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Sub-Mol % Catalyst Loading and Ligand-Acceleration in the Copper-Catalyzed Coupling of Aryl Iodides and Terminal Alkyenes

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Aryl alkynes and related conjugated enynes are important precursors for the synthesis of pharmaceuticals, natural products, and organic materials.^[1] They can conveniently be produced from terminal alkynes and aryl or vinyl halides or triflates by the well-known palladium-copper co-catalyzed Sonogashira-Hagihara reaction.^[2] Motivated by the high price and toxicity of palladium, there has been considerable effort to minimize the amount of this metal in the reaction mixture.^[3] Already a decade before the discovery of the Sonogashira-Hagihara protocol,^[2a] stoichiometric couplings between aryl iodides and copper acetylides, in the absence of palladium, had been reported.^[4] The subsequently developed copper-catalyzed versions of this so-called Castro-Stephens reaction initially involved complexes with phosphane ligands.^[5] Later, copper catalysts with more stable and readily available nitrogen-^[6] or oxygen-based ligands,^[7] as well as unsupported catalysts^[8] and copper nanoparticles were introduced for this process.^[9] Compared to the palladium- or palladium/copper-catalyzed versions, these protocols have significant drawbacks. First, copper also catalyzes the oxidative homocoupling of terminal alkynes (the so-called Glaser reaction)^[10] leading to lower yields of the desired cross-coupling products and complicating their purifications. Second, copper loadings of more than 5 mol% and high reaction temperatures are generally required to obtain acceptable yields. Although copper is a cheap and abundant metal, such high catalyst loadings lead to other problems. Apart from a more difficult product purification, large amounts of copper(I) acetylides will be formed, which, depending on the acetylene used, can be highly explosive.

Inspired by the recent findings on catalyzed cross-coupling reactions with ppm-level copper loadings,^[11] we decid-

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ed to investigate a possible use of low copper concentrations in Castro–Stephens couplings of aryl halides and terminal alkynes. As a catalyst precursor, the air- and moisture-stable Cu^{II} complex [Cu(DMEDA)₂]Cl₂·H₂O (1)^[12] was chosen (DMEDA = *N,N*'-dimethylethylenediamine). To minimize contamination with trace amounts of other catalytically active metals, this compound was synthesized starting from 99.995 % pure CuCl₂ and 99 % + pure DMEDA using HPLC-grade solvents. The remaining metal impurities were determined by ICP-MS, which showed that the resulting complex contained 8 ppm of Mn, 1 ppm of Ni, and less than 4 ppb of Pd.

For the initial screening, the reaction between iodobenzene and phenylacetylene was selected (Table 1). Based on previous work on similar catalyst systems,^[6a] a combination

Table 1. The coupling of phenylacetylene and iodobenzene: Screening of catalyst and ligand concentrations.^[a]

1 (X mol%), DMEDA (V mol%)	
solvent, 135 °C, 22 h	

Entry	x	у	Solvent	Yield [%] (GC)	
	[mol %]	[mol %]		3 h	22 h
1	-	-	1,4-dioxane	0	0
2	_	30	1,4-dioxane	0	0
3	1	-	1,4-dioxane	4	20
4	0.5	-	1,4-dioxane	3	14
5	0.5	30	1,4-dioxane	48	>99
6	0.5	1×10^4	DMEDA	>99	>99

[a] Performed in closed vials at 135°C.

of (distilled) 1,4-dioxane as solvent and Cs_2CO_3 (99.9% +) as base was chosen. The reactions were performed by using 1 mmol of phenyl acetylene and 1.5 mmol of iodobenzene in 1 mL of solvent, under an argon atmosphere. Glaser-type homocoupling products were not observed under these conditions. No reaction occurred in the absence of copper complex **1** (Table 1, entries 1 and 2). This demonstrated the es-

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sential role of the copper catalyst and revealed that any ppmlevel amounts of metals present in the base, substrates, solvent, and ligand did not catalyze the reaction.

With 0.5 or 1 mol% of the catalyst the yield of the coupling product was low even after 22 h. Because previous studies in C-X cross-coupling reactions had shown that the efficiency of the catalysis was affected by the ligand concentration,^[11,13] the reaction was performed in the presence of 30 mol % of additional DMEDA (60 equiv relative to **1**). To our delight, the product was obtained in 48% and quantitative yield after 3 and 22 h, respectively, using only 0.5 mol % complex 1 of (Table 1, entry 5). This improvement corresponded to a more than twelve-fold increase in reaction rate. Without copper, the presence of ligand did not lead to the formation of



Figure 1. Kinetic measurements on the coupling between iodobenzene and phenylacetylene in 1,4-dioxane (\bullet) and toluene ($_{\odot}$) at 135 °C. Dependence of the reaction rate on the iodobenzene (A), phenylacetylene (B), copper (C), and DMEDA (D) concentration.

diphenylalkyne (Table 1, entry 2). Conceptionally, these observations indicate that this is a prime example of *ligand-ac-celerated catalysis (LAC)*.^[14]

