Mechanistic Insights into Copper-Catalyzed Sonogashira–Hagihara-Type Cross-Coupling Reactions: Sub-Mol% Catalyst Loadings and Ligand Effects

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Abstract: An efficient catalytic system for Sonogashira–Hagihara-type reactions displaying ligand acceleration in the copper-catalyzed formation of C(sp^2)−C(sp) bonds is described. The structure of the ligand plays a key role for the coupling efficiency. Various copper sources show excellent catalytic activity, even in sub-mol% quantities. A wide variety of substituents is tolerated in the substrates. Mechanistic details have been revealed by kinetic measurements and DFT calculations.

Keywords: copper · density functional calculations · ligand acceleration · low catalyst loading · reaction mechanisms · Sonogashira–Hagihara reaction

Introduction

The palladium/copper co-catalyzed Sonogashira–Hagihara reaction is one of the most powerful synthetic methods for the construction of C(sp^2)−C(sp) bonds.[1] It provides straightforward access to aryl alkynes and related conjugated enynes, which are widely used as precursors for pharmaceuticals, natural products, and organic materials.[2,3] Variants of the Sonogashira–Hagihara reaction allow the use of palladium catalysts in the absence of a traditionally used copper co-catalyst, and under optimized reaction conditions the cross-coupling reactions can even occur at room temperature.[4,5] However, palladium is not only expensive, but also toxic,[6] which limits the use of Sonogashira–Hagihara reactions in large-scale operations. Replacing palladium by cheaper and more abundant transition metals such as iron and copper has thus become a prime research goal.

Various iron-based catalytic systems have been described,[7] since our first report on the catalytic effects of iron salts in Sonogashira–Hagihara-type reactions.[8] With copper the situation is different, because stoichiometric couplings between aryl iodides and copper acetylides[9] have long been known through the work by Stephens and Castro.[10] The more recently reported couplings that only required catalytic quantities of copper have been based on successful copper/ligand combinations. As ligands, Lewis bases such as phosphines[11] as well as nitrogen-[12] and oxygen-containing[13] molecules proved particularly effective. In addition, a preformed copper complex,[14] unsupported catalysts,[15] and copper nanoparticles were found to work well in these cross-coupling reactions.[16]

Although these non-precious metals proved catalytically active in Sonogashira–Hagihara-type reactions, there are still many shortcomings that need to be addressed. For example, in many copper-catalyzed couplings, competing Glaser–Hay-type homocouplings of the employed alkynes have been observed,[17] which lowered the yield and complicated the purification of the desired cross-coupling adducts. Furthermore, the commonly employed high catalyst loadings (in the range of 5–10 mol%) have posed safety concerns, because, depending on the acetylene used, significant amounts of highly explosive copper(I) acetylides can be formed during the coupling reaction.[18]

Since the recent findings on the dramatic effect of ppm-levels of copper catalysts in carbon–heteroatom bond formations,[19] we decided to investigate the effect of low copper concentrations in Sonogashira–Hagihara-type couplings of aryl halides and terminal alkynes. An efficient catalyst system requiring a sub-mol% copper loading was described in our previous communication.[20] Similarly, Norrby and co-workers elaborated an efficient copper-catalyzed C−N coupling reaction employing a sub-mol% catalyst loading.[19b, 21] Herein, we describe our findings in detail and reveal the full scope of the reaction. In addition, we discuss mechanistic aspects of the reaction that have been investigated by kinetic measurements and DFT calculations.
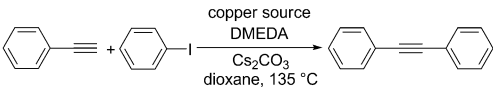
Results and Discussion

Initial investigations focused on the catalytic efficacies of various copper sources in the coupling reaction of phenylacetylene and iodobenzene in the presence of N,N'-dimethylethylenediamine (DMEDA, in large excess with respect to copper) and 1,4-dioxane as solvent. The results are summarized in Table 1. Notably, almost all copper sources

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Table 1. The effect of the copper source.[a]

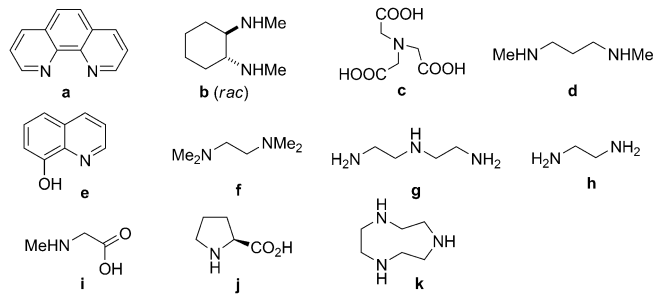| Entry	Copper source	GC Yield [%]	
		3 h	22 h
1	CuI	36	98
2	CuCl$_2$	36	90
3	Cu$_2$O	22	99
4	Cu(OAc)$_2$	35	97
5	Cu(CF$_3$SO$_3$)$_2$	33	98
6	CuCl	30	88
7	CuO	33	85
8	[Cu(DMEDA)$_2$]Cl$_2$·H$_2$O	30	90
9	no copper addition	0	8

[a] Reaction conditions: iodobenzene (1.5 mmol), phenylacetylene (1 mmol), catalyst (0.5 mol%), Cs$_2$CO$_3$ (2 mmol), DMEDA (0.3 mmol), and dioxane (1 mL) under argon atmosphere at 135 °C.

yielded the desired product in good to excellent yields, whereas without a copper catalyst only a very low yield was obtained (Entry 9). In view of the high sensitivity of palladium impurities in cross-couplings of iodides and terminal acetylenes,[22] the last result was of particular importance. Apparently, none of the reagents (starting materials, base, solvents etc.) contained enough palladium to effect the cross-coupling itself.[23] From the yields determined after a reaction time of 3 h it became clear that the rate of the coupling reaction was essentially independent of the copper source. This suggested that, irrespective of the initial copper source used, the same catalytically active species was formed under the reaction conditions. The oxidation state of copper in the catalyst precursor had no influence on the productivity of the catalyst. This has often been observed in copper-catalyzed cross-coupling reactions. Probably in this case, DMEDA, a secondary amine, served as both ligand and reactant, reducing the Cu^{II} precursors in situ, as was observed in the analogous Fe^{III} systems.[24]

Next, the effect of the ligand on the reaction was investigated. Previously, we had shown that the reaction most likely involved the formation of a Cu^I–acetylide species, even when Cu^{II} precursors (in combination with DMEDA) were used.[20] As not all ligands investigated here were expected to reduce Cu^{II} to Cu^I as readily as DMEDA, a Cu^I precursor copper(I) iodide was applied in the present study (in 0.5 mol% quantity). The use of DMEDA required, as stated earlier,[20] a large excess (20–30 mol%) to obtain high reaction rates using low copper loadings. With the goal of identifying an improved copper/ligand combination that effectively catalyzed the cross-coupling with a reduced ligand loading, a screening of ligands was performed by using both 1 and 30 mol% of ligand (Table 2).

