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Direct Arylation of Benzene with Aryl Bromides using High-Temperature/High-Pressure Process Windows: Expanding the Scope of C–H Activation Chemistry

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Abstract: A detailed investigation on the direct arylation of benzene with aryl bromides by using first-row transition metals under high-temperature/high-pressure (high-*T*/*p*) conditions is described. By employing a parallel reactor platform for rapid reaction screening and discovery at elevated temperatures, various metal/ligand/base combinations were evaluated for their ability to enable biaryl formation through C–H activation. The combination of cobalt(III) acetylacetonate and lithium bis(trimethylsilyl)amide was subjected to further process intensification at 200 °C (15 bar), allowing a significant reduction of the catalyst/base loading and a dramatic increase in catalytic efficiency (turnover frequency) by a factor of 1000 compared to traditional protocols. The high-throughput screening additionally identified novel nickel- and copper-based metal/ligand combinations that favored an amination pathway competing with C–H activation, with the addition of ligands, such as 1,10-phenanthroline, having a profound influence on the selectivity. In addition to metal-based catalysts, high-*T*/*p* process windows were also successfully applied to transition-metal-free systems, utilizing 1,10-phenanthroline as organocatalyst.

Keywords: biaryls · cross-coupling · transition-metal catalysis · microwave chemistry · novel process windows · organocatalysis

Introduction

The C–H bond is the most fundamental and probably most common linkage in organic chemistry and therefore represents a potentially ubiquitous functional group in organic synthesis. Selective replacement reactions of the C–H bond, resulting in the formation of new bond types, especially C–C, but also C–O, C–N, or C–X linkages, are of significant interest for fundamental research and the chemical industry.[1] For example, the synthesis of biaryl scaffolds by direct arylation of arenes with aryl halides (or other electrophiles) has become an area of intense research activity in the past few years, mainly owing to the environmentally friendly character of the atom economic C–H activation chemistry.[2] In many instances, these direct arylation/C–H activation processes still require the use of noble metal catalysts based on Pd, Rh, Pt, Ir, or Ru.[2] Importantly, following a recent trend toward more sustainable concepts in catalysis,[3] the number of publications describing readily available first-row transition-metal catalysts for these direct arylations has dramatically increased during the last two years.[4–15] Thus, several catalysts based on inexpensive Cu,[4,5] Co,[6,7] Fe,[8–13] and Ni[14,15] systems have been demonstrated to be able to promote C–H bond arylations of this type in the presence of a base. In addition, transition-metal-free organocatalytic protocols, using either 1,10-phenanthroline (phen) derivatives,[16,17] *N,N*-dimethylethane-1,2-diamine (DMEDA),[18] or quinoline-1-amino-carboxylic acid,[19] have been disclosed.[20]

From a mechanistic point of view, when aryl halides react with simple arenes to form biaryls, the mechanism has been proposed to follow a radical pathway involving a single-electron-transfer step,[6,7,12–19] also called "homolytic aromatic substitution" (HAS).[21] Similar biaryl formations using conventional radical-type reagents, such as tris(trimethylsilyl)silane (TTMSS), either alone[22] or in combination with azobis-isobutyronitrile (AIBN),[23] are also known.

However, for all of the reported first-row transition-metal-catalyzed[4–15] and organocatalytic direct arylation methods,[16–19] long reaction times (2–48 h) in combination with high catalyst and base loadings are required, clearly limiting the practical use of these otherwise appealing synthetic methods. In the present paper, we explore the concept of high-temperature/high-pressure (high-*T*/*p*) process windows[24] for the rapid discovery and screening of novel catalyst/ligand/base combinations in these direct arylation/C–H activation processes, employing a dedicated high-throughput/parallel experimentation platform. We also demonstrate that these high-*T*/*p* process windows (200 °C, 15 bar) can be used to obtain reaction conditions that utilize significantly lower catalyst loadings and, at the same time, are able to drastically reduce the required reaction times from typically 48 h to 5 min without loss of selectivity.

