silane.**[38] This compound was isolated from the reaction of 2-bromotoluene with trimethylsilylacetylene (0.5 mol % Pd/*t*-BuPCy$_2$) according to the general procedure as yellow oil (yield 91%). **(2-Ethylphenyl)ethynyltrimethylsilane.**[39] This compound was isolated from the reaction of 1-bromo-2-ethylbenzene with trimethylsilylacetylene (0.5 mol % Pd/*t*-BuPCy$_2$) according to the general procedure as yellow oil (yield 88%).

■ ASSOCIATED CONTENT

Supporting Information

Documentation of synthetic work, gas chromatographic measurements, and selected chromatograms; copies of NMR spectra and high-resolution mass spectrometry. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Chinchilla, R.; Najera, C. *Chem. Rev.* **2007**, *107*, 874−922. (b) Doucet, H.; Hierso, J.-C. *Angew. Chem., Int. Ed.* **2007**, *46*, 834−871. (c) Plenio, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6954−6956. (d) Chinchilla, R.; Najera, C. *Chem. Soc. Rev.* **2011**, *40*, 5084−5121. (e) Jenny, N. M.; Mayor, M.; Eaton, T. R. *Eur. J. Org. Chem.* **2011**, *2011*, 4965−4983.

(2) (a) Lauterbach, T.; Livendahl, M.; Rosellón, A.; Espinet, P.; Echavarren, A. M. *Org. Lett.* **2010**, *12*, 3006−3009. (b) Gonda, Z.; Tolnai, G. L.; Novák, Z. *Chem.—Eur. J.* **2010**, *16*, 11822−11826. (c) Leadbeater, N. E. *Nature Chem.* **2010**, *2*, 1007−1009.

(3) Dudnik, A. S.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2010**, *49*, 2096−2098.

(4) (a) Matsuyama, N.; Kitahara, M.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 2358−2361. (b) Kim, S. H.; Chang, S. *Org. Lett.* **2010**, *12*, 1868−1871. (c) Brand, J. P.; Charpentier, J.; Waser, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 9346−9349.

(5) Nie, X.; Liu, S.; Zong, Y.; Sun, P.; Bao, J. *J. Organomet. Chem.* **2011**, *696*, 1570−1573.

(6) (a) Tougerti, A.; Negri, S.; Jutand, A. *Chem.—Eur. J.* **2007**, *13*, 666−676. (b) Amatore, C.; Bensalem, S.; Ghalem, S.; Jutand, A.; Medjour, Y. *Eur. J. Org. Chem.* **2004**, 366−371. (c) Vikse, K. L.; Henderson, M. A.; Oliver, A. G.; McIndoe, J. S. *Chem. Commun.* **2010**, *46*, 7412−7414.

(7) (a) Brenstrum, T.; Gerristma, D. A.; Adjabeng, G. M.; Frampton, C. S.; Britten, J.; Robertson, A. J.; McNulty, J.; Capretta, A. *J. Org. Chem.* **2004**, *69*, 7635−7639. (b) Lipshutz, B. H.; Chung, D. W.; Rich, B. *Org. Lett.* **2008**, *10*, 3793−3796. (c) Hundertmark, T.; Littke, A. F.; Buchwald, S. L.; Fu, G. C. *Org. Lett.* **2000**, *2*, 1729−1731. (d) Köllhofer, A.; Plenio, H. *Adv. Synth. Catal.* **2005**, *347*, 1295−1300. (e) Hierso, J.-C.; Beauperin, M.; Meunier, P. *Eur. J. Inorg. Chem.* **2007**, *24*, 3767−3780. (f) Hierso, J.-C.; Fihri, A.; Amardeil, R.; Meunier, P.; Doucet, H.; Santelli, M.; Ivanov, V. V. *Org. Lett.* **2004**, *6*, 3473−3476. (g) Torborg, C.; Zapf, A.; Beller, M. *Chem. Sus. Chem.* **2008**, *1*, 91−96. (h) Lee, D.-H.; Qiu, H.; Cho, M.-H.; Lee, I.-M.; Jin, M.-J. *Synlett* **2008**, 1657−1660. (i) Bolliger, J. L.; Frech, C. M. *Adv. Synth. Catal.* **2009**, *351*, 891−902. (j) Roy, S.; Plenio, H. *Adv. Synth. Catal.* **2010**, *352*, 1014−1022. (k) Fleckenstein, C. A.; Plenio, H. *Organometallics* **2007**, *26*, 2758−2767. (l) Fleckenstein, C. A.; Plenio, H. *Organometallics* **2008**, *27*, 3924−3932. (m) Feuerstein, M.; Doucet, H.; Santelli, M. *J. Mol. Catal. A: Chem.* **2006**, *256*, 75−84. (n) Nishihara, Y.; Inoue, E.; Okada, Y.; Takagi, K. *Synlett* **2008**, *19*, 3041−3045. (o) Moon, J.; Jeong, M.; Nam, H.; Ju, J.; Moon, J. H.; Jung, H. M.; Lee, S. *Org. Lett.* **2008**, *10*, 945−948. (p) Fleckenstein, C. A.; Plenio, H. *Green Chem.* **2008**, *10*, 563−570. (q) Severin, R.; Reimer, J.; Doye, S. *J. Org. Chem.* **2010**, *75*, 3518−3521. (r) Hillerich, J.; Plenio, H. *Chem. Commun.* **2003**, 3024−3025.