As revealed by the entries in Table 2, the ligand structure has a profound influence on the catalytic activity. By using 30 mol% of **a**, **b**, and **g** (Table 2, entries 1, 2 and 7) the coupling product was obtained in excellent yields after 22 h. These ligands were characterized by the presence of two or

Table 2. Ligand screening.[a]

Entry	Ligand	GC Yield [%]			
		1 mol%		30 mol%	
		3 h	22 h	3 h	22 h
1	**a**	11	80	47	97
2	**b**	3	19	46	98
3	**c**	1	9	nd[b]	1
4	**d**	1	10	9	53
5	**e**	12	37	7	41
6	**f**	1	10	3	22
7	**g**	2	28	38	95
8	**h**	1	12	6	25
9	**i**	0	13	2	15
10	**j**	1	18	0.6	12
11	**k**	0	14	nd[b]	nd[b]

[a] Reaction conditions: iodobenzene (1.5 mmol), phenylacetylene (1 mmol), CuI (0.5 mol%), Cs$_2$CO$_3$ (2 mmol), ligand (0.01 or 0.3 mmol), and dioxane (1 mL) under argon at 135 °C. [b] Not done.

more nitrogen donor groups and their ability to form stable five-membered chelates when coordinated to a metal center. Ligands containing oxygen donor moieties, often used in other copper-catalyzed processes,[13] proved much less effective in this transformation under the employed reaction conditions. Ligands containing secondary or aromatic nitrogen donor groups yielded more active catalysts than those having primary and tertiary amine moieties. It is most probable that primary amines do not possess sufficiently strong donor properties to displace the acetylene moieties in [Cu(acetylide)]$_n$ to form the active monomeric catalyst. In addition, if the rate-determining reaction between the monomeric active catalyst and the aryl halide is an oxidative process, as our previous kinetic study suggested, strongly donating ligands would be required to facilitate this reaction. The tertiary amino groups in **f**, on the other hand, may have been too sterically demanding to form stable chelates when bound to copper. The results observed with **d**, which is similar in structure to DMEDA, but forms a six-membered chelate when bonded to a metal center, also suggested that the formation of a stable chelate was crucial for obtaining an active catalyst system. Intriguingly, ligand **k**, which should have formed a five-membered chelate in a similar fashion to DMEDA (as well as **a**, **b**, and **g**), did not yield an effective catalyst. The case of ligand **k** will be discussed further in the context of our computational investigations.

With 1 mol% of ligand, only phenanthroline (**a**) afforded the product in good yield (80%, Table 2, entry 1). Notably, the catalytic activity was still more than four times lower

than when 30 mol % of ligand was employed. The decrease in activity was less dramatic than for secondary-amine-based ligands **b** and **g**, reflecting the strong coordination of pyridine-based ligands to copper. This was also illustrated by ligand **e**. Although the catalyst with this pyridyl-containing ligand was only moderately active when used at 30 mol % in combination with 0.5 mol % of CuI, it did not show a significant drop in activity when used at 1 mol % with the same copper loading. Mao and co-workers previously disclosed that 20 mol % of ligand **e** and 10 mol % CuI as catalyst were very effective for this coupling reaction.[13b] For this particular ligand, it therefore seemed that coordination to the metal was not an issue, but that the intrinsic activity of the monomeric catalyst was lower than those of catalysts based on ligands **a**, **b**, and **g**.

In our previous communication, we reported on the influence of electronic effects of the substrates (aryl iodides and alkynes) on the rate of the coupling reaction, which indicated the nature of the rate-determining step of the reaction.[20] Here, we have extended the scope of our methodology by using a sub-mol % copper catalyst loading for the coupling of a variety of sterically and electronically different aryl iodides and terminal alkynes. Electronic effects will be discussed further within the framework of the computational investigation.

Various aryl iodides were employed as electrophiles in this coupling reaction (Table 3). Both electron-poor and electron-rich aryl iodides were coupled with phenylacetylene in good to excellent yields. For example, the reactions of 4-CF$_3$C$_6$H$_4$I and 3-MeC$_6$H$_4$I with phenylacetylene provided the desired coupling products **3fa** and **3ga** in 93 and 86 % yield, respectively (entries 6 and 7). The sterically hindered 2,6-dimethyliodobenzene also reacted well, affording the corresponding product **3ha** in 80 % yield (entry 8). As representative halogenoarenes, iodopyridines and iodothiophenes were subjected to the previously optimized reaction conditions. The reactions of 3- and 2-iodopyridine proceeded well to provide the desired products **3ia** and **3ja** in good yields (entries 9 and 10). 3-Iodothiophene reacted with phenylacetylene, leading to product **3ka** in decent yield (entry 11). Attempts to couple aryl bromides or chlorides with phenylacetylene under the same reaction conditions remained unsuccessful.

Subsequently, the methodology was applied to different aryl alkynes by using the previously optimized reaction conditions (Table 4). All coupling reactions proceeded well, although the yields varied considerably. The electronic properties of the arene group of the alkynes played a significant role on the outcome of this reaction. In the case of electron-rich alkynes, the desired products were obtained in good yields (Table 4, entries 1–4). Alkynes with electron-withdrawing groups also reacted with iodobenzene, providing the products in moderate to good yields; 4-fluoro- and 4-cyanophenylacetylene led to **3af** and **3ag** in 67 and 24 % yield, respectively (Table 4, entries 5 and 6). Interestingly, raising the amount of DMEDA to 50 mol % led to an increase in yield of **3ag** to 50 %. The cross-coupling reactions
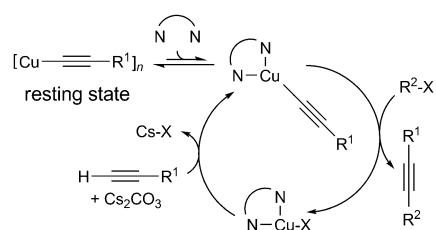
Table 3. Couplings of various aryl iodides with phenylacetylene.[a]

$$\text{Ar-I} + \equiv\!\!-\text{Ph} \xrightarrow[\substack{\text{DMEDA, Cs}_2\text{CO}_3 \\ \text{dioxane, argon, 135 °C}}]{\text{[Cu(DMEDA)}_2\text{]Cl}_2\cdot\text{H}_2\text{O}} \text{Ar}\equiv\!\!-\text{Ph}$$