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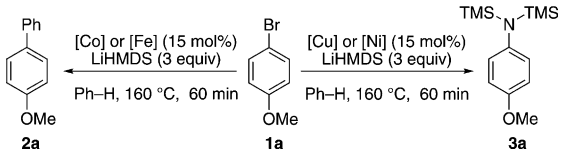
Results and Discussion

Parallel catalyst/ligand/base screening using high-*T*/*p* conditions: In a recent publication, Shi and co-workers reported an evaluation of various transition-metal catalysts in combination with different ligands and KO*t*Bu as base for the direct arylation of unactivated benzene with aryl bromides using a standard oil-bath setup (80–100 °C for 48 h).[25] Based on these studies, we decided to perform a parallel reaction screening under high-*T*/*p* conditions that would allow us to assess the performance of a particular catalyst/ligand/base combination in a rapid and efficient manner. For this purpose, we have employed a microtiter-plate-type high-throughput experimentation platform made out of silicon carbide ceramic that enables the parallel processing of 24 reactions (0.3–3 mL volume) at temperatures of 200 °C under sealed vessel (autoclave) conditions at internal pressures of up to 20 bar (Figure 1).[26] Owing to the high thermal conductivity and large heat capacity of silicon carbide (SiC), the microtiter plate is heated up very rapidly without temperature gradients when placed on a standard hotplate/magnetic stirrer.[26] Therefore, high reaction homogeneity, ideally suited for parallel reaction screening, is typically obtained by using SiC plate systems of this type.[27,28]

Figure 1. Silicon carbide 6×4 deep well reaction screening platform fitted with 5 mL Pyrex reaction vials with PTFE seals (PTFE = polytetrafluoroethylene) and screw caps.

As an initial reference point for our screening efforts, we considered a recently reported Co-catalyzed arylation protocol, offering the possibility of carrying out these reactions without an additional ligand.[7] The optimized conditions utilized Co(III) acetylacetonate (15 mol%) as a catalyst and lithium bis(trimethylsilyl)amide (LiHMDS, 3 equiv) as base and provided the desired biaryl structures in moderate to good yields after 48 h at 80 °C.[7] Therefore, we decided to employ three equivalents of LiHMDS in combination with a broad range (17 examples) of first-row transition-metal catalysts (15 mol%) in our initial screening experiments. Selecting the direct arylation of benzene (solvent) with 4-bromoanisole (**1a**) as a model reaction, a reaction temperature



Scheme 1. The selectivity switches between direct arylation/C–H activation and amination, depending on the utilized metal.

of 160 °C (estimated internal pressure about 8 bar) and a reaction time of 1 h were chosen for the parallel screening experiments (compare Scheme 1).

The catalytic activity of several Co, Ni, Fe, Cr, Co, and Mn complexes or salts was initially evaluated in the absence of any ligand (Figure 2, no ligand). Surprisingly, depending on the metal used, we observed two entirely different reaction pathways. All Co catalysts and [Fe(acac)$_3$] resulted in the anticipated formation of biaryl **2a** in moderate to high conversions, as determined by GC-FID analysis (FID = flame ionization detector, Scheme 1). As expected, the best results were obtained with the already published [Co(acac)$_3$]/LiHMDS-promoted system.[7] In addition, $CoBr_2$, $CoCl_2$, [Co(acac)$_2$], and [Fe(acac)$_3$] showed some activity for the direct arylation/C–H activation, but only with comparatively low efficiency, which is in agreement with previous literature reports (Figure 2, no ligand).[7] With Ni and Cu catalysts, an unforeseen amination reaction was discovered (Scheme 1). The product obtained in these experiments was readily identified as 4-methoxy-bis(trimethylsilyl)aniline (**3a**) by GC-MS analysis, apparently formed by the reaction of LiHMDS with 4-bromoanisole (**1a**). It is worth noting that the Pd-catalyzed variation (requiring a phosphine ligand) of this amination reaction has been disclosed independently by Hartwig and Buchwald in 2001.[29] The now-discovered, ligand-free Cu- and Ni-catalyzed methods nicely complement the previous Pd-based protocols (see below for further mechanistic studies and preparative results).

