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The Gold-Catalyzed Hydroarylation of Alkynes with Electron-Rich Heteroarenes – A Kinetic Investigation and New Synthetic Possibilities

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Abstract: The gold-catalyzed mono-hydroarylation and two-fold hydroarylation of alkynes with electron-rich heteroarenes was analyzed by a ^{1}H NMR kinetic study. The obtained rate constants for the decreasing alkyne concentration provide information on the reactivity of this addition reaction. The examinations show the orthogonal reactivity of gold and a proton for the two reaction steps. The first hydroarylation is exclusively promoted by gold(I), whereas the second step is premised on a proton which will be reversibly derived from the formation of σ,π-acetylide complexes from the terminal alkynes or by interaction with solvents. Based on kinetic data, it was possible to synthesize a large range of mono-adducts in moderate to good yields, furthermore the synthesis of hetero-di-adducts, bearing two different substituents, was explored.

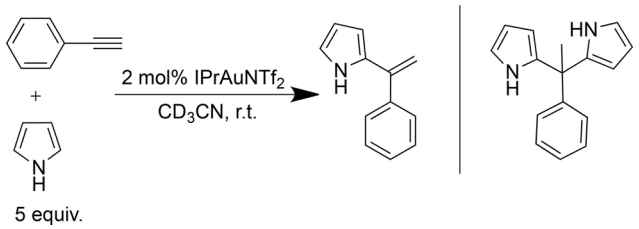
Keywords: gold catalysis; hydroarylation; kinetic studies; nucleophilicity scale; proton catalysis

Introduction

In heterocyclic chemistry, the functionalization of electron-rich heteroarenes, especially of simple nitrogen heterocycles receives significant attention due to their relevance as pharmaceutical agents and natural products.[1] During the last two decades, the interest in the direct catalytic intermolecular hydroarylation, a highly atom-economical process that adds an aryl- or heteroaryl-H bond to an unsaturated C–C bond, has arisen. π-Acidic metal catalysts such as ruthenium,[2] rhodium,[3] palladium,[4] platinum,[5] nickel,[6] gold[7] as well as gallium[8] and indium[9] promote the transformation. In the majority of cases the metal-catalyzed hydroarylation reaction delivers the mono-adduct. However, the gold-catalyzed addition reaction of electron-rich heteroarenes to terminal alkynes provides only the product of di-addition.[7] For example, Luo et al. reported on the gold-catalyzed two-fold hydroarylation of terminal alkynes with heterocyclic compounds like pyrroles, indoles, furans and thiophenes.[7b] In 2007, Echavarren et al. observed the gold-catalyzed mono-hydroarylation reaction of alkynes and indoles.[7e] No detailed studies regarding the kinetics of the gold-catalyzed transformation have been reported to date. The mechanistic details were recently determined theoretically by DFT calculations,[10] however, without any experimental proof. This encouraged us to shed light on the kinetics of these transformations with the aim to obtain further mechanistic details as well as the possibility to extend the synthetic scope of this useful reaction. The results of our study are summarized in this contribution.

Results and Discussion

The addition reaction of pyrrole to phenylacetylene was chosen as a test reaction. In order to exclude possible reactions without the catalyst, pyrrole was reacted with phenylacetylene. As expected no reaction was observed both without any catalyst and even in the presence of 5 mol% of trifluoromethanesulfonimide. Since an exclusion of water is not necessary in gold catalysis, a potential addition of water to phenylacetylene and a subsequent addition or condensation of/with the pyrrole was investigated by reactions of acetophenone with pyrrole with added $IPrAuNTf_2$ as catalyst, again no reaction was observed. $IPrAuNTf_2$, which is known in the literature to be a highly efficient and regio-selective catalyst, was used as benchmark system.[11] For the hydroarylation reaction one



Scheme 1. Gold-catalyzed alkyne hydroarylation with electron-rich heteroarenes.

equivalent of phenylacetylene was treated with five equivalents of freshly distilled pyrrole and 2 mol% $IPrAuNTf_2$ in acetonitrile-d_3 at 25 °C (Scheme 1).

The heteroarene was added in excess, otherwise only a partial conversion of the alkyne was observed. Furthermore, the mechanism[7b] postulated in the literature is based on the use of at least two equivalents of pyrrole, too. The reaction kinetics were observed by GC first. One equivalent of phenylacetylene was treated with five equivalents of pyrrole and 2 mol% of $IPrAuNTf_2$ using *n*-dodecane as internal standard. To stop the reaction at a certain point of time, the catalyst was quickly removed by filtration over silica gel. Within nine hours, 22 samples were isolated and analyzed by gas chromatography (Figure 1).

Due to the higher precision of NMR kinetics and higher resolution in time, the further kinetic measurements were conducted by *in situ* monitoring with ^{1}H NMR spectroscopy at 25 °C. The spectroscopic principle is based on a continuous measurement procedure (see the Supporting Information for further details). Within a period of maximum ten hours (only neglectable further conversion was observed by GC detection even after extended reaction times of up to 14 days or more), 256 ^{1}H NMR spectra were recorded. In Figure 2 four selected ^{1}H NMR spectra are shown as an illustration of the starting material consumption and the product formation.

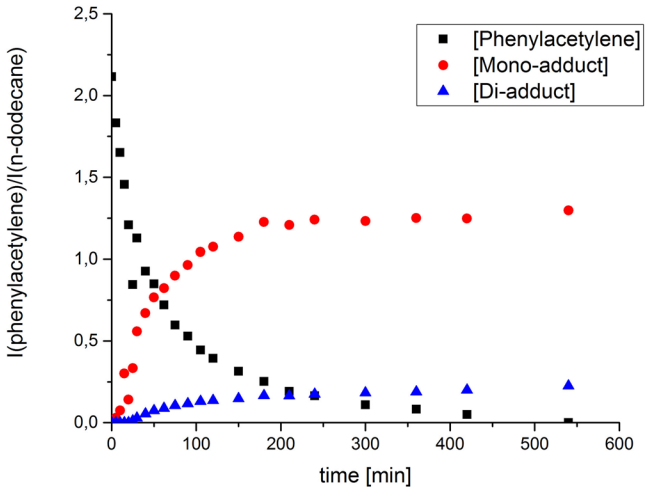


Figure 1. Kinetic profile of the hydroarylation reaction of phenylacetylene with pyrrole.

The kinetic analysis was conducted by the integration of characteristic reactant/product peaks at a specific time (Figure 2). Besides, the phenylacetylene

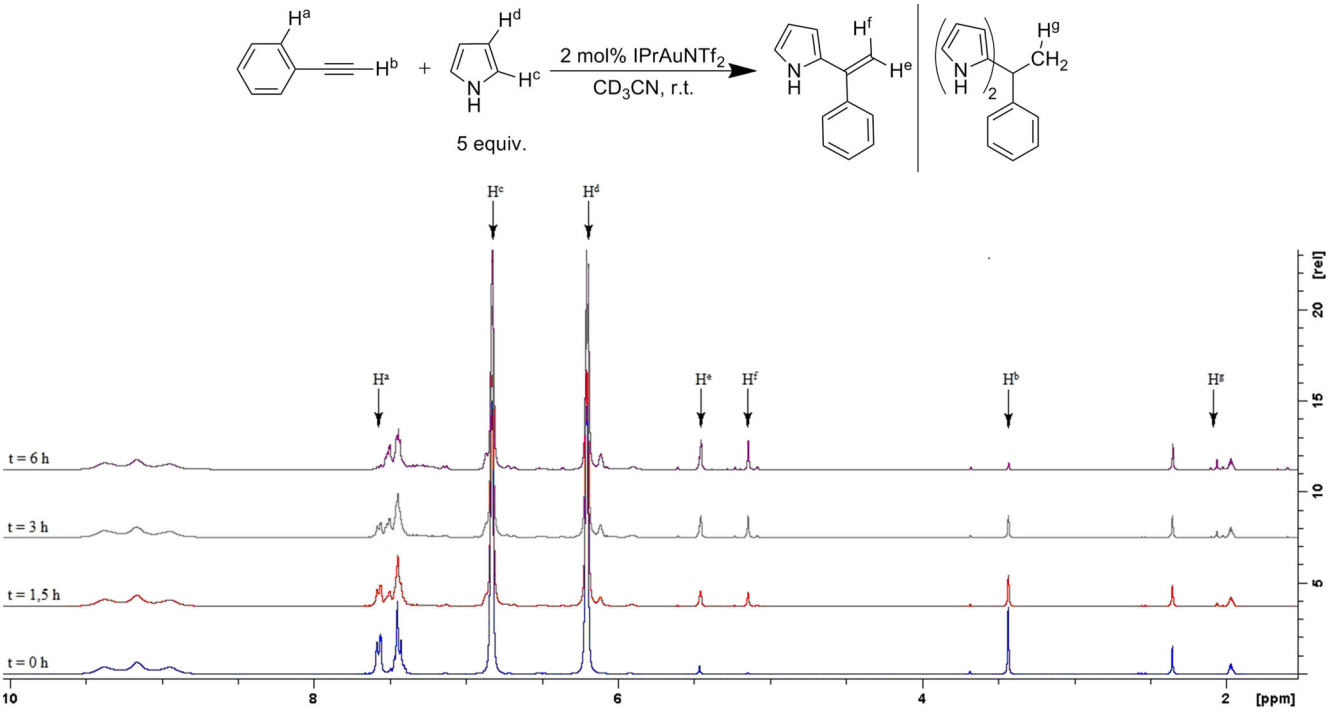


Figure 2. Selected ^{1}H NMR spectra of the hydroarylation of phenylacetylene with pyrrole.