Entry	Aryl iodide	Product	Yield [%][b]
1		**3aa**	94
2	O$_2$N—	**3ba**	75
3	NC—	**3ca**	88
4	F—	**3da**	85
5	MeO—	**3ea**	86
6	F$_3$C—	**3fa**	93
7	Me	**3ga**	86
8	Me / Me	**3ha**	80
9		**3ia**	84
10		**3ja**	86
11		**3ka**	54

[a] Reaction conditions: aryl iodide (1.5 mmol), alkyne (1 mmol), [Cu(DMEDA)$_2$]Cl$_2$·H$_2$O (0.5 mol %), Cs$_2$CO$_3$ (2 mmol), DMEDA (0.3 mmol), and dioxane (1 mL) under argon atmosphere at 135 °C. [b] After column chromatography.
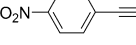
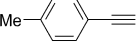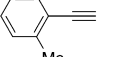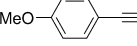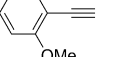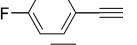of heteroaryl alkynes 2- and 3-pyridylacetylene with iodobenzene proceeded smoothly, leading to the formation of **3ah** and **3ai** in 44 and 35 % yield, respectively (Tabl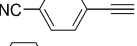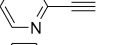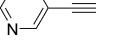e 4, entries 7 and 8). For a substrate with a strongly electron-deficient nitro group, however, no desired product was observed (Table 4, entry 9).

Mechanistic aspects of the C–C bond formation: In our previous communication, we proposed a mechanism for this ligand-accelerated catalytic reaction (Scheme 1).[20,25] Kinetic measurements revealing that the reaction was first order in copper at low concentrations, but became independent of copper at higher concentrations, suggested that the resting

Scheme 1. Proposed reaction mechanism.[20]

Table 4. Couplings of various aryl alkynes with phenyl iodide.[a]

$$Ar\text{—}\equiv\text{ + Ph-I }\xrightarrow[\substack{\text{DMEDA, Cs}_2\text{CO}_3 \\ \text{dioxane, argon, 135 °C}}]{[\text{Cu(DMEDA)}_2]_2\text{Cl}_2\cdot\text{H}_2\text{O}}\text{ Ar}\text{—}\equiv\text{—Ph}$$

Entry	Aryl alkyne	Product	Yield [%][b]
1	Me—⟨⟩—≡	3ab	83
2	⟨⟩(Me)—≡	3ac	85
3	MeO—⟨⟩—≡	3ad (3ea)	70
4	⟨⟩(OMe)—≡	3ae	63
5	F—⟨⟩—≡	3af (3da)	67
6	NC—⟨⟩—≡	3ag (3ca)	24 (50)[c]
7	⟨N⟩—≡	3ah (3ja)	44
8	⟨N⟩—≡	3ai (3ia)	35
9	O₂N—⟨⟩—≡	3aj (3ba)	–

[a] For conditions, see Table 3, footnote [a]. [b] After column chromatography. [c] Use of 50 mol% of DMEDA.

state of the catalyst was a polymeric complex that was in equilibrium with an active monomeric catalyst.[26] Elemental analysis showed that the resting state contained no nitrogen atoms and that its composition of carbon and hydrogen corresponded to [Cu(phenylacetylene)]$_n$.[20] Kinetic measurements further revealed first order dependencies in iodobenzene as well as in DMEDA, which indicated that these species were involved in the early part of the catalytic cycle, somewhere between the resting state and the rate-limiting step.[20]

The following mechanistic scenario was suggested based on kinetic measurements and the well-established catalytic cycle for the Pd/Cu co-catalyzed Sonogashira–Hagihara reaction[1a–d,g] at sufficient concentration in pyridine: the DMEDA ligand activates the resting state by dissolving the [Cu(phenylacetylene)]$_n$ polymer and forming a soluble [Cu-(DMEDA)(phenylacetylene)] complex. This complex reacts with the aryl halide, which results in coupling of the organic parts through C–C bond formation and a [Cu(DMEDA)(I)] complex. The [Cu(DMEDA)(phenylacetylene)] complex, which is proposed to be the active state of the catalyst, is regenerated through transmetallation with cesium phenylacetylenate.[20]

To gain a deeper insight into the reaction mechanism, the effect of several electronically different aryl halides were investigated. It was found that just as in C–N bond-forming reactions catalyzed by similar catalysts,[26a,27] the reaction was accelerated by the presence of electron-withdrawing substituents on the aryl iodide.[20] This observation and the fact that the reaction rate was independent of the phenylacetylene concentration made us confident that the rate-lim-

iting step was neither the dissolution of the resting state nor the transmetallation step, but the C–C bond formation. Consequently, the latter was set into the focus of our theoretical investigations.

The $C(sp^2)$–$C(sp)$ coupling reaction between Cu^I–phenylacetylide bound to DMEDA and 4-iodotoluene was modeled by using density functional theory (DFT) calculations.[28] Searching the potential energy surface (PES) for transition states (TS), TS^1 (Figure 1a) was found in which the $C(sp^2)$–I bond of the aryl halide breaks simultaneously as the $C(sp^2)$–$C(sp)$ bond of the product forms (the C–I bond is 2.695 Å and the C–C bond is 2.263 Å). The imaginary frequency of TS^1 (378.0 cm^{-1}) clearly corresponds to the reaction coordinate of interest; however, the activation energy via TS^1 (174.2 kJ mol^{-1}) is much too high for a reaction that proceeds at 135 °C.