Using these reaction conditions, several other base/solvent combinations that are common in copper-catalyzed crosscoupling reactions were then investigated (see Table S1 in the Supporting information). Also relatively mild and cheap inorganic bases such as K₂CO₃ and K₃PO₄ proved highly effective. In contrast, neither KOH, KOtBu, NaOAc nor, to our surprise, NEt₃ gave the coupling product. As solvent, 1,2-dimethoxyethane and toluene could also be employed, whereas DMF, DMSO, and 1,2-dichoroethane proved unsuitable. Although both reactants and the product were insoluble in water, the reaction did proceed in its presence. Performing the reaction in DMEDA, a liquid with a boiling point of 118°C, had a highly beneficial effect, leading to complete conversion within 3 h (Table 1, entry 6). This provided further evidence of the significant rate-enhancement by this diamine.

To gain more insight into this ligand-accelerated process, kinetic studies were performed and the dependence of the reaction rate on the concentrations of the various reaction components was investigated (Figure 1). In both 1,4-dioxane and toluene (using 0.005 mmol of **1** and 0.3 mmol of DMEDA in 1 mL of solvent) the reaction rate showed a first-order rate dependence on the iodobenzene concentration over a range of $0-2 \text{ mol } L^{-1}$ (Figure 1, A). Despite larger fluctuations in the measurements, the reaction rate

appeared to be independent of the alkyne concentration over a concentration range of $0.2-1.6 \text{ mol } L^{-1}$ (Figure 1, B). The dependence of the reaction rate on the amount of copper in the reaction mixture was evaluated at copper concentrations of 0-6.3 mmol L^{-1} (0-1 mol% of 1 relative to alkyne), using the previously described reaction conditions. In toluene, the reaction rate was first-order dependent on the copper concentration at very low copper loadings, and above 0.8 mmol L^{-1} (0.11 mol %), it became independent of the copper concentration. In dioxane, the reaction rate exhibited a non-linear rate-dependence on the copper concentration over the range studied here (Figure 1, C). The effect of the ligand on the reaction rate was studied at ligand concentrations between 0-1.5 mol L⁻¹ (0-450 mol % relative to the alkyne), using the reaction conditions described before. In the absence of additional ligand, the rate of the reaction was very low in both solvents ($0.008 \text{ mol } L^{-1}$ product h^{-1} in dioxane, and $0.003 \text{ mol } \text{L}^{-1}$ product h^{-1} in toluene). The ligand had a profound accelerating effect (Figure 1, D). In toluene, a first-order rate dependence was observed over the entire concentration range. In dioxane, the reaction was first-order dependent on the concentration of the ligand up to a concentration of $0.7 \text{ mol } L^{-1}$, which corresponded to a ligand-to-metal ratio of 200:1 and a ligand-to-alkyne ratio of 1:1. At higher concentrations, the rate dependence started to deviate from first order.

These kinetic measurements shed light on the mechanism of the reaction. The observed order in copper suggested that

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the resting state of the catalyst was a dimeric or polymeric complex that was in equilibrium with an active monomeric catalyst.^[15,16] The first order in both iodobenzene and DMEDA demonstrated that these two reagents were involved early in the catalytic cycle leading from the catalyst resting state up to and including the rate-determining step. Taking into account the partial order in copper, the initial steps in the



Scheme 1. The proposed reaction mechanism for the catalytic Castro–Stephens reaction (black) and the well-established catalytic cycle for the palladium-copper co-catalyzed Sonogashira–Hagihara reaction (gray); with M = Cs in this study.

catalytic cycle were likely to involve first, a reversible coordination of the ligand to the polymeric resting state of the catalyst, converting it into an active monomeric catalyst, and second, reaction of this monomeric species with iodobenzene (Scheme 1). The zeroth order in phenyl acetylene indicated that this substrate was either already coordinated to the catalyst in its resting state, or that it was only involved in the catalytic cycle after the rate-determining step (as it is the case in the corresponding palladium-catalyzed process).

The nature of the resting state of the catalyst was investigated by performing stoichiometric reactions at 135°C in dioxane, systematically omitting components from the reaction mixture. When 1 was combined with phenylacetylene in the absence of a base, no reaction occurred and 1 was recovered. Heating of 1 in the presence of Cs_2CO_3 , but in the absence of iodobenzene and phenylacetylene, resulted in a color change from deep blue to dark green, and the formation of a black precipitate. A similar behavior was observed when this reaction was performed in the presence of excess ligand. When 1 was allowed to react with an over-stoichiometric quantity of phenylacetylene in the presence of Cs_2CO_3 , the reaction mixture rapidly turned bright yellow, and a yellow precipitate was formed. A similar color change was observed under catalytic conditions, although there the concentration of 1 was much lower and the color change more difficult to detect. The solid was isolated, washed with water and diethyl ether and then extensively dried. Elemental analysis revealed that this compound contained no nitrogen, and its carbon and hydrogen contents corresponded to $[Cu(phenylacetylene)]_n$, a known Cu^{I} coordination polymer.^[5b,17] In the coupling reaction this compound was active under the previously described conditions.