peak at 3.4 ppm and the aromatic signals of the terminal alkyne were included. The concentration decrease of the excessive amount of pyrrole was calculated by integration of the present doublet peaks at 6.2 and 6.8 ppm. The amount of mono-adduct was determined by integration of the doublet signals at 5.2 and 5.5 ppm. The signal at 2.1 ppm represents the di-adduct. By extrapolation of the determined values close to $y=0$, the integral at the time $t=0$ was achieved by graphical analysis. Subsequently, the substance concentration was gained by conversion of integrals considering the for all applied reactions constant initial concentration of each compound. An exponential decrease of starting material and a saturation curve concerning the increase of products was observed (Figure 3a). A similar method was used to examine the hydroarylation reaction of phenylacetylene and kryptopyrrole. However, in this case the concentration profile pursued a consecutive reaction progress as expected for the formation of the two-fold addition product if one assumes that the first addition is faster than the second addition step (Figure 3b). As in the upper example, this clearly shows that also in the presence of a gold catalyst conditions for an enrichment of a two-fold hydroarylation can be found. The slower second hydroarylation in Figure 3b also indicates a yet unknown synthetic potential for a selective mono-hydroarylation.

Based on the integration method, the order of reaction was determined.[12] As a result of graphic correlation, the order of reaction and then the rate constant were determined by standard kinetic methods. The error is a result of error propagation of random faults concerning sample preparation. Systematic errors as a consequence of influence of the measurement object by instrument were excluded. The coefficient of determination R^2 is a criterion to describe a linear relation. A regression has a goodness-of-fit if the coefficient of determination is close to one. Serial kinetic measurements were investigated next. For the simplified approach, the rate constant of the hydroarylation reaction of one equivalent of phenylacetylene with five equivalents of pyrrole catalyzed by 2 mol% $IPrAuNTf_2$ was standardized to one. The decreasing concentration of phenylacetylene was used because of the formation of two products. Due to limited time on the instruments, it was not possible to observe a complete consumption for each reaction. Initially, the influence of the heteroarene concentration on the reaction rate was determined for the addition of pyrrole to phenylacetylene (Table 1). A linear growth of the rate constant with an increasing pyrrole concentration was noticed (Figure 4).

The ratio of mono- to di-adduct was examined after a reaction time of ten hours. Interestingly, if compared to higher pyrrole concentrations, the addition of only one equivalent of pyrrole leads to a higher selectivity towards the di-adduct! With regard to the catalyst loading (Table 2), a linear dependency of the rate constant on the $IPrAuNTf_2$ concentration was recognized (Figure 5). However, the point of intersection of the regression line and the x-axis at 0.7 mol% indicates catalyst poisoning by halides or basic compounds introduced by the solvent or by impurities in the starting materials.[13] The ratio of mono- to di-adduct concentration operates completely independently of the catalyst concentration.

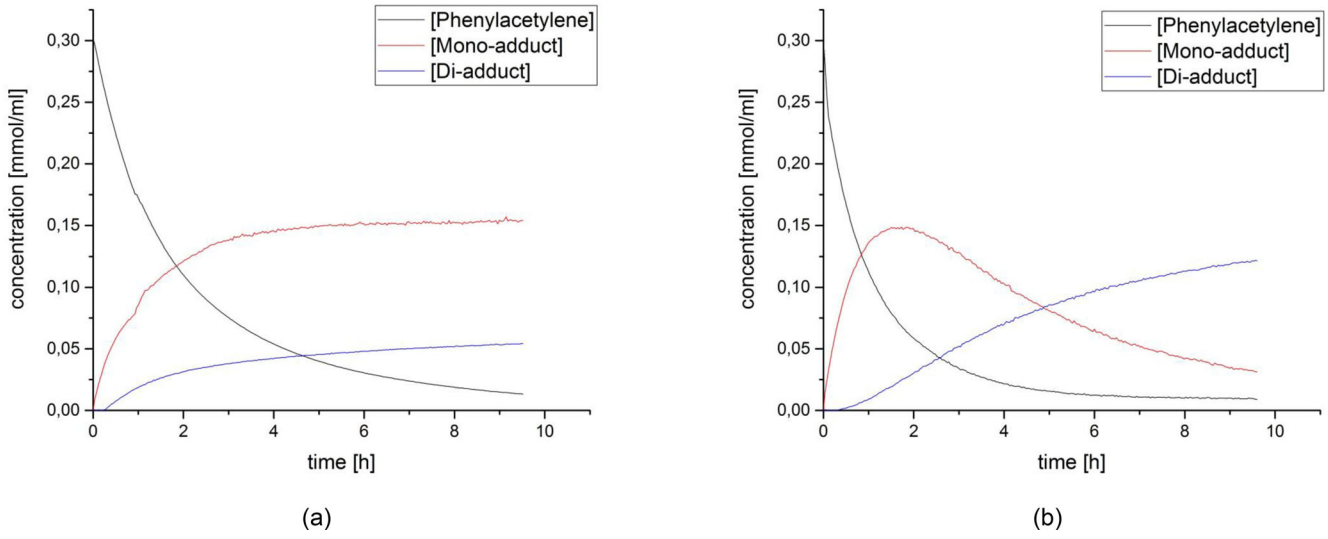
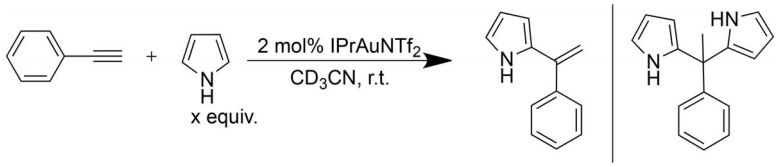


Figure 3. Concentration profile; (a) hydroarylation of phenylacetylene with pyrrole; (b) hydroarylation of phenylacetylene with kryptopyrrole.

Table 1. Variation of the heteroarene concentration.[a]



Entry	[Pyrrole] [equiv.]	Consumption[b] [%]	Ratio (Mono-/Di-adduct) $t=10$ h	k [L/(mol h)]	R^2	k_{rel}
1	1	51	1:1.6	0.066 ± 0.003	0.937	0.21 ± 0.01
2	2	82	1:1	0.155 ± 0.007	0.985	0.49 ± 0.02
3	5	100	2.8:1	0.316 ± 0.021	0.996	1.00 ± 0.07
4	10	100	3.3:1	0.675 ± 0.022	0.998	2.13 ± 0.07

[a] *Reaction conditions:* phenylacetylene (196 µmol, 0.302 mmol/mL), pyrrole (196–1958 µmol), $IPrAuNTf_2$ (2 mol%), CD_3CN at $T=25$ °C, observed by ^1H NMR kinetic for 10 h under air in NMR tubes.
[b] Consumption of the phenylacetylene determined by ^1H NMR kinetic after 10 h.