In the search for a reaction pathway with a lower activation energy, TS^2 (Figure 1a) was identified in which the $C(sp^2)$–I bond is cleaved oxidatively on Cu^I, resulting in the Cu^{III} intermediate [(DMEDA)Cu^{III}I(CCPh)(CPhMe)] (Figure 1a). The imaginary frequency (78.8 cm^{-1}) corresponds to the dissociation of the C–I bond, and following the reaction coordinate in the forward direction led to the formation of the trigonal bipyramidal Cu^{III} intermediate in Figure 1a. The activation energy via TS^2 is 85 kJ mol^{-1}, which corresponds to a relatively fast reaction at 135 °C. However, since the –CCPh and –PhMe ligands are in *trans* position with respect to each other, reductive elimination would require the Cu^{III} complex to undergo a conformational change to align the two ligands in neighboring positions. Several attempts were made to locate a TS for such a rearrangement, but all attempts of constrained optimization along various hypothetical reaction coordinates for rearrangement led back to the reactants when the constraints were released. The explanation is probably the kinetic and thermodynamic instability of the Cu^{III} complex with respect to the reactants. The Cu^{III} intermediate is 70.3 kJ mol^{-1} endothermic with respect to the reactants and only 14.7 kJ mol^{-1} more stable than the preceding TS^2; therefore, even a minor perturbation of the geometry led back to the reactants. To elucidate whether a sequential mechanism should be considered, Cu^{III} intermediates were searched for in all possible trigonal bipyramidal and square pyramidal configurations of the DMEDA, –I, –CCPh and –PhMe ligands. Of all these attempts, the Cu^{III} intermediate in Figure 1a was the only configuration found to be a local energy minimum on the potential energy surface.

Even if no stable Cu^{III} intermediate in which the carbon atoms to be coupled were in neighboring position could be located, a transition state that would lead to such a configuration was found by rotating the 4-iodotoluene molecule in TS^2 180 degrees about an imaginary axis going through the Cu atom and being orthogonal with respect to the $C(sp^2)$–I bond (Figure 1a). This led to the location of TS^3, for which the activation energy is 88.3 kJ mol^{-1}. Even though TS^3 is very similar to the TS for oxidative addition (TS^2), relaxation of TS^3 led directly to the final product. To exclude the
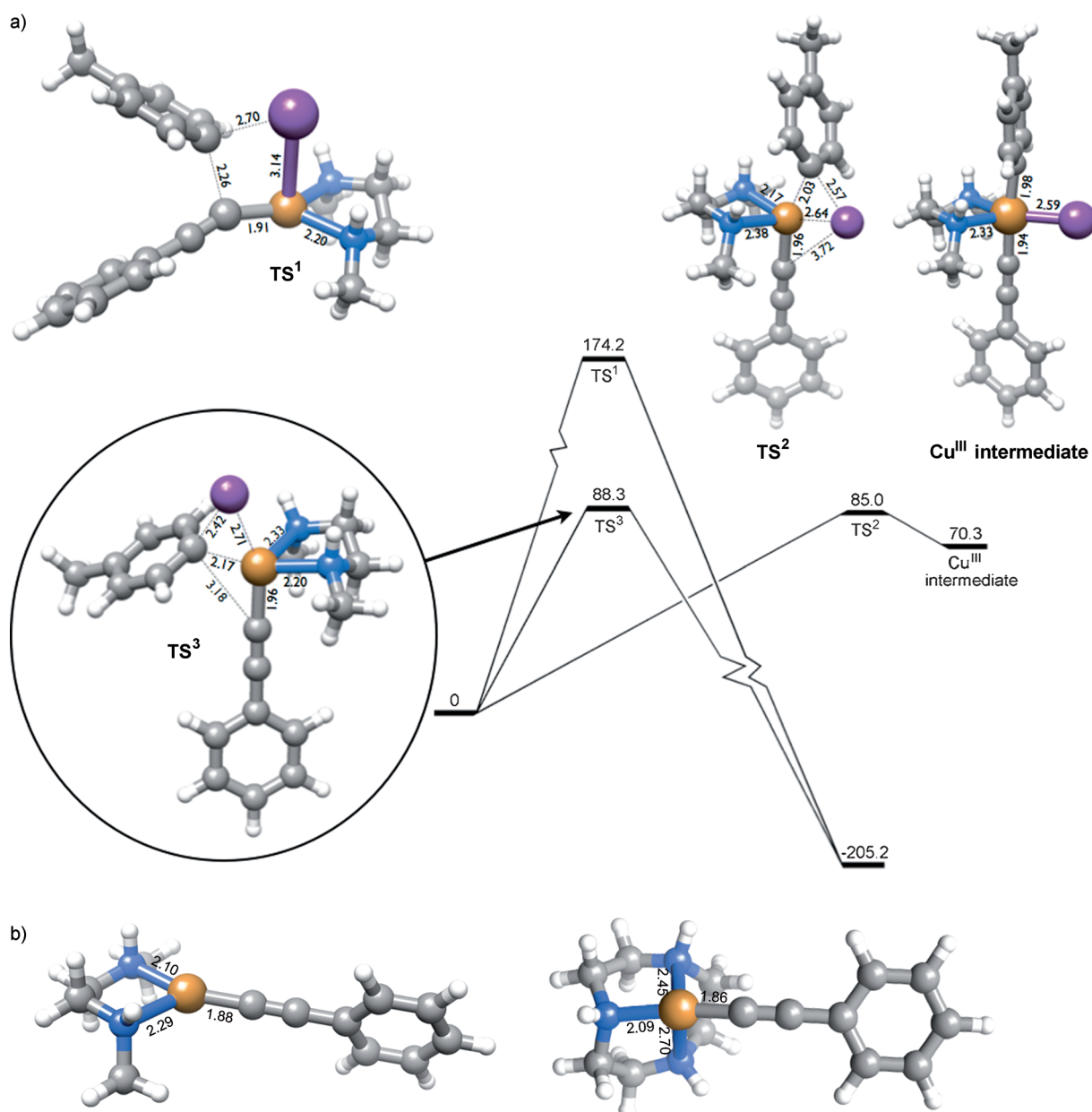
Figure 1. a) Free energy [kJ mol^{-1}] profile and optimized transition states for the copper-catalyzed coupling of phenylacetylene with 4-iodotoluene. b) Optimized geometries of the copper–acetylide in complex with DMEDA (left) and ligand **k** (right).

existence of a stable Cu^{III} intermediate following TS^3 towards the product, several attempts were made to locate such a complex by geometry optimization with a larger basis set (LACV3P++**),[29] by optimization in a solution-like dielectric field ($\varepsilon = 2.2$),[30] and by optimization with the dispersion-corrected hybrid functional M06.[31] None of these attempts succeeded and invariably led to the formation of the product, which makes us confident that there is no stable Cu^{III} intermediate following TS^3.