(8) (a) Köllhofer, A.; Pullmann, T.; Plenio, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 1056−1058. (b) Fleckenstein, C. A.; Plenio, H. *Chem.—Eur. J.* **2007**, *13*, 2701−2716. (c) Torborg, C.; Huang, J.; Schulz, T.; Schäffner, B.; Zapf, A.; Spannenberg, A.; Börner, A.; Beller, M. *Chem.—Eur. J.* **2009**, *15*, 1329−13363. (d) Komáromi, A.; Novák, Z. *Chem. Commun.* **2008**, 4968−4970. (e) Gelman, D.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 5993−5996. (f) Jin, M.-J.; Lee, D.-H. *Angew. Chem., Int. Ed.* **2010**, *49*, 1119−1122. (g) Lee, D.-H.; Kwon, Y.-J.; Jin, M.-J. *Adv. Synth. Catal.* **2011**, *353*, 3090−3094.

(9) (a) Christmann, U.; Vilar, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 366−374. (b) Barrios-Landeros, F.; Carrow, B. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 8141−8154. (c) Li, Z.; Fu, Y.; Guo, Q.-X.; Liu, L. *Organometallics* **2008**, *27*, 4043−4049.

(10) Hartwig, J. F. *Inorg. Chem.* **2007**, *46*, 1936−1947.