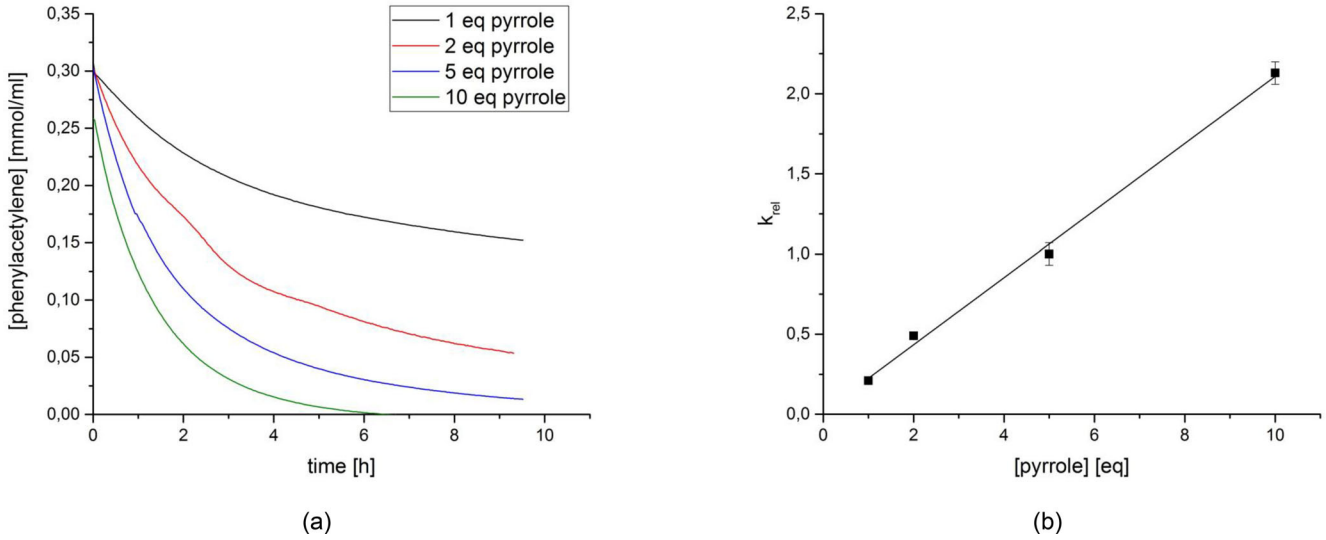
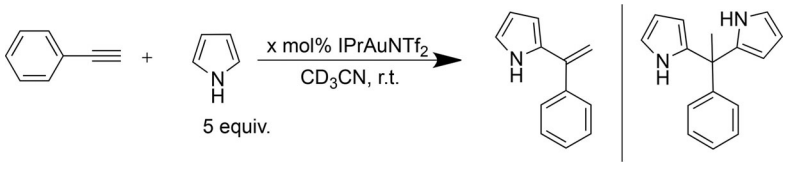


Figure 4. (a) Decrease of the concentration of the starting material; (b) linear trend of the plot of k_{rel} against [pyrrole].

Table 2. Variation of the catalyst concentration.[a]



Entry	[$IPrAuNTf_2$] [mol%]	Consumption[b] [%]	Ratio (Mono-/Di-adduct) $t=10$ h	k [L/(mol h)]	R^2	k_{rel}
1	1	80	2.5:1	0.105 ± 0.007	0.988	0.33 ± 0.02
2	2	100	2.8:1	0.316 ± 0.021	0.996	1.00 ± 0.07
3	3	100	2.4:1	0.617 ± 0.011	0.989	1.95 ± 0.03
4	5	100	2.4:1	1.185 ± 0.010	0.999	3.76 ± 0.03

[a] *Reaction conditions:* phenylacetylene (196 µmol, 0.302 mmol/mL), pyrrole (979 µmol), $IPrAuNTf_2$ (1–5 mol%), CD_3CN at $T=25$ °C, observed by ^1H NMR kinetic for 10 h under air in NMR tubes.
[b] Consumption of the phenylacetylene determined by ^1H NMR kinetic after 10 h.

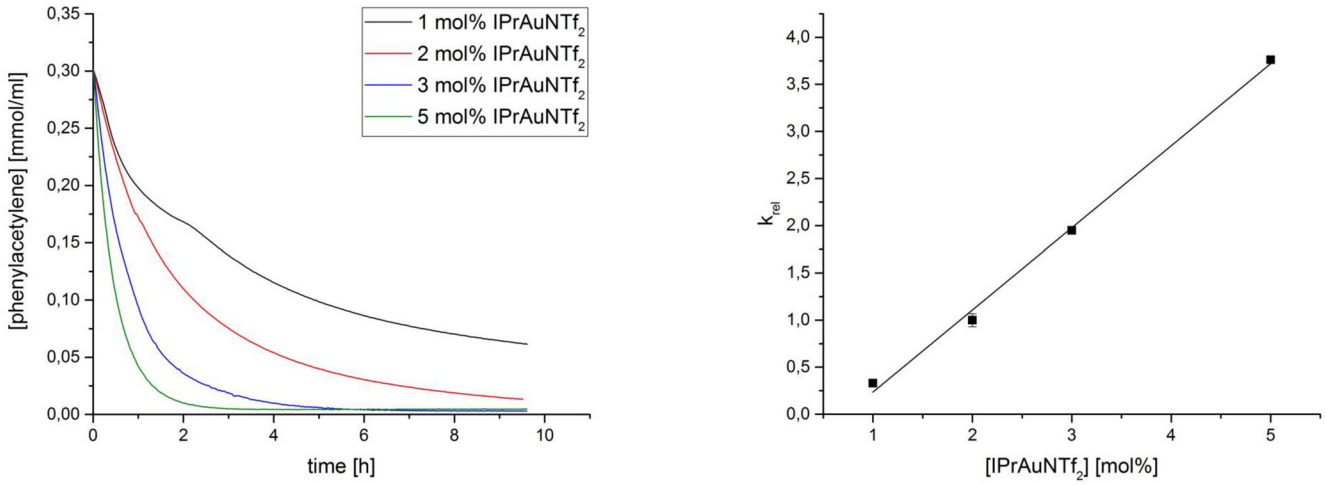
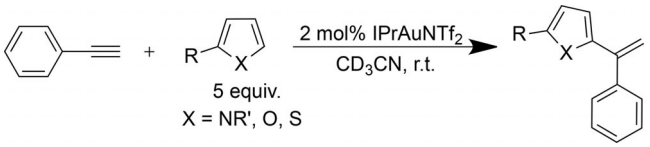


Figure 5. (a) Decrease of the concentration of the starting material; (b) linear trend of the plot of k_{rel} against [$IPrAuNTf_2$].

For the hydroarylation of phenylacetylene with different electron-rich heteroarenes significant deviations of the rate constants were observed (Table 3, Figure 6).

In a first set of experiments differently substituted pyrroles bearing one or more alkyl substituents were converted. In comparison to unsubstituted pyrroles and as expected, an up to eleven times faster reaction was observed for the more electron-rich systems (entries 1–6). Indole derivatives reacted considerable slower than the pyrrole systems (entries 8–10). In consideration of heterocycles with increasing amount of N-atoms, like in imidazole, the nucleophilicity is reduced in such a way that nearly no reactivity was observed (entry 7). The hydroarylation of phenylacetylene with 2-methylfuran, 2-methylthiophene and thiophene shows almost no conversion (entries 11–13). With regard to the kinetic examination of the nucleophilic attack of the electron-rich heteroarenes, the observed sequence of reactivity to a large extent correlates with the predictions of Mayr et al.[14] Minimal discrepancies are merely within the sequence of alkyl-

Table 3. Variation of electron-rich heteroarenes.[a]



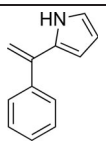
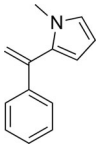
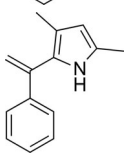
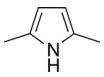
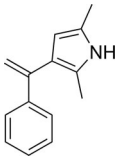
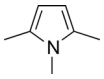
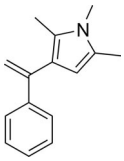
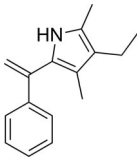
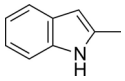
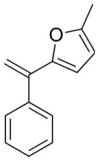
Entry	Heteroarene	Consumption[b] [%] $t=10$ h	Time[c] [h]	Product and Yield[d]	k [L/(mol h)]	R^2	k_{rel}
1		100 (2.8:1)	10	 **1a** (65%)	0.316 ± 0.021	0.996	1.00 ± 0.07
2		100 (3.8:1)	2	 **1b** (57%)	1.309 ± 0.001	0.997	4.15 ± 0.01
3		100 (1:4.4)	1	 **1c** (6%)	0.685 ± 0.022	0.993	2.17 ± 0.07

Table 3. (Continued)