For the reaction between 4-iodotoluene and [(DMEDA)Cu^I(CCPh)], the computed activation energy for C–C bond formation via TS^3 (88.3 kJ mol^{-1}) is in good agreement with the experimentally determined activation

energy of (83.3 ± 1.3) kJ mol^{-1}.[32] Transition states of TS^3 type were located for a selection of the substrates of the experimental scope of our previous communication (Table 5).[20] The computed activation energies correlate well with the HOMO–LUMO gap (HOMO of the copper–acetylide complexes and LUMO of the aryl halides), and it was found that the strongly electron-withdrawing NO$_2$ group has a great influence on the kinetics of the reaction by lowering the LUMO of the aryl halide and thereby reducing the activation energy by more than 10 kJ mol^{-1} as compared with the other substrates. This effect of the NO$_2$ group was observed experimentally as well. The turnover frequency (TOF) for the reaction of [(DMEDA)Cu^I(CCPh)]

Table 5. Computational results.[a]

Alkyne/aryl iodide	$E_{HOMO} - E_{LUMO}$ [eV]	$\Delta G^{\pm}/\Delta G^{\circ}$ [kJ mol^{-1}]
F_3C—⬡—≡—⬡—I	4.00	90.7/−194.8
⬡—≡—Me—⬡—I	3.63	88.3/−205.2
⬡—≡—⬡—I	3.55	85.3/−205.7
⬡—≡—O_2N—⬡—I	1.47	75.2/−211.5

[a] $E_{HOMO} - E_{LUMO}$ is the energy difference between the interacting orbitals. $\Delta G^{\pm}$ is the activation free energy, while ΔG° is the reaction free energy.

with 4-IPhNO$_2$ was about ten times faster than any of the other reactions.[20] Furthermore, the relative TOFs of the other substrates were in qualitative agreement with the computed activation energies.[20] This correlation of experimental and theoretical data and the good agreement between the measured and computed activation energies in absolute numbers indicate that the rate-limiting step of this reaction is the concerted C—I bond dissociation and C—C bond formation.

The structure of TS^3 might also explain why ligand **k** gave such poor results (Table 2). In TS^3 (Figure 1 a), the acetylide is strongly bent out of the copper–DMEDA plane as compared to the reactant (Figure 1 b, left). This bending seems to be necessary to reduce the activation energy, because the activation energy for TS^1 (in which the DMEDA–Cu–acetylide angle is much smaller) is very high. However, ligand **k** probably prevents the acetylide from beeing bent, since it coordinates copper with three N atoms, making the complex rigid (Figure 1 b, right).

As a final note on the mechanism it should be mentioned that for the LCuZMe/IPh (L=β-diketone or phenanthroline, Z=−O or −NH) systems, Buchwald and co-workers have shown that the reaction is initiated by single electron transfer (SET) from the copper complex to the aryl halide.[33] In the present system ([(DMEDA)Cu^{I}CCPhX]/IPhY, X=−H or −CF$_3$, Y=−H, −CH$_3$, or −NO$_2$), however, SET is endothermic with almost 500 kJ mol^{-1}, making such a mechanism impossible (even though the subsequent reaction steps of the SET-initiated mechanism are exothermic, the endothermicity of the SET would be a lower limit for the activation energy, which would make the reaction extremely slow). In contrast to the C—heteroatom bond forming reaction in which reductive elimination would involve two strongly σ-donating moieties, here, the coupling involves one σ donor and one moiety having low-lying acceptor orbitals, a much more favorable combination for bond formation. Thus, we feel confident that the reaction of the present system does not operate through the SET mechanism.

Conclusion

We developed a Sonogashira–Hagihara-type reaction for the construction of carbon(sp^2)−carbon(sp) bonds, which is catalyzed by sub-mol% quantities of a copper catalyst being accelerated by diamine ligands. Varying the metal source and the ligand revealed that a number of copper catalysts were efficient for this reaction and that the structure of the ligand had a major impact in the coupling efficiency. The catalytic system tolerates various electron-poor and electron-rich aryl(hetero) iodides and aryl(hetero) alkynes, providing the desired products in moderate to excellent yields. Mechanistic aspects have been elucidated by kinetic measurements and DFT calculations. The latter suggest that the reaction proceeds by a concerted breaking of the phenyl iodide bond and formation of the new C—C bond, and that this is the rate-liniting step. Calculations on various electronically modified systems reproduce the experimentally observed trends.

Experimental Section

Experimental details

Representative procedure for the copper-catalyzed coupling (synthesis of 3 aa): A 10 mL sealable tube, equipped with a magnetic stir bar, was charged with Cs$_2$CO$_3$ (2.0 mmol). The aperture of the tube was then covered with a rubber septum and purged by using argon for 10 min. Using a syringe, phenylacetylene (1.0 mmol), iodobenzene (1.5 mmol), DMEDA (0.30 mmol), a solution (0.1 mL) of [Cu(DMEDA)$_2$]Cl$_2$·H$_2$O in MeOH (prepared by dissolving 16 mg (0.05 mmol) of the copper complex in 1 mL of HPLC-grade MeOH), and dioxane (1 mL) were sequentially added. The septum was then replaced by a teflon-coated screw cap, and the reaction vessel was placed in a pre-heated oil bath at 135 °C. After stirring for 22 h, the mixture was cooled to room temperature and diluted with ethyl acetate. The resulting solution was filtered through a pad of silica gel and concentrated. Purification of the product was performed by column chromatography on silica gel (eluent: hexane), affording **3 aa** (0.94 mmol, 167.5 mg) as a white solid in 94 % yield.

Computational details

All geometries were fully optimized in gas-phase by using the hybrid density functional B3LYP[28] and the LACVP* basis set as implemented in Jaguar 7.0.[34] LACVP* is the split valence Pople-style basis set 6–31G(d), supplemented by the Los Alamos effective core potential for copper.[29] Final gas-phase electronic energies were evaluated by using the larger basis set LACV3P** (6–311G(d,p) plus the Los Alamos ECP for copper). The dispersion corrected hybrid functional M06 was used in attempts to locate a hypothetical high-energy Cu^{III}-intermediate.[31] Solvent effects were evaluated by using the self-consistent reaction field (SCRF) model and the Poisson–Boltzmann solver in Jaguar 7.0.[30] The solvent 1,4-dioxane was defined by a dielectric constant (ε) of 2.2 and a probe radius of 2.0 Å. In all cases, the solvent effects on the activation energies were smaller than 8.0 kJ mol^{-1}. Transition state optimizations and zero point effects (ZPE) were computed by using Gaussian 03 at the B3LYP/LACVP* level of theory.[35] All transition states were verified to be first-order saddle points on the potential energy surface, meaning that there is one and only one imaginary frequency calculated from the Hessian matrix of the optimized structure.