Since several Cu and Ni catalysts have been employed previously in these direct arylation/C–H activation reactions in combination with a ligand and a strong base, such as KO*t*Bu,[14,15,25] we decided to carry out two additional cycles of parallel-screening reactions. Here, again three equivalents of LiHDMS were employed as base, but now 30 mol% of either 1,10-phenanthroline (Figure 2, 1,10-phenanthroline) or DMEDA (Figure 2, DMEDA) were used to investigate the effect of added ligands, in particular on the selectivity (direct arylation vs. amination). Both ligand types often have been used in direct arylation/C–H activation chemistry of this type.[12,13,15,25]

An evaluation of the 1,10-phenanthroline experiments demonstrated (Figure 2, 1,10-phenanthroline) that, by using otherwise identical conditions than in the first set of experiments, this ligand on its own (in the absence of any transition-metal catalyst) is able to catalyze the biaryl formation in a more efficient way than in combination with several of the metal catalysts investigated. This result is in agreement with the data presented by Shi and co-workers[16] and will be

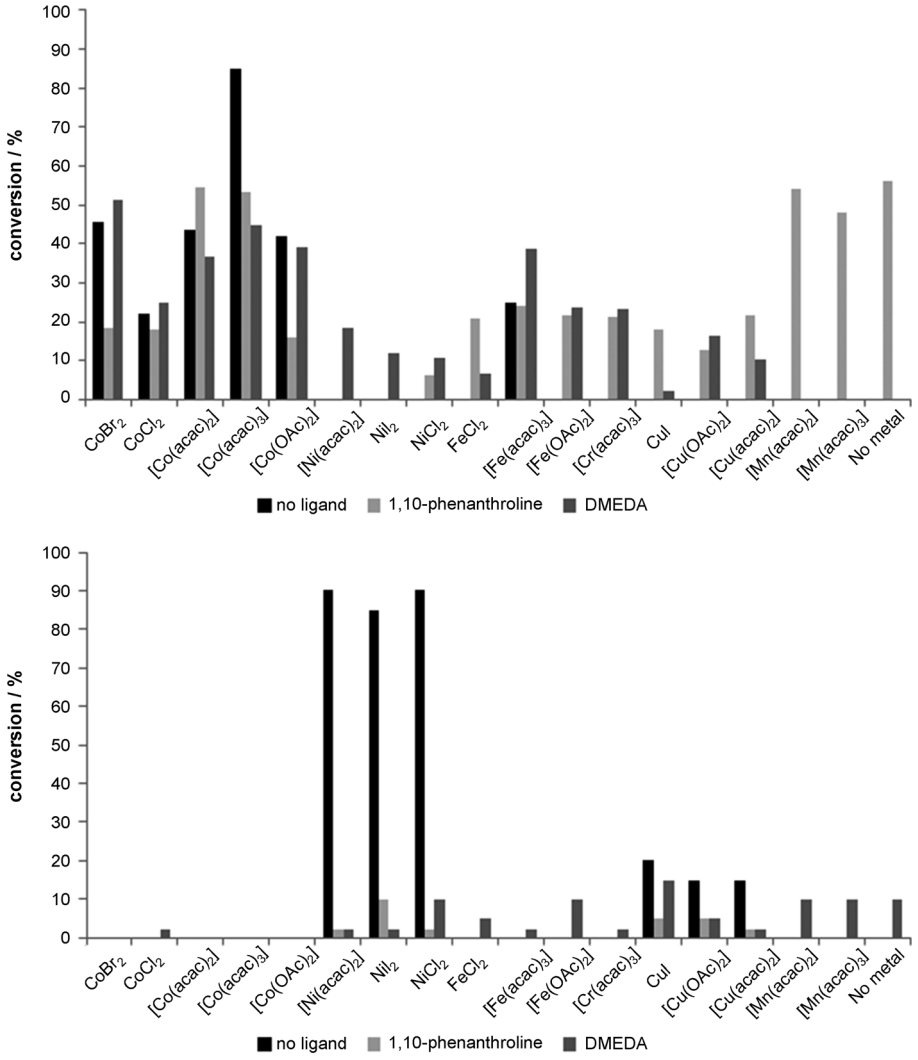


Figure 2. Conversion toward biaryl formation (top) and amination (bottom) for the parallel screening of 17 transition-metal catalysts in three different experiments under high-*T*/*p* conditions (Figure 1). Experiment 1: no ligand (■); experiment 2: 1,10-phenanthroline (30 mol%, ■); experiment 3: DMEDA (30 mol%, ■). General reaction conditions (Scheme 1): **1a** (0.13 mmol), benzene (2 mL), catalyst (15 mol%), LiHMDS (3 equiv), ligand (30 mol%), 160 °C, 1 h. Conversion from substrate to product was determined by GC-FID using *n*-dodecane as internal standard. See Table S1 in the Supporting Information for numerical data.

discussed in more detail below. With the exception of NiI_2 and $[Ni(acac)_2]$, all reactions resulted in the formation of the target biaryl molecule. It is worth noting that various Co species had a higher efficiency when no ligand was added. $[Co(acac)_2]$ and $[Co(acac)_3]$ resulted in similar yields, which may indicate that the same catalytically active species is ultimately formed from both precursors. Fe catalysis also resulted in lower yields compared to the organocatalytic version, whereas Mn catalysts gave comparably high yields.