Entry	Heteroarene	Consumption[b] [%] $t=10$ h	Time[c] [h]	Product and Yield[d]	k [L/(mol h)]	R^2	k_{rel}
4		100 (1:2.0)	0.2	 **1d** (39%)	3.556 ± 0.043	0.994	11.27 ± 0.14
5		100 (1:1.5)	0.3	 **1e** (38%)	1.300 ± 0.092	0.992	4.12 ± 0.29
6		100 (1:3.3)	2	 **1f** (41%)	0.546 ± 0.025	0.990	1.73 ± 0.08
7		2	–	–	–	–	–
8		70 (1:11.8)	–	–[e]	0.074 ± 0.006	0.998	0.24 ± 0.02
9		57 (1:2.2)	–	–[e]	0.042 ± 0.005	0.991	0.13 ± 0.02
10		85 (Only di-adduct)	–	–[f]	0.119 ± 0.002	0.983	0.38 ± 0.01
11		20[g]	72	 **1g** (6%)	0.003 ± 0.004	0.988	0.01 ± 0.01
12		< 1	–	–	–	–	–
13		<< 1	–	–	–	–	–

[a] *Reaction conditions:* phenylacetylene (196 µmol, 0.302 mmol/mL), heteroarene (979 µmol), $IPrAuNTf_2$ (2 mol%), CD_3CN at $T=25$ °C, observed by ^1H NMR kinetic for 10 h under air in NMR tubes.
[b] Consumption of the phenylacetylene determined by ^1H NMR-kinetic; in parentheses is the ratio of mono- to di-adduct determined by ^1H NMR-kinetic.
[c] Reaction time to yield the mono-adduct.
[d] Yield of product isolated by flash column chromatography.
[e] Product is not isolated due to same polarity within reaction mixture.
[f] Exclusive formation of the di-adduct.
[g] Product signals were too small to determine a significant ratio.

substituted pyrroles. This might originate from the application of different electrophiles as well as varying solvents in the literature. The ratio of mono- to di-adduct concentration after a measurement period of ten hours is dependent on different electron-rich heteroarenes. The addition reaction of 1-methylindole to phenylacetylene turned out to be the only reaction that selectively delivered the di-adduct while all the other reactions delivered mixtures after full conversion of the alkyne. As visible from the kinetic analysis, maximum concentrations of mono-adduct are obtained at early stages of the reaction which encouraged us to isolate these species by stopping the reactions early. In dependency of the applied nucleophile a strong adaption of reaction times needed to be done leading to reaction times ranging from few minutes to more than a week. By following this strategy, mono-adducts **1a–f** could be obtained in good to mod-

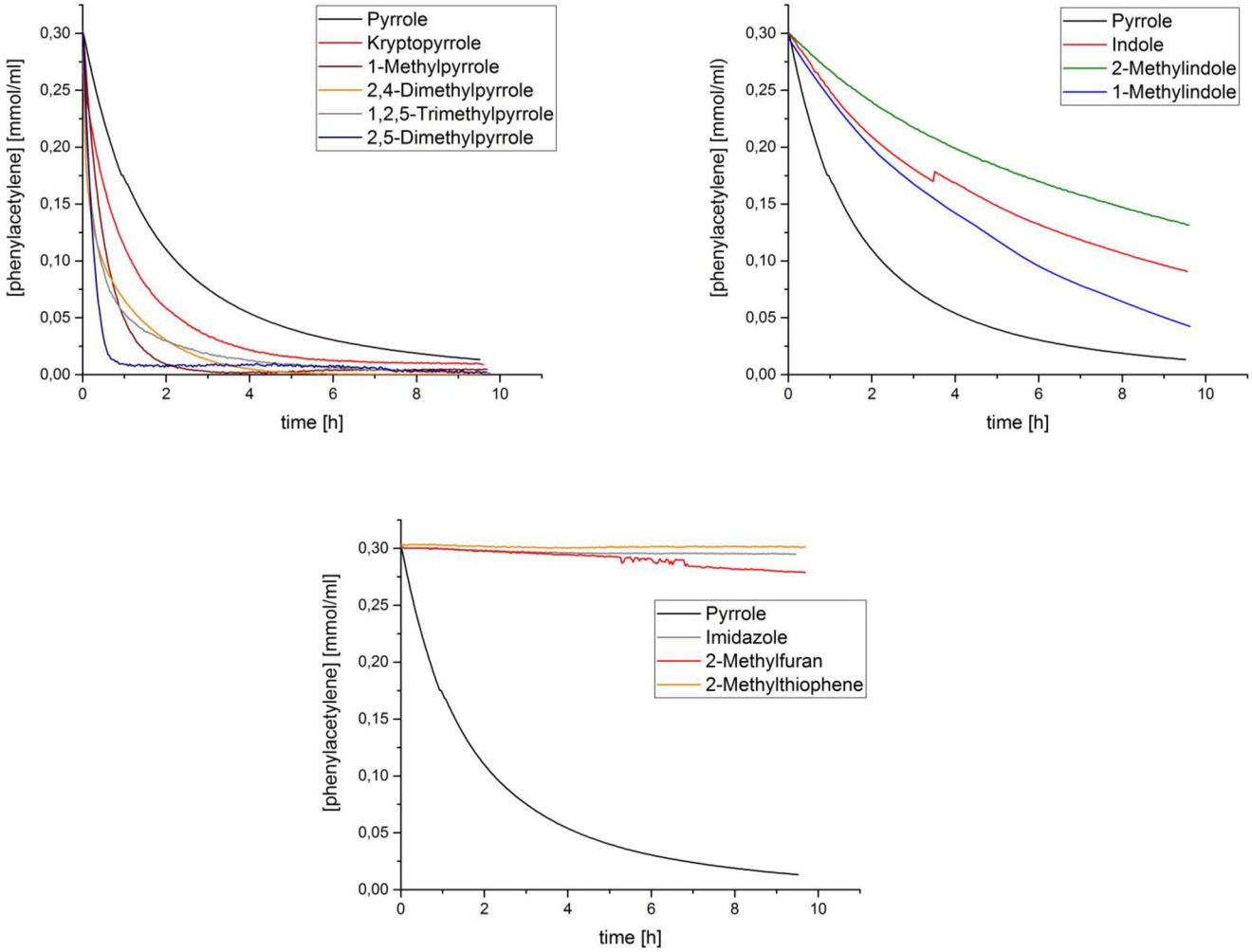
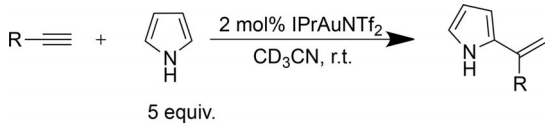


Figure 6. Reaction progress; decrease of the concentration of phenylacetylene.

erate yields (38–65%), demonstrating that under carefully adjusted conditions mono-adducts can also be synthesized in the presence of a gold catalyst. The yield of the mono-adduct **1g** is with 6% relatively low due to low conversion. The mono-adducts of phenylacetylene with various indole derivatives could not be isolated due to the same polarity as the two-fold addition product within the reaction mixture. The central problem of the purification was the rapidly occurring polymerization of the mono-adducts.[15] The hydroarylation of different alkynes with pyrrole as benchmark system shows substantial variation in their rate constants (Table 4, Figure 7). Thereby, reactions of alkynes with aryl groups which include either electron-withdrawing or electron-donating groups were accentuated. Moreover, also internal alkynes and various aliphatic alkynes were used.

In direct comparison to cyclohexylacetylene, it is noteworthy that the aromatic compound phenylacetylene exhibits a twice as fast reaction progress (entries 1 and 5). The rate constant for 1-octyne is an order of magnitude smaller than that in the case of phenylacetylene (entry 6). This effect should be based on the stabilization of the aromatic π-system. The reaction of 3-phenyl-1-propyne shows a rate constant reduced by 25% in comparison to phenylacetylene. The trend that compounds with electron-withdrawing groups on the aromatic ring indicate an accelerated attack of a nucleophile compared to electron-donating substituents is not dominating. Apart from 4-biphenylacetylene, the rate constants of alkyl-substituted phenylacetylene derivatives achieved the highest values (entries 2 and 7–9). By using halide-substituted phenylalkynes, an expedited reaction was observed (entries 10–13). The influence of the position of this substituent was determined as well. The conversion of *o*-, *m*- and *p*-chlorophenylacetylenes demonstrated only little discrepancies concerning the rate constant.