Characterization data

Diphenylacetylene (3 aa): Yield: 94 % (white solid); m.p. 60 °C (lit.[3a] 60–61 °C); ^{1}H NMR (400 MHz, CDCl$_3$): δ=7.56–7.53 (m, 4H), 7.36–7.34 ppm (m, 6H); ^{13}C NMR (100 MHz, CDCl$_3$): δ=131.6, 128.3, 128.2, 123.2, 89.4 ppm; MS (EI): m/z (%): 178 [M]$^+$ (100), 176 (16), 85 (18), 83

(26), 57 (7); elemental analysis calcd (%) for $C_{14}H_{10}$ (178.08): C 94.34, H 5.66; found: C 94.35, H 5.72; the ^{1}H and ^{13}C NMR spectra were identical to those previously reported for this compound.[3a]

1-Nitro-(4-phenylethynyl)benzene (3 ba): Yield: 75 % (yellow solid); m.p. 117–118 °C (lit.[3a] 120–122 °C); ^{1}H NMR (400 MHz, CDCl₃): δ = 8.22 (d, J = 8.8 Hz, 2H), 7.67 (d, J = 9.1 Hz, 2H), 7.58–7.55 (m, 2H), 7.40–7.39 ppm (m, 3H); ^{13}C NMR (100 MHz, CDCl₃): δ = 146.9, 132.2, 131.8, 130.2, 129.2, 128.5, 123.6, 122.1, 94.6, 87.6 ppm; MS (EI): m/z (%): 223 [M]⁺ (100), 193 (24), 177 (19), 176 (60), 165 (21), 151 (23); elemental analysis calcd (%) for $C_{14}H_9NO_2$ (223.06): C 75.33, H 4.06, N, 6.27; found: C 75.42, H 4.13, N 6.35; the ^{1}H and ^{13}C NMR spectra were identical to those previously reported for this compound.[3a]

1-Cyano-(4-phenylethynyl)benzene (3 ca): Yield: 88 % (light yellow solid); m.p.: 107–108 °C (lit.[3a] 109–110 °C); ^{1}H NMR (400 MHz, CDCl₃): δ = 7.65–7.59 (m, 4H), 7.56–7.54 (m, 2H), 7.40–7.37 ppm (m, 3H); ^{13}CNMR (100 MHz, CDCl₃,): δ = 132.0, 131.9, 131.7, 129.1, 128.5, 128.2, 122.2, 118.5, 111.4, 93.8, 87.8 ppm; MS (EI): m/z (%): 203 [M]⁺ (100), 202 (12), 101 (11), 88 (9); elemental analysis calcd (%) for $C_{15}H_9N$ (203.24): C 88.64, H 4.46, N 6.89; found: C 88.70, H 4.51, N 6.93; the ^{1}H and ^{13}C NMR spectra were identical to those previously reported for this compound.[3a]

1-Fluoro-(4-phenylethynyl)benzene (3 da): Yield: 85 % (white solid); m.p. 109–110 °C (lit.[3a] 108–110 °C); ^{1}H NMR (400 MHz, CDCl₃): δ = 7.54–7.50 (m, 4H), 7.39–7.33 (m, 3H), 7.08–7.03 ppm (m, 2H); ^{13}C NMR (100 MHz, CDCl₃): δ = 162.4 (J_{C-F} = 249.1 Hz), 133.4 (J_{C-F} = 8.3 Hz), 131.5, 128.3 (2C), 123.0, 119.3 (J_{C-F} = 3.5 Hz), 115.6 (J_{C-F} = 22.0 Hz), 89.0, 88.3 ppm; ^{19}F NMR (376 MHz, CDCl₃): δ = −111.03 ppm; MS (EI): m/z (%): 196 [M]⁺ (100), 194 (6), 170 (4); elemental analysis calcd (%) for $C_{14}H_9F$ (196.22): C 85.69, H 4.62; found: C 85.70, H 4.65; the ^{1}H and ^{13}C NMR spectra were identical to those previously reported for this compound.[3a]

1-Methoxy-(4-phenylethynyl)benzene (3 ea): Yield: 86 % (white solid); m.p. 57–59 °C (lit.[3a] 58–60 °C); ^{1}H NMR (400 MHz, CDCl₃): δ = 7.53–7.46 (m, 4H), 7.37–7.32 (m, 3H), 6.90–6.87 (m, 2H), 3.83 ppm (s, 3H); ^{13}C NMR (100 MHz; CDCl₃): δ = 159.5, 133.0, 131.4, 128.2, 127.9, 123.5, 115.3, 114.0, 89.4, 88.1, 55.4; H, 5.81 ppm; MS (EI): m/z (%): 208 [M]⁺ (100), 202 (5), 193 (44), 165 (34), 104 (8); elemental analysis calcd (%) for $C_{15}H_{12}O$ (208.26): C 86.51, H 5.81; found: C 86.52, H 5.90; the ^{1}H and ^{13}C NMR spectra were identical to those previously reported for this compound.[3a]

1-Trifluoromethyl-(4-phenylethynyl)benzene (3 fa): Yield: 93 % (white solid); m.p. 103–104 °C (lit.[3a] 108–110 °C); ^{1}H NMR (400 MHz, CDCl₃): δ = 7.65–7.60 (m, 4H), 7.57–7.54 (m, 2H), 7.39–7.36 ppm (m, 3H); ^{13}C NMR (100 MHz, CDCl₃): δ = 131.7 (2C), 129.8 (J = 32.8 Hz), 128.8, 128.4, 127.1, 125.2 (J = 3.7 Hz), 122.7 (q, J_{C-F} = 253.2 Hz), 122.5, 91.7, 88.0 ppm; ^{19}F NMR (376 MHz, CDCl₃): δ = −62.82 ppm; MS (EI): m/z (%): 246 [M]⁺ (100), 227 (9), 196 (8), 176 (10), 98 (8); elemental analysis calcd (%) for $C_{15}H_9F_3$ (246.23): C 73.17, H 3.68; found: C 73.19, H 3.79; the ^{1}H and ^{13}C NMR spectra were identical to those previously reported for this compound.[3a]