The results obtained from the screening of the DMEDA ligand (Figure 2, DMEDA) support a "catalyst–ligand theory": generally, when DMEDA was used in combination with metal catalysts the biaryl scaffold **2a** was observed, while in the absence of metals the amination product **3a** was obtained selectively. Several metal species, including Ni, Cu, or Cr, apparently require additional ligands for the direct arylation of unactivated arenes. While phenanthroline allows the possibility that this reaction is catalyzed by the ligand itself, DMEDA-mediated reactions strongly support the hypothesis that, in this case, ligand–catalyst combinations are required for successful biaryl couplings. The exception to this observation is Mn. Here, without ligand no reaction occurred, while the addition of either phenanthroline or DMEDA exhibited the same result as the respective transition-metal-free reaction. It is therefore likely that the tested Mn species are catalytically inactive in these reactions.

The screening experiments described above clearly demonstrate that, in particular, Ni and Cu catalysts require ligands to be effective in the direct arylation of unactivated benzene with aryl bromides (in the absence of ligands, the amination pathway is preferred for those catalysts). The results of the individual screening campaigns described above are therefore rather interesting from a mechanistic point of view. Although no detailed mechanistic pathway can currently be formulated, it appears likely that the direct arylation/C–H activation pathway follows a homolytic aromatic substitution mechanism involving a single-electron-transfer step,[6,7,12,15–19,25] whereas the competing amination probably takes place through a Buchwald–Hartwig amination-type mechanism.[30] The role of the ligands in discriminating between these two pathways is currently under investigation in our laboratories.

Optimization of Co-catalyzed direct arylations under high-*T*/*p* conditions: The high-throughput-screening results described in the preceding section allowed us to rapidly determine suitable catalyst/ligand/base combinations for the direct arylation of benzene with an aryl bromide. Owing to the parallel nature of the high-*T*/*p* screening experiments and the relatively short reaction time (1 h), a large set of reaction conditions can, in principle, be identified by using the very simple and inexpensive experimental setup shown in Figure 1.[26–28] In the next phase of our investigations, we

wanted to further optimize some of the most promising and interesting catalyst/ligand combinations, found in the high-throughput/low-volume screens, and to confirm these results in preparative experiments. One of the most promising catalysts derived from our screening data, in agreement with previous literature results,[7] was [Co(acac)$_3$] in combination with LiHMDS as base, leading to >80% conversion to the product after 1 h at 160°C (Figure 2, no ligand).