Table 4. Variation of alkynes.[a]



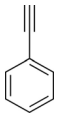
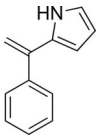
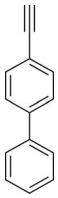
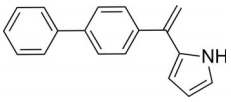
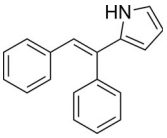
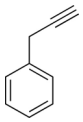
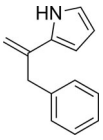
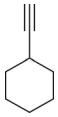
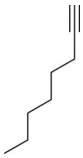
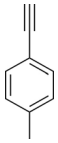
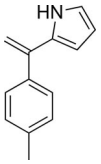
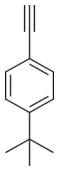
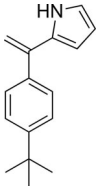
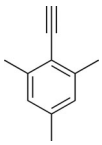
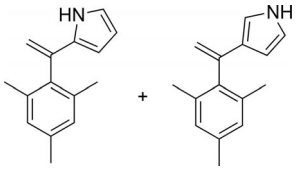
Entry	Alkyne	Consumption[b] [%] $t = 10$ h	Time[c] [h]	Product and Yield[d]	k [L/(mol h)]	R^2	k_{rel}
1		100 (2.8:1)	10	 **1a** (65%)	0.316 ± 0.021	0.996	1.00 ± 0.07
2		100 (1.4:1)	2	 **1h** (78%)	0.920 ± 0.048	0.996	2.92 ± 0.15
3		9	504	 **1i** (35%)	–	–	–
4		89[e]	24	 **1j** (33%)	0.237 ± 0.009	0.994	0.75 ± 0.03
5		91 (1:41.0)	1	trace	0.140 ± 0.010	0.995	0.44 ± 0.03
6		72 (1:2.6)	14	trace	0.028 ± 0.006	0.896	0.09 ± 0.02
7		94 (only mono-adduct)	3.5	 **1k** (60%)	0.586 ± 0.042	0.995	1.86 ± 0.13
8		87 (only mono-adduct)	14	 **1l** (45%)	0.525 ± 0.024	0.931	1.66 ± 0.08
9		100 (only mono-adduct)	5	 **1m** (72%) + **1n** (7%)	0.665 ± 0.016	0.998	2.11 ± 0.05

Table 4. (Continued)

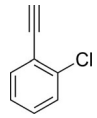
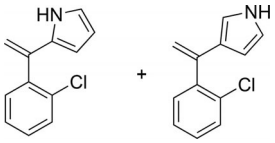
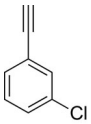
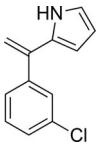
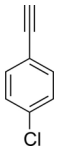
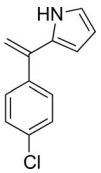
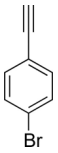
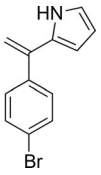
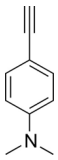
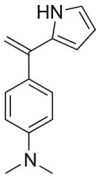
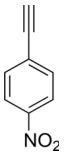
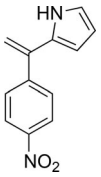
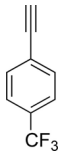
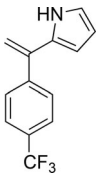
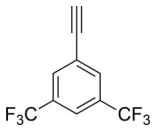
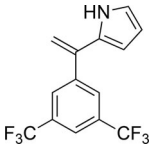
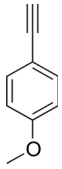
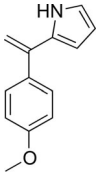
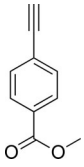
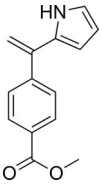
Entry	Alkyne	Consumption[b] [%] $t = 10$ h	Time[c] [h]	Product and Yield[d]	k [L/(mol h)]	R^2	k_{rel}
10		100 (2.8:1)	10	 **1o** (40%) + **1p** (8%)[f]	0.488 ± 0.003	0.999	1.55 ± 0.01
11		100 (4.7:1)	10	 **1q** (40%)	0.396 ± 0.002	0.999	1.25 ± 0.01
12		100 (1.9:1)	10	 **1r** (40%)	0.408 ± 0.001	0.999	1.29 ± 0.00
13		100 (1.6:1)	4	 **1s** (78%)	0.525 ± 0.008	0.999	1.66 ± 0.03
14		35 (only mono-adduct)	72	 **1t** (7%)[f]	0.024 ± 0.006	0.968	0.08 ± 0.02
15		92 (1.2:1)	2.5	 **1u** (66%)	0.155 ± 0.004	0.997	0.49 ± 0.01
16		98 (only mono-adduct)	4	 **1v** (46%)	0.201 ± 0.009	0.995	0.64 ± 0.03
17		90 (3.3:1)	6	 **1w** (70%)[f]	0.148 ± 0.002	0.996	0.47 ± 0.01
18		81 (1.8:1)	1.5	 **1x** (41%)[f]	0.186 ± 0.019	0.947	0.59 ± 0.06

Table 4. (Continued)

Entry	Alkyne	Consumption[b] [%] $t=10$ h	Time[c] [h]	Product and Yield[d]	k [L/(mol h)]	R^2	k_{rel}
19		92 (only mono-adduct)	10	 **1y** (57%)	0.166 ± 0.003	0.998	0.53 ± 0.01

[a] *Reaction conditions:* alkyne (196 μmol, 0.302 mmol/mL), pyrrole (979 μmol), $IPrAuNTf_2$ (2 mol%), CD_3CN at $T=25$ °C, observed by ^1H NMR kinetic for 10 h under air in NMR tubes.
[b] Consumption of the phenylacetylene determined by ^1H NMR kinetic; in parentheses is the ratio of mono- to di-adduct determined by ^1H NMR kinetic.
[c] Reaction time to yield the mono-adduct.
[d] Yield of product isolated by flash column chromatography.
[e] No ratio of mono- to di-adduct was determined because of overlapping signals.
[f] The ^1H NMR spectra contain signals of impurities caused by occurring polymerization.

Further reactions with electron-withdrawing trifluoromethyl, carboxylic acid ester and nitro groups on the aromatic ring showed a half as fast reaction progress in contrast to phenylacetylene (entries 15–17 and 19). The rate constant of 4-methoxyphenylacetylene is comparable to the results of 4-trifluoromethylphenylacetylene; this result cannot be explained yet, but has been verified by repetitions of these experiments. The reaction of diphenylacetylene consumed only 9% of the starting material within the measurement period of ten hours. Consequently, diphenylacetylene and 4-(dimethylamino)phenylacetylene exhibit the lowest rate constants of the used alkynes (entries 3 and 14). In addition to the kinetic data, the ratio of mono- to di-adduct concentration after a measurement period of ten hours was analyzed. The reaction mixtures with electron-donating groups contain after the obtained reaction time almost exclusively mono-adducts. Whereas, the hydroarylation of electron-withdrawing alkynes show a 2:1 ratio of mono-adduct to di-adduct on average. Only the reactions of cyclohexylacetylene and 1-octyne have a substantial incidence of di-adduct. In addition to the kinetic research, the isolation of the maximum yield of mono-adduct was addressed. As in the upper case, the reaction time was modified for each alkyne. Following this principle, the mono-adducts **1h–y** were synthesized in good to moderate yields (33–78%). The hydroarylation of cyclohexylacetylene and 1-octyne yielded nevertheless no mono-product. As mentioned before the central problem for purification was the rapidly occurring polymerization of the mono-adducts.[15]

Although the electron-rich heteroarenes were used in excess, the kinetic research shows that the reaction just stops after reaching a ratio of mono- to di-adduct which is specific for each reaction (Figure 3). For example, the hydroarylation of phenylacetylene with pyrrole after a reaction time of six hours showed no further change of the mono- to di-adduct ratio even after prolonged reaction times. Only the reaction of 3-ethyl-2,4-dimethylpyrrole proceeded until almost exclusively the di-adduct was formed. From the reaction progress it becomes obvious that the presence of phenylacetylene is essential for a further conversion to the di-adduct. The mono- to di-adduct ratio examined after a reaction time of ten hours for the hydroarylation of phenylacetylene with various pyrrole concentrations is an excellent evidence for this discovery (Table 2). Thereby, if compared to higher pyrrole concentrations, the addition of only one equivalent of pyrrole leads to a higher selectivity towards the di-adduct which seems to be contraintuitive. But, higher pyrrole concentrations induce a fast formation of the mono-adduct and therefore after short reaction times all of the phenylacetylene is consumed and the further conversion to the di-adduct stops. The observed phenomena might be explained by a competing proton-catalyzed step that is operating for the second addition step. The presence of protons in the media might be derived by the reversible formation of σ,π-acetylide complexes, a process that is known to produce one equivalent of the corresponding acid.[16] After the consumption of phenylacetylene, this equilibrium of σ,π-acetylide complexes/free protons with phenylacetylene is shifted back, which then stops the acid-catalyzed second hydroarylation. To prove this assumption, 5 mol% of trifluoromethanesulfonimide were added to the reaction of phenylacetylene with pyrrole and indeed the transformation of mono- to di-adduct was completed after only a few minutes [Scheme 2, Eq. (1)]. In order to exclude a possible gold-catalyzed reaction, the isolated mono-adduct **1a** was reacted with pyrrole and 5 mol% of trifluoromethanesulfonimide [Scheme 2, Eq. (2)]. A gold-cata-