1-Methyl-(3-phenylethynyl)benzene (3 ga): Yield: 86 % (colorless liquid); ^{1}H NMR (400 MHz, CDCl₃): δ = 7.57–7.53 (m, 2H), 7.39–7.33 (m, 5H), 7.24 (t, J = 7.6 Hz, 1H), 7.15 (d, J = 7.6 Hz, 1H), 2.36 ppm (s, 3H); ^{13}C NMR (100 MHz, CDCl₃): δ = 138.0, 132.2, 131.6, 129.1, 128.7, 128.4, 128.3, 128.2, 128.1, 123.0, 89.6, 89.1, 21.4 ppm; MS (EI): m/z (%): 192 [M]⁺ (100), 191 (31), 189 (24), 165 (12), 82 (5); elemental analysis calcd (%) for $C_{15}H_{12}$ (192.26): C 93.71, H 6.29; found: C 93.75, H 6.43; the ^{1}H and ^{13}C NMR spectra were identical to those previously reported for this compound.[5d]

1,3-Dimethyl-(2-phenylethynyl)benzene (3 ha): Yield: 80 % (colorless liquid); ^{1}H NMR (400 MHz, CDCl₃): δ = 7.58–7.56 (m, 2H), 7.40–7.35 (m, 3H), 7.17–7.08 (m, 3H), 2.54 ppm (s, 6H); ^{13}C NMR (100 MHz, CDCl₃): δ = 140.2, 131.3, 128.3, 128.0, 127.7, 126.7, 123.8, 122.9, 97.8, 87.1, 21.3 ppm; MS (EI): m/z (%): 206 [M]⁺ (100), 204 (25), 202 (29), 192 (14), 189 (27), 165 (16), 89 (10); elemental analysis calcd (%) for $C_{16}H_{14}$ (206.28): C 93.16, H 6.84; found: C 93.19, H 6.95; the ^{1}H and ^{13}C NMR spectra were identical to those previously reported for this compound.[3b]

3-(Phenylacetylene)pyridine (3 ia): Yield: 84 % (white solid); m.p. 49–50 °C (lit.[3c] 50 °C); ^{1}H NMR (400 MHz, CDCl₃): δ = 8.77 (dd, J = 2.1 Hz, J = 0.8 Hz, 1H), 8.54 (dd, J = 4.9 Hz, J = 1.7 Hz, 1H), 7.82–7.79 (m, 1H), 7.56–7.53 (m, 2H), 7.38–7.35 (m, 3H), 7.30–7.26 ppm (m, 1H); ^{13}C NMR (100 MHz, CDCl₃): δ = 152.2, 148.5, 138.3, 131.6, 128.7, 128.4, 123.0, 122.5, 120.4, 92.6, 86.0 ppm; MS (EI): m/z (%): 179 [M]⁺ (100), 178 (22), 152 (8), 151 (10), 126 (11), 76 (8); elemental analysis calcd (%) for $C_{13}H_9N$ (179.22): C 87.12, H 5.06, N 7.82; found: C 87.15, H,5.21, N 7.86; the ^{1}H and ^{13}C NMR spectra were identical to those previously reported for this compound.[3c]

2-(Phenylacetylene)pyridine (3 ja): Yield: 86 % (yellow oil); ^{1}H NMR (400 MHz, CDCl₃): δ = 8.61 (d, J = 5.0 Hz, 1H), 7.69–7.64 (m, 1H), 7.61–7.59 (m, 2H), 7.52 (dd, J = 8.0 Hz, J = 1.1 Hz, 1H), 7.36–7.34 (m, 3H), 7.24–7.20 ppm (m, 1H); ^{13}C NMR (100 MHz, CDCl₃): δ = 150.0, 143.4, 136.1, 132.0, 128.9, 128.3, 127.1, 122.7, 122.2, 89.2, 88.6 ppm; MS (EI): m/z (%): 179 [M]⁺ (100), 178 (38), 151 (12), 76 (9), 51 (5); elemental analysis calcd (%) for $C_{13}H_9N$ (179.22): C 87.12, H 5.06, N 7.82; found: C 87.21, H 5.31, N 7.83; the ^{1}H and ^{13}C NMR spectra were identical to those previously reported for this compound.[3d]

3-(Phenylethynyl)thiophene (3 ka): Yield: 54 % (white solid); m.p. 43–44 °C (lit.[3e] 44–45 °C); ^{1}H NMR (400 MHz, CDCl₃): δ = 7.54–7.51 (m, 3H), 7.37–7.34 (m, 3H), 7.32–7.30 (m, 1H), 7.21 ppm (dd, J = 5.0 Hz, J = 1.4 Hz, 1H); ^{13}C NMR (100 MHz, CDCl₃): δ = 131.5, 129.8, 128.5, 128.3, 128.2, 125.3, 123.2, 122.3, 88.9, 84.5 ppm; MS (EI): m/z (%): 184 [M]⁺ (100), 152 (14), 139 (25), 121 (4); elemental analysis calcd (%) for $C_{12}H_8S$ (184.26): C 78.22, H 4.38; found: C 78.24, H 4.45; the ^{1}H and ^{13}C NMR spectra were identical to those previously reported for this compound.[3f]

1-Methyl-(4-phenylethynyl)benzene (3 ab): Yield: 83 % (white solid); m.p. 71–72 °C (lit.[3a] 72–73 °C); ^{1}H NMR (300 MHz, CDCl₃): δ = 7.55–7.52 (m, 2H), 7.44 (dd, J = 6.6 Hz, J = 1.8 Hz, 2H), 7.37–7.33 (m, 3H), 7.16 (d, J = 8.0 Hz, 2H), 2.38 ppm (s, 3H); ^{13}C NMR (75 MHz, CDCl₃): δ = 138.4, 131.5 (2C), 129.1, 128.3, 128.1, 123.5, 120.2, 89.5, 88.7, 21.5 ppm; MS (EI): m/z (%): 192 [M]⁺ (100), 191 (41), 189 (22), 165 (14), 95 (8); elemental analysis calcd (%) for $C_{15}H_{12}$ (192.26): C 93.71, H 6.29; found: C 93.71, H 6.32; the ^{1}H and ^{13}C NMR spectra were identical to those previously reported for this compound.[3a]

1-Methyl-(2-phenylethynyl)benzene (3 ac): Yield: 85 % (colorless oil); ^{1}H NMR (400 MHz, CDCl₃): δ = 7.47–7.45 (m, 2H), 7.42 (d, J = 7.5 Hz, 1H), 7.29–7.24 (m, 3H), 7.15 (dd, J = 6.2 Hz, J = 1.5 Hz, 2H), 7.10–7.06 (m, 1H), 2.44 ppm (s, 3H); ^{13}C NMR (100 MHz, CDCl₃): δ = 140.1, 131.8, 131.5, 129.4, 128.3, 128.2, 128.1, 125.5, 123.5, 123.0, 93.3, 88.4, 20.9 ppm; MS (EI): m/z (%): 192 [M]⁺ (100), 191 (41), 189 (23), 165 (12), 95 (6); elemental analysis calcd (%) for $C_{15}H_{12}$ (192.26): C 93.71, H 6.29; found: C 93.70, H 6.41; the ^{1}H and ^{13}C NMR spectra were identical to those previously reported for this compound.[3g]