(11) (a) Clarke, M. L.; Frew, J. J. R. *Organomet. Chem.* **2009**, *35*, 19−46. (b) Fleckenstein, C. A.; Plenio, H. *Chem. Soc. Rev.* **2010**, *39*, 694−711.
(12) Fey, N.; Orpen, A. G.; Harvey, J. N. *Coord. Chem. Rev.* **2009**, *253*, 704−722.
(13) Harper, K. C.; Sigman, M. S. *Science* **2011**, *333*, 1875−1878.
(14) Shaughnessy, K. H.; Kim, P.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 2123−2132.
(15) an der Heiden, M. R.; Plenio, H.; Immel, S.; Burello, E.; Rothenberg, G.; Hoefsloot, H. C. J. *Chem.—Eur. J.* **2008**, *14*, 2857−2866.
(16) (a) O'Brien, C. J.; Kantchev, E. A. B.; Chass, G. A.; Hadei, N.; Hopkinson, A. C.; Organ, M. G.; Setiadi, D. H.; Tang, T.-H.; Fang, D.-C. *Tetrahedron* **2005**, *61*, 9723−9735. (b) Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Org. Lett.* **2005**, *7*, 1991−1994. (c) Nasielski, J.; Hadei, N.; Achonduh, G.; Kantchev, E. A. B.; O'Brien, C. J.; Lough, A.; Organ, M. G. *Chem.—Eur. J.* **2010**, *16*, 10844−10853. (d) Organ, M. G.; Abdel-Hadi, M.; Avola, S.; Dubovyk, I.; Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Sayah, M.; Valente, C. *Chem.—Eur. J.* **2008**, *14*, 2443−2452.
(17) (a) Guram, A. S.; King, A. O.; Allen, J. G.; Wang, X.; Schenkel, L. B.; Chan, J.; Bunel, E. E.; Faul, M. M.; Larsen, R. D.; Martinelli, M. J.; Reider, P. J. *Org. Lett.* **2006**, *8*, 1787−1789. (b) Guram, A. S.; Wang, X.; Bunel, E. E.; Faul, M. M.; Larsen, R. D.; Martinelli, M. J. *J. Org. Chem.* **2007**, *72*, 5104−5112.
(18) Fleckenstein, C. A.; Plenio, H. *Chem.—Eur. J.* **2008**, *14*, 4267−4279.
(19) Ljungdahl, T.; Pettersson, K.; Albinsson, B.; Martensson, J. *J. Org. Chem.* **2006**, *71*, 1677−1687.
(20) an der Heiden, M.; Plenio, H. *Chem. Commun.* **2007**, 972−974.
(21) There is an important difference with respect to the previous study: Earlier we focussed on low catalyst loading, this time we took a more practical approach and optimized for faster substrate conversion.
(22) Satyanarayana, T.; Kagan, H. B. *Adv. Synth. Catal.* **2005**, *347*, 737−748.
(23) The 0.1 mol % [Pd] of catalyst used is relative to the acetylene and to the sum of the seven aryl bromides.
(24) For 1-ethynyl-2,4,6-trimethylbenzene and 1-ethynyl-2,4,6-triethylbenzene a short inhibition period was not taken into account for the exponential fit. The time was set to zero after the initiation period at the onset of the Sonogashira conversion.
(25) Hansch, C.; Leo, A. In *Exploring QSAR: Fundamentals and Applications in Chemistry and Biology*; Heller, S. R., Ed.; American Chemical Society: Washington, DC, 1995; pp 69−96.
(26) Li, H.; Grasa, G. A.; Colacot, T. J. *Org. Lett.* **2010**, *12*, 3332−3335.
(27) *Greene's Protective Groups in Organic Synthesis*, 4th ed.; Wuts, P. G. M., Green, T. W., Eds.; Wiley-VCH: Weinheim, 2006.
(28) The reaction temperature was lowered to 50 °C because of the low bp of trimethylsilylacetylene; otherwise, a significant loss of this substrate during the probe sampling might have taken place.
(29) The prounced steric bulk of Me_3SiCCH also results in a significant inhibition period (ca. 30 min) during which no substrate conversion is observed.
(30) Ljungdahl, T.; Bennur, T.; Dallas, A.; Emtenäs, H.; Martensson, J. *Organometallics* **2008**, *27*, 2490−2498.
(31) Pérez-Rodríguez, M.; Braga, A. A. C.; Garcia-Melchor, M.; Pérez-Temprano, M. H.; Casares, J. A.; Ujaque, G.; de Lera, A. R.; Álvarez, R.; Maseras, F.; Espinet, P. *J. Am. Chem. Soc.* **2009**, *131*, 3650−3657.
(32) (a) Fuson, R. C.; Corse, J. *J. Am. Chem. Soc.* **1938**, *60*, 2063−2066. (b) Whitesides, G. M.; Eisenhut, M.; Bunting, W. M. *J. Am. Chem. Soc.* **1974**, *96*, 5398−5407.
(33) Maji, M. S.; Murarka, S.; Studer, A. *Org. Lett.* **2010**, *12*, 3878−3881.
(34) Komáromi, A.; Tolnai, G. L.; Novák, Z. *Tetrahedron Lett.* **2008**, *49*, 7294−7298.
(35) Adjabeng, G.; Brenstrum, T.; Frampton, C. S.; Robertson, A. J.; Hillhouse, J.; McNulty, J.; Capretta, A. *J. Org. Chem.* **2004**, *69*, 5082−5086.
(36) Feuerstein, M.; Berthiol, F.; Doucet, H.; Santelli, M. *Synthesis* **2004**, *8*, 1281−1289.
(37) Park, K.; Bae, G.; Moon, J.; Choe, J.; Song, K. H.; Lee, S. *J. Org. Chem.* **2010**, *75*, 6244−6251.
(38) Panda, J.; Virkler, P. R.; Detty, M. R. *J. Org. Chem.* **2003**, *68*, 1804−1809.
(39) Koumbis, A.; Kyzas, C.; Savva, A.; Varvoglis, A. *Molecules* **2005**, *10*, 1340−1350.