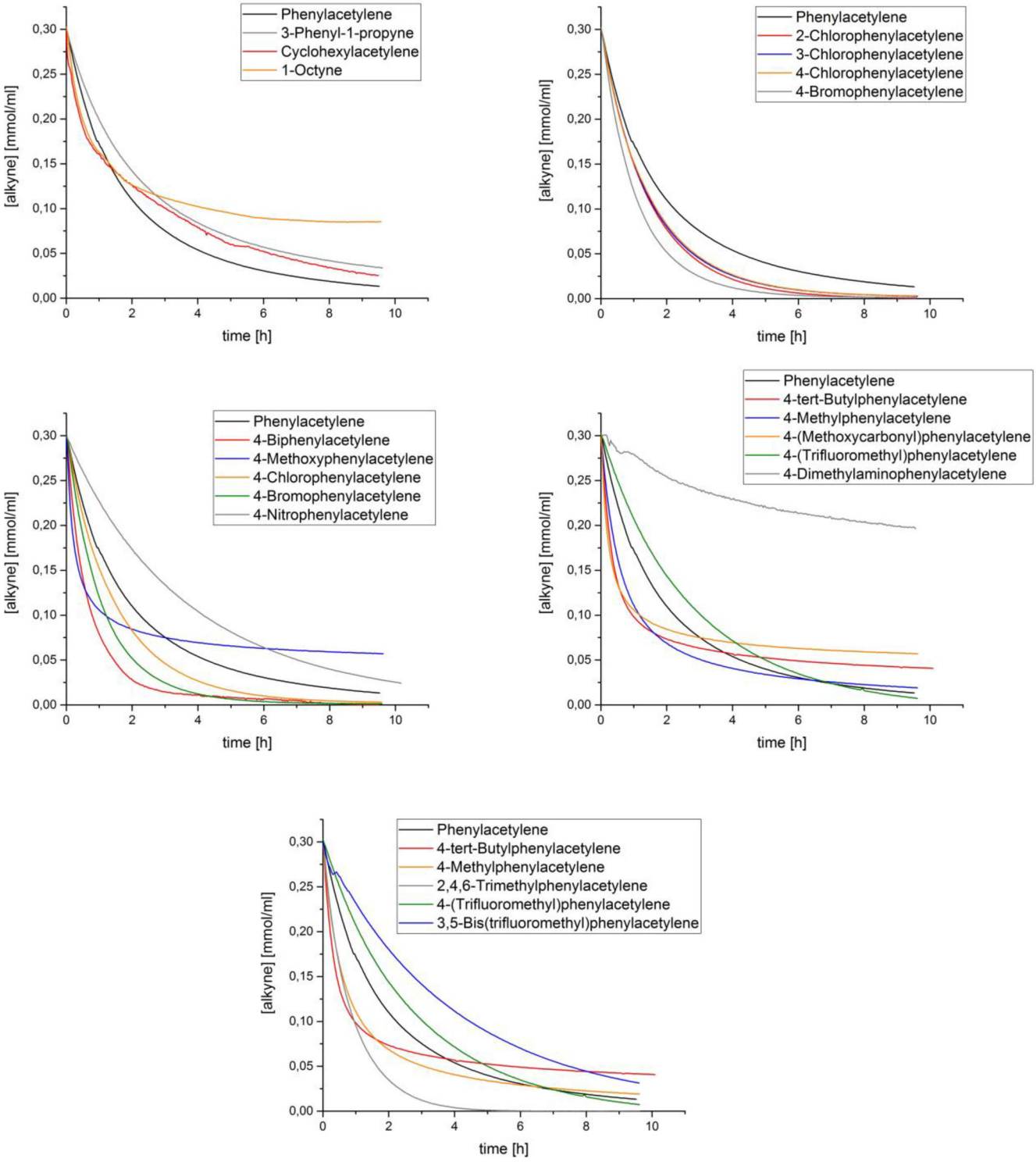
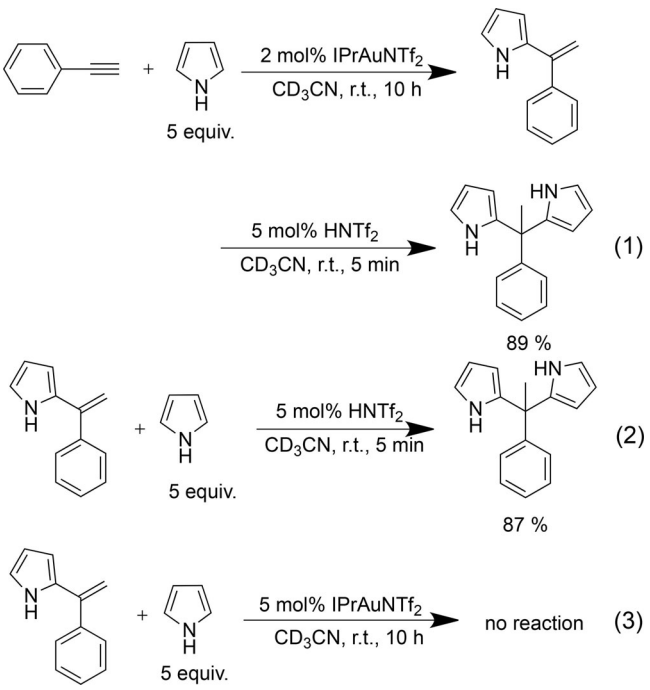


Figure 7. Reaction progress; decrease of the concentration of the starting material.

lyzed addition reaction of pyrrole onto the mono-adduct **1a** was inter alia investigated by the addition of $IPrAuNTf_2$ [Scheme 2, Eq. (3)]. As expected, in the absence of a proton source no reaction was observed.

As a result of these control experiments, the formation of the di-adduct is an exclusively proton-catalyzed step. As a consequence, we were curious if these two pathways can be coupled in order to obtain the hetero-di-hydroarylation of phenylacetylene with various electron-rich heteroarenes a two-step, one-pot



Scheme 2. Mechanistic investigation.

synthesis. Therefore, first one equivalent of phenylacetylene was treated with an appropriate amount of heteroarene and the after a specific reaction time five equivalents of a different heteroarene and 5 mol% of trifluoromethanesulfoneimide were added. The results of this study are shown in Table 5.

The appropriation of this method allows the synthesis of homo-di-adducts (entry 1) as well as hetero-di-adducts (entries 2–12). As expected, the addition reaction of pyrrole with phenylacetylene proceeded smoothly to afford di-adduct **2a** with 89% yield. The hetero-di-adducts **2b–j** were gained in moderate to good yields (10–84%). Here, the ^{1}H NMR kinetic research is playing a key role. On the basis of the measurements, it was possible to predict the ratio of mono- to di-adduct as well as the reaction speed for specific electron-rich heteroarenes. In combination of both aspects, the chronological order of adding the heteroarenes was calculated. On two representative reactions the relevance of the chronological order was demonstrated. The change of chronological order of addition of pyrrole and 2,4-dimethylpyrrole decreased the yield of 50% (entry 3) to 2% (entry 4). Moreover, entries 5 and 6 point out that the yield is decreasing enormously as soon as the reaction is not conducted in a two-step, one-pot principle. Thereby, a loss of 63% yield was determined. The moderate yields of the hetero-di-adducts **2b**, **f–j** depend on the close polarity of the reaction mixture. Another reason for reduced yields is the loss of selectivity for nucleophiles with nearly similar rate constants.

Conclusions

In conclusion, the mono- and two-fold hydroarylation reaction of alkynes with electron-rich heteroarenes was examined and optimized by ^{1}H NMR kinetics. Thereby, the rate constants for diverse reaction conditions as well as the detailed reaction progress were determined. It was demonstrated that the electronic effect of the substituents on phenylacetylene significantly affects the rate constant. However, the addition of electron-rich heteroarenes onto functionalized phenylacetylenes is not following a defined pattern. Inter alia, the measurements showed that a specific mono- to di-adduct ratio was formed in the reactions (depending on the applied starting materials) and even though nucleophile was still present no further reaction was monitored in the presence of the gold catalyst. Based on the kinetic data, by stopping the reaction at an early stage, the mono-adducts could be isolated in moderate to good yields (33–78%). Moreover, from the obtained kinetic data it became obvious that protons reversibly derived from the formation of σ,π-acetylide complexes from the terminal alkynes are crucial for the second step of the addition cascade. This observation is in accordance with recently published density functional theory (DFT) calculations.[10] By employing the *orthogonal reactivity of gold and a proton* for the two reaction steps, the synthesis of hetero-di-adducts could be achieved in moderate to good yields (10–84%). Based on the collected kinetic data and the possibility of converting the obtained intermediates, this opens up new synthetic possibilities for further applications in the synthesis of hetero-addition products.