1-Methoxy-(4-phenylethynyl)benzene [3 a (3 ea)]: Yield: 70 % (white solid); m.p. 57–59 °C (lit.[3a] 58–60 °C); ^{1}H NMR (400 MHz, CDCl₃): δ = 7.53–7.47 (m, 4H), 7.34–7.32 (m, 3H), 6.90–6.87 (m, 2H), 3.83 ppm (s, 3H); ^{13}C NMR (100 MHz, CDCl₃): δ = 159.5, 133.0, 131.4, 128.2, 127.9, 123.5, 115.3, 114.0, 89.4, 88.1, 55.4 ppm; MS (EI): m/z (%): 208 [M]⁺ (100), 202 (5), 193 (44), 165 (34), 104 (8); elemental analysis calcd (%) for $C_{15}H_{12}$ (208.26): C 86.51, H 5.81; found: C 86.53, H 6.01.

1-Methoxy-(2-phenylethynyl)benzene (3 ae): Yield: 63 % (yellow oil); ^{1}H NMR (400 MHz, CDCl₃): δ = 7.57–7.54 (m, 2H), 7.51–7.48 (dd, J = 7.1 Hz, J = 1.4 Hz, 1H), 7.35–7.27 (m, 4H), 6.95–6.86 (m, 2H), 3.90 ppm (s, 3H); ^{13}C NMR (100 MHz, CDCl₃): δ = 159.8, 133.5, 131.6, 129.7, 128.2, 128.0, 123.5, 120.4, 112.4, 110.7, 93.4, 85.8, 55.9 ppm; MS (EI): m/z (%): 208 [M]⁺ (100), 207 (67), 179 (12), 178 (22), 165 (32), 164 (14); elemental analysis calcd (%) for $C_{15}H_{12}$ (208.26): C 86.51, H 5.81; found: C 86.57, H 6.10; the ^{1}H and ^{13}C NMR spectra were identical to those previously reported for this compound.[5d]

1-Fluoro-(4-phenylethynyl)benzene [3 af (3 da)]: Yield: 67 % (white solid); m.p. 109–110 °C (lit.[3a] 108–110 °C); ^{1}H NMR (400 MHz, CDCl₃): δ = 7.54–7.51 (m, 4H), 7.37–7.34 (m, 3H), 7.07–7.03 ppm (m, 2H); ^{13}C NMR (100 MHz, CDCl₃): δ = 162.4 (J_{C-F} = 249.1 Hz), 133.4 (J_{C-F} = 8.3 Hz), 131.5, 128.3 (2C), 123.0, 119.3 (J_{C-F} = 3.5 Hz), 115.6 (J_{C-F} = 22.0 Hz), 89.0, 88.3 ppm; ^{19}F NMR (376 MHz, CDCl₃): δ = −111.04 ppm;

MS (EI): m/z (%): 196 [M]$^+$ (52), 83 (68), 71 (40), 57 (100); elemental analysis calcd (%) for C$_{14}$H$_9$F (196.22): C 85.69, H 4.62; found: C 85.73, H 4.75.

1-Cyano-(4-phenylethynyl)benzene [3ag (3ca)]: Yield: 24% (50% yield with 50 mol% of DMEDA; white solid); m.p. 107–108°C (lit.[3a] 109–110°C); ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.66–8.60 (m, 4H), 7.56–7.53 (m, 2H), 7.39–7.37 ppm (m, 3H); ^{13}CNMR (75 MHz, CDCl$_3$): δ = 132.0, 131.8, 129.1, 128.5, 128.2, 122.2, 118.5, 111.5, 93.8, 87.7 ppm; MS (EI): m/z (%): 203 [M]$^+$ (100), 143 (10), 105 (48), 83 (11); elemental analysis calcd (%) for C$_{15}$H$_9$N (203.24): C 88.64, H 4.46, N 6.89; found: C 88.65, H 4.62, N 6.92.

2-(Phenylacetylene)pyridine [3ah (3ja)]: Yield: 44% (green oil); ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.62–8.60 (m, 1H), 7.69–7.63 (m, 1H), 7.61–7.58 (m, 2H), 7.53–7.50 (m, 1H), 7.38–7.33 (m, 3H), 7.24–7.20 (m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 150.0, 143.4, 136.1, 132.0, 128.9, 128.3, 127.1, 122.7, 122.2, 89.2, 88.6 ppm; MS (EI): m/z (%): 179 (M$^+$, 100), 178 (33), 151 (8), 126 (6), 51 (6); elemental analysis calcd (%) for C$_{13}$H$_9$N (179.22): C 87.12, H 5.06, N 7.82; found: C 87.15, H 5.35, N 7.84.

3-(Phenylacetylene)pyridine [3ai (3ia)]: Yield: 35% (white solid); m.p. 49–50°C°C (lit.[3c] 50°C); ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.77 (dd, J = 2.1 Hz, J = 0.9 Hz, 1H), 8.49 (dd, J = 5.1 Hz, J = 1.5 Hz, 1H), 7.83–7.79 (m, 1H), 7.56–7.52 (m, 2H), 7.39–7.35 (m, 3H), 7.30–7.26 ppm (m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 152.2, 148.5, 138.4, 131.7, 128.8, 128.4, 123.0, 122.5, 120.5, 92.6, 85.9 ppm; MS (EI): m/z (%): 179 [M]$^+$ (100), 178 (21), 151 (11), 105 (68), 77 (23); elemental analysis calcd (%) for C$_{13}$H$_9$N (179.22): C 87.12, H 5.06, N 7.82; found: C 87.13, H 5.30, N 7.85.

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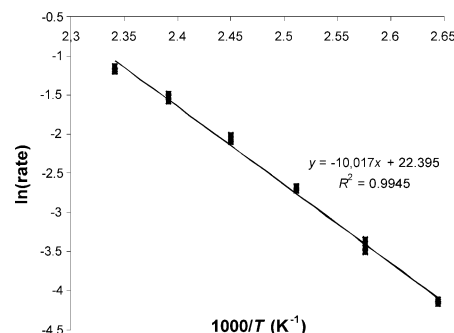
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