From these results we deduce the following scenario: DMEDA acts as reductant of **1**, in analogy to other secondary amines that are known to reduce Cu^{II} to $Cu^{I,[18]}$ Subsequently, a Cu^{I} acetylide is formed, which upon agglomeration loses its nitrogen ligands. This product is insoluble in common organic solvents, but it dissolves in pyridine and DMEDA to give light-green highly oxidation-sensitive solutions. The resting state of the catalyst therefore seems to be a polynuclear copper–acetylide species, and the role of the large excess of ligand is to generate a highly electron-rich monomeric acetylide complex that is able to react with the

aryl halide (Scheme 1). With the goal of gaining a deeper insight into the initial steps of the reaction, conversions of several electronically different aryl halides were investigated (Table 2). Reaction rates, expressed in mol product $mol^{-1}Cuh^{-1}$, were determined at two different catalyst loadings to explore whether all substrates showed the same nonlinear dependence of the reaction rate on the catalyst con-

Table 2. The coupling of aryl acetylenes and aryl iodides: Turnover frequencies at two different catalyst loadings. 1 (0.5 or 0.05 mol%),

I	R ¹ -{	$= + X - Ar \frac{DMEL}{Cs_2Cc}$ 1,4-dic	→ (30 mbr%) → R D ₃ (2 equiv), oxane 135 °C	1-{Ar	
Entry	$\mathbf{v} = \mathbf{R}^1$	X–Ar	Turnover frequencies [h ⁻¹] Cu (0.5 mol%) Cu (0.05 mol%)		
1	Н	IF	24	90	
2	Н	IMe Me	29	99	
3	Н	I	29	106	
4	Н	I-OMe	33	110	
5	Н		35	115	
6	Н		114	247	
7	Н	I → ⊂ ⊂ F₃	152	631	
8	Н	I-CN	238	820	
9	Н		310	979	
10	Н	Br	<1	n.d. ^[a]	
11	OMe		13	n.d. ^[a]	
12	Me		18	n.d. ^[a]	
13	CF ₃		37	n.d. ^[a]	

[a] n.d. = not determined.

centration as previously observed for iodobenzene. Indeed, for all substrates the measured turnover frequencies were approximately three times higher at 0.05 mol% than at 0.5 mol% of copper. This indicated that the large differences in reaction rate could indeed be attributed to the intrinsic reactivities of the aryl halides towards the catalyst, and were not caused by different amounts of active catalyst in the reaction mixture.

As in C–N bond-forming reactions catalyzed by similar catalyst systems,^[15a,19] the reaction was accelerated by the presence of electron-withdrawing substituents on the aryl iodide. Two substrates fell outside this trend. 4-Fluoroiodo-benzene (Table 2, entry 1) was less active, while 4-methoxy-iodobenzene (Table 2, entry 4) was more active than expected based on the Hammett σ values of the two substituents.^[20] In addition, *p*-NO₂ and *p*-CN substituents on the arene ring led to extraordinarily high turnover frequencies, indicative of a significant buildup of negative charge on the arene during the reaction. Unfortunately, bromobenzene was not converted under these reaction conditions.

Despite the reaction rate being independent of the alkyne concentration (Figure 1, B), differences were observed when electronically modified aryl acetylenes were applied (Table 2, entries 5, 11-13). This behavior indicated that the coordination of the alkyne to the catalyst took place prior to the rate-determining step of the reaction, and therefore the alkyne was already present in the resting state of the catalyst. The addition of electron-withdrawing substituents to the alkyne favors the coordination of the donating diamine ligand to the copper-acetylide resting state of the catalyst, leading to a higher concentration of the active monomeric catalyst in solution. It also provided evidence that the reaction was indeed catalyzed by copper and not co-catalyzed by any traces of palladium that may be present in the reaction mixture. In the latter case, the acetylide would only be transferred to the active palladium catalyst after oxidative addition of the aryl halide to palladium (Scheme 1). If this step or the subsequent C-C bond formation would then determine the overall reaction rate, the kinetic measurements would show a positive order in alkyne. If, on the other hand, the rate-determining step preceded this transmetallation step, the electronic properties of the alkyne should not influence the overall reaction rate.

In conclusion, we have demonstrated that Castro–Stephens reactions can readily be performed using sub-mol% copper loadings. The process is a striking example of *ligand-accelerated catalysis*, in which the addition of DMEDA ligand converts the resting state of the catalyst into an unprecedentedly active monomeric Cu¹ acetylide species. Although a large excess of the ligand is required to activate the copper catalyst, the relatively low boiling point of DMEDA allows recovery and recycling of the ligand through distillation. Further research will be focused on elucidating the exact nature of the rate-determining step of this process and on developing ligand structures that coordinate more strongly to Cu¹ acetylide complexes. Based on the proposed mechanism this should lead to increased amounts of

active catalyst in solution and higher reaction rates/lower reaction temperatures.

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