Experimental Section

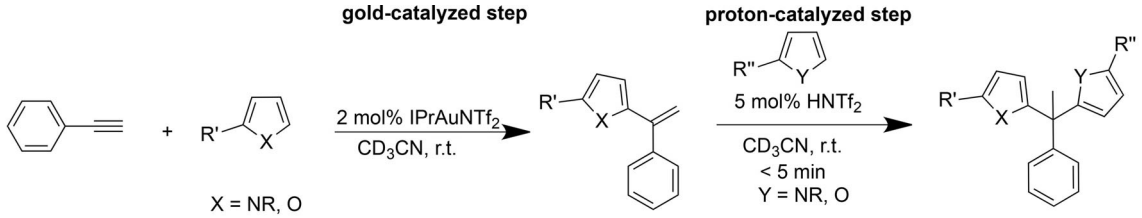
General Procedure 1 for the ^{1}H NMR Kinetic

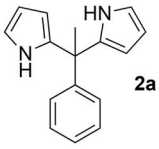
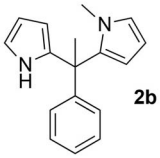
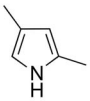
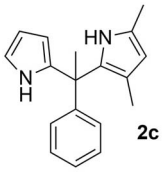
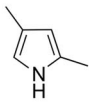
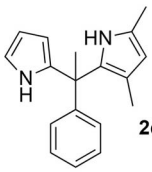
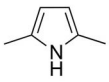
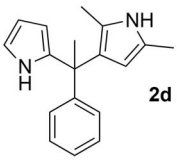
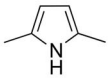
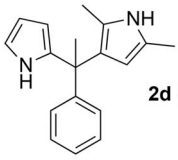
To an NMR tube charged with a solution of alkyne (1 equiv.) and freshly distilled heteroarene (5 equiv.) in acetonitrile-d_3, IPrAuNTf$_2$ (0.02 equiv.) was added. The reaction was observed at $T = 25\,°C$ by ^{1}H NMR kinetic for 10 h. Here, the equipment Avance DRX-300, after an instrument defect Avance DRX-400, of Bruker Devices was selected. Due to the often varying relaxation times, the measurement period differs from substance to substance.

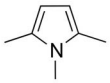
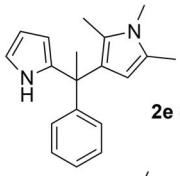
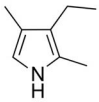
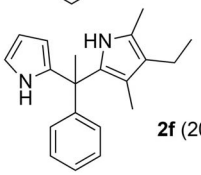
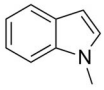
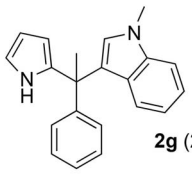
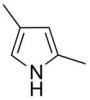
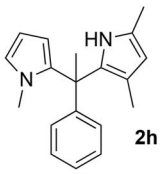
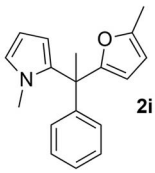
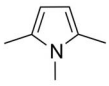
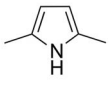
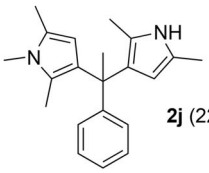
General Procedure 2 for the Mono-Hydroarylation of Alkynes with Electron-Rich Heteroarenes

To a reaction mixture of alkyne (1 equiv.) and freshly distilled heteroarene (5 equiv.) in acetonitrile-d_3, IPrAuNTf$_2$ (0.02 equiv.) was added. The reaction was conducted without stirring at room temperature for a certain time (see Table 3 and Table 4). The solvent was removed under reduced pressure. The crude residue was purified by column chromatog-

Table 5. Synthesis of di-adducts.[a]



Entry	Heteroarene X	Heteroarene Y	Time [h][b]	Product and Yield
1		-	10	 **2a** (89%)
2			10	 **2b** (23%)
3			10	 **2c** (50%)
4			4	 **2c** (2%)
5			10	 **2d** (82%)
6			-[d]	 **2d** (19%)

Entry	Heteroarene X	Heteroarene Y	Time [h][b]	Product and Yield
7			10	 **2e** (84%)
8			10	 **2f** (20%)
9			10	 **2g** (20%)
10			3	 **2h** (31%)
11			3	 **2i** (10%)
12			6	 **2j** (22%)

[a] *Reaction conditions:* phenylacetylene (1 equiv., 0.302 mmol/mL^{-1}), heteroarene X (1–5 equiv.), heteroarene Y (5 equiv.), $HNTf_2$ (5 mol%), $IPrAuNTf_2$ (2 mol%), CD_3CN at $T = 25\,°C$.
[b] Reaction time to start the proton-catalyzed step.
[c] Yield of product isolated by flash column chromatography.
[d] One-step, one-pot reaction.

raphy on silica gel (petroleum ether/ ethyl acetate) to afford the corresponding product.

2-(1-Phenylvinyl)-1*H*-pyrrole (1a):[17] Phenylacetylene (21.5 μL, 196 μmol, 1 equiv.), pyrrole (67.9 μL, 979 μmol, 5 equiv.) and $IPrAuNTf_2$ (3.4 mg, 4 μmol, 0.02 equiv.) were dissolved in 0.56 mL acetonitrile-d_3 following the general procedure 2. The reaction was stopped after 10 hours. Purification by column chromatography (SiO_2, PE/EA = 200:1) afforded **1a** as orange oil; yield: 21 mg (127 μmol, 65%); R_f (PE/EA = 200:1) = 0.13. ^{1}H NMR (300 MHz, CD_3CN): δ = 5.08 (d, J = 0.5 Hz, 1H), 5.40 (d, J = 0.5 Hz, 1H), 6.03–6.06 (m, 1H), 6.13–6.16 (m, 1H), 6.81–6.83 (m, 1H), 7.37–7.41 (m, 3H), 7.42–7.47 (m, 2H), 9.33 (bs, 1H); ^{13}C NMR (75 MHz, CD_3CN): δ = 109.00 (t, 1C), 109.74 (d, 1C), 110.10 (d, 1C), 120.17 (d, 1C), 128.92 (d, 1C), 129.20 (d, 2C), 129.24 (d, 2C), 132.66 (s, 1C), 141.95 (s, 1C), 142.70 (s, 1C); IR (film): $\tilde{\nu}$ = 3424, 3266, 3089, 3055, 3024, 2974, 1610, 1572, 1547, 1492, 1444, 1251, 1081, 1027, 883, 776, 701, 645 cm^{-1}; MS (EI$^+$): m/z (%) = 169.1 (100) $[M]^+$, 154.1 (50) $[M-CH_3]^+$; HR-MS (EI$^+$): m/z = 169.0894, calcd. for $C_{12}H_{11}N$: 169.0891.

1,2,5-Trimethyl-3-(1-phenylvinyl)-1*H*-pyrrole (1e): Phenylacetylene (43.0 μL, 392 μmol, 1 equiv.), 1,2,5-trimethylpyrrole (264.9 μL, 1958 μmol, 5 equiv.) and $IPrAuNTf_2$ (6.8 mg, 8 μmol, 0.02 equiv.) were dissolved in 1.0 mL acetonitrile-d_3 following the general procedure 2. The reaction was aborted after 20 minutes. Purification by column chromatography (SiO_2, PE/EA = 200:1) afforded **1e** as orange oil; yield: 31 mg (147 μmol, 38%); R_f (PE/EA = 200:1) = 0.09. ^{1}H NMR (300 MHz, CD_3CN): δ = 1.96 (s, 3H), 2.16 (s, 3H), 3.37 (s, 3H), 5.05 (d, J = 2.0 Hz, 1H), 5.26 (d, J = 2.0 Hz, 1H), 5.63 (m, 1H), 7.29–7.34 (m, 5H); ^{13}C NMR (75 MHz, CD_3CN): δ = 11.64 (q, 1C), 12.36 (q, 1C), 30.67 (q, 1C), 107.41 (d, 1C), 111.79 (t, 1C), 124.74 (s, 1C), 127.91 (s, 1C), 128.27 (d, 1C), 128.48 (d, 2C), 128.69 (s, 1C), 129.00 (d, 2C), 144.00 (s, 1C), 146.42 (s, 1C); IR (Film): $\tilde{\nu}$ = 3346, 3080, 3054, 3023, 2927, 2857, 1699, 1657, 1603, 1572, 1491, 1444, 1398, 1377, 1254, 1156, 1027, 882, 780, 701, 620 cm^{-1}; GS-MS (EI): m/z (%) = 211.1 (100) $[M]^+$; HR-MS (EI$^+$): m/z = 211.1341, calcd. for $C_{15}H_{17}N$: 211.1631.

2-{1-([1,1′-biphenyl]-4-yl)vinyl}-1*H*-pyrrole (1h): 4-Biphenylacetylene (69.8 mg, 392 μmol, 1 equiv.), pyrrole (135.8 μL, 1958 μmol, 5 equiv.) of pyrrole and $IPrAuNTf_2$ (6.8 mg, 8 μmol, 0.02 equiv.) were dissolved in 1.16 mL acetonitrile-d_3 following the general procedure 2. The reaction was stopped after 2 hours. Purification by column chromatography (SiO_2, PE/EA = 200:1) afforded **1h** as yellowish solid; yield: 75 mg (306 μmol, 78%); R_f (PE/EA = 200:1) = 0.08; mp 115 °C. ^{1}H NMR (300 MHz, CD_3CN): δ = 5.13 (s, 1H), 5.40 (s, 1H), 6.05–6.07 (m, 1H), 6.12–6.15 (m, 1H), 6.81–6.83 (m, 1H), 7.35–7.41 (m, 1H), 7.45–7.54 (m, 4H), 7.64–7.71 (m, 4H), 9.37 (bs, 1H); ^{13}C NMR (75 MHz, CD_3CN): δ = 109.12 (t, 1C), 109.75 (d, 1C), 110.12 (d, 1C), 120.22 (d, 1C), 127.69 (d, 2C), 127.83 (d, 2C), 128.53 (d, 1C), 129.79 (d, 2C), 129.95 (d, 2C), 132.56 (s, 1C), 141.07 (s, 1C), 141.36 (s, 1C), 141.41 (s, 1C), 142.26 (s, 1C); IR (ATR): $\tilde{\nu}$ = 3431, 3055, 3029, 2926, 1603, 1580, 1547, 1487, 1448, 1332, 1117, 1096, 1033, 1007, 883, 847, 804, 770, 729, 697 cm^{-1}; GS-MS (EI): m/z (%) = 245.1 (100) $[M]^+$, 230.0 (80) $[M\text{-}CH_3]^+$; HR-MS (EI$^+$): m/z = 245.1201, calcd. for $C_{18}H_{15}N$: 245.1204; m/z = 230.1014, calcd. for $C_{17}H_{12}N$: 230.0970.

General Procedure 3 for the Two-Fold Hydroarylation of Alkynes with Various Electron-Rich Heteroarenes

To an NMR tube charged with a solution of alkyne (1 equiv.) and freshly distilled heteroarene (1.1–5 equiv.) in acetonitrile-d_3, $IPrAuNTf_2$ (0.02 equiv.) was added. Consumption of the starting material was controlled by TLC and ^{1}H NMR. A different heteroarene (5 equiv.) and trifluoromethanesulfonimide (0.05 equiv.) were added after a specific time. The reaction was completed after 5 minutes. The solvent was removed under reduced pressure. The crude residue was purified by flash chromatography over silica gel (petroleum ether/ ethyl acetate) to afford the corresponding product.

2,5-Dimethyl-3-[1-phenyl-1-(1*H*-pyrrol-2-yl)ethyl]-1*H*-pyrrole (2d): Phenylacetylene (43.0 μL, 0.392 mmol, 1 equiv.), pyrrole (136.0 μL, 1.958 mmol, 5 equiv.) and $IPrAuNTf_2$ (6.8 mg, 0.008 mmol, 0.02 equiv.) were dissolved in 0.5 mL acetonitrile-d_3 following the general procedure 3. After 10 hours, 2,5-dimethylpyrrole (199.0 μL, 1.958 mmol, 5 equiv.) and trifluoromethanesulfonimide (5.5 mg, 0.020 mmol, 0.05 equiv.) were added. Purification by column chromatography (SiO_2, PE/EA = 20:1) afforded **2d** as orange-red solid; yield: 85 mg (0.322 mmol, 82%); mp 56 °C; R_f (PE/EA = 8:1) = 0.38. ^{1}H NMR (300 MHz, CD_3CN): δ = 1.57 (s, 3H), 1.91 (s, 3H), 2.11 (s, 3H), 5.38–5.39 (m, 1H), 5.74–5.76 (m, 1H), 5.98–6.01 (m, 1H), 6.59–6.62 (m, 1H), 7.14–7.18 (m, 3H), 7.22–7.25 (m, 2H), 8.44 (bs, 1H), 8.54 (bs, 1H); ^{13}C NMR (100 MHz, CD_3CN): δ = 12.53 (q, 1C), 12.75 (q, 1C), 30.27 (q, 1C), 44.64 (s, 1C), 106.32 (d, 1C), 107.47 (d, 1C), 108.03 (d, 1C), 117.18 (d, 1C), 122.93 (s,1C), 124.64 (s, 1C), 126.53 (d, 1C), 126.62 (s, 1C), 128.39 (d, 2C), 128.60 (d, 2C), 140.32 (s, 1C), 150.99 (s, 1C); IR (film): $\tilde{\nu}$ = 3418, 3382, 3098, 3083, 3056, 3021, 2976, 2932, 1596, 1555, 1493, 1444, 1397, 1370, 1243, 1202, 1183, 1099, 1081, 1027, 943, 790, 763, 704, 643 cm^{-1}; MS (EI$^+$): m/z (%) = 264.1 (35) $[M]^+$, 249.1 (100) $[M-CH_3]^+$; HR-MS (EI$^+$): m/z = 264.1605, calcd. for $C_{18}H_{20}N_2$: 264.1621; m/z = 249.1369, calcd. for $C_{17}H_{17}N_2$: 249.1386.

3,5-Dimethyl-2-[1-(1-methyl-1*H*-pyrrol-2-yl)-1-phenylethyl]-1*H*-pyrrole (2h): Phenylacetylene (21.5 μL, 0.196 mmol, 1 equiv.), 1-methylpyrrole (86.9 μL, 0.979 mmol, 5 equiv.) and $IPrAuNTf_2$ (3.4 mg, 0.004 mmol, 0.02 equiv.) were dissolved in 0.5 mL acetonitrile-d_3 following the general procedure 3. After 3 hours, 2,4-dimethylpyrrole (100.8 μL, 0.979 mmol 5 equiv.) and trifluoromethanesulfonimide (2.8 mg, 0.010 mmol, 0.05 equiv.) were added. Purification by column chromatography (SiO_2, PE/EA = 50:1) afforded **2h** as orange oil; yield: 17 mg (0.061 mmol; 31%); R_f (PE/EA = 40:1) = 0.39. ^{1}H NMR (400 MHz, CD_3CN): δ = 1.52 (s, 3H), 2.02 (s, 3H), 2.10 (d, J = 0.4 Hz, 3H), 3.11 (s, 3H), 5.57–5.58 (m, 2H), 5.90–5.92 (m, 1H), 6.56–6.57 (m, 1H), 7.14- 7.17 (m, 2H), 7.29–7.33 (m, 3H), 7.98 (bs, 1H); ^{13}C NMR (100 MHz, CD_3CN): δ = 12.14 (q, 1C), 12.80 (q, 1C), 29.56 (q, 1C), 35.96 (q, 1C), 45.69 (s, 1C), 106.53 (d, 1C), 109.35 (d, 1C), 110.52 (d, 1C), 116.02 (s, 1C), 124.51 (d, 1C), 127.28 (d, 1C), 128.72 (d, 2C), 129.02 (d, 2C), 129.44 (s, 1C), 129.77 (s, 1C), 139.19 (s, 1C), 148.21 (s, 1C); IR (ATR): $\tilde{\nu}$ = 3452, 3057, 2981, 2934, 2871, 1700, 1595, 1492, 1444, 1396, 1297, 1227, 1094, 1066, 1028, 786, 759, 706, 638 cm^{-1}; MS (EI$^+$): m/z (%) = 278.1 (36) $[M]^+$, 263.1 (100)

$[M-CH_3]^+$; HR-MS (EI^+): $m/z = 278.1772$, calcd. for $C_{19}H_{22}N_2$: 278.1777; $m/z = 263.1538$, calcd. for $C_{18}H_{19}N_2$: 263.1542.

Acknowledgements

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16 The Gold-Catalyzed Hydroarylation of Alkynes with Electron-Rich Heteroarenes – A Kinetic Investigation and New Synthetic Possibilities

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