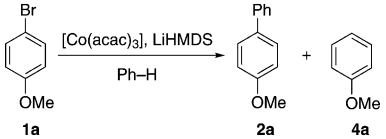
For further reaction optimization on a larger scale (4 mL) and at higher temperatures, we moved from the SiC microtiter plate, fitted with disposable 5 mL sealed glass vessels (Figure 1), to a 10 mL cylindrical reaction vial made entirely out of SiC ceramic. Used in combination with a dedicated microwave reactor (see Figure S1 in the Supporting Information), the strongly microwave-absorbing reaction vessel can be rapidly heated to extreme temperatures and used for processing up to 5 mL reaction volume at temperatures up to 300°C and 30 bar of pressure, allowing for accurate internal temperature measurement/control and magnetic stirring at the same time.[31] It must be emphasized that, although a microwave instrument is used for heating, this type of processing does not involve any genuine microwave dielectric heating of the reaction mixture, since the strongly microwave-absorbing SiC vessel is effectively shielding the contents of the vessel from the electromagnetic field.[31] In contrast, genuine microwave dielectric heating of the direct arylation reaction mixtures described herein is almost impossible because the reaction solvent, benzene, is microwave transparent (see Figures S2 and S3 in the Supporting Information). Using the SiC setup described above, a reaction temperature of 200°C can typically be attained within less than 2 min, leading to an internal reaction pressure of approximately 15 bar.

Utilizing this equipment, it was feasible to carry out an in-depth reaction optimization of the [Co(acac)$_3$]-catalyzed direct arylation of benzene with 4-bromoanisole (**1a**) in a high-*T*/*p* process window. In a preliminary set of experiments, the same catalyst (15 mol%) and base loadings (3 equiv) as in the screening reactions were used to determine the influence of the reaction temperature on side reactions (Table 1). In all cases, the main side reaction in the direct arylation was the dehalogenation of the aryl halide (about 10%). In addition, trace amounts of biphenyl, derived by benzene homocoupling, and the amination reaction (Scheme 1) were observed in some cases. Notably, the ratio between anisole by-product (**4a**) and the desired biaryl compound **2a** was more or less independent of the reaction temperature. Remarkably, even at a comparatively low temperature of 140°C the reaction can be carried out with full conversion in 10 min by using the same amounts of catalyst and base as described in the literature (entry 1). It is worth noting that the reaction time in all microwave experiments includes neither the heating time nor the cooling period. The isolated yield of 81% from an experiment performed at 200°C for 10 min (entry 3) compares nicely with the yield stated in the original reference for the 48 h run at 80°C (85%).[7]

The influence of the substrate concentration was also investigated. An increase of the aryl halide molarity from 65 to 87 mM resulted in a negligible increase of the side reaction (Table S2 in the Supporting Information). When the substrate concentration was set to 170 mM, comparatively large amounts of anisole were obtained, which resulted in a significant decrease of the desired arylation product. This experiment clearly reveals that these direct arylation protocols, indeed, need a large excess of the unactivated arene to produce satisfying results. Hence, for all further experiments the aryl halide was used at a concentration of 65 mM.

To radically enhance the efficiency of this arylation reaction, we evaluated the possibility of both a reduction of the Co catalyst and the LiHMDS base, as well as a minimization of the reaction time (Table 2). Initially, an attempted decrease of both the catalyst (5 mol%) and the base loading (2 equiv) at 140°C resulted in low conversion (entry 2). The

Table 1. Influence of the reaction temperature on the selectivity of the direct arylation of benzene with 4-bromoanisole (**1a**).[a]

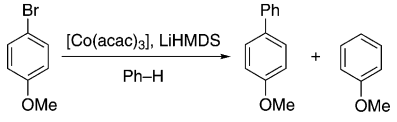


1a **2a** **4a**

	Co(acac)$_3$ [mol%]	LiHMDS [equiv]	*T* [°C]	*P* [bar]	*t* [min]	Conv.[b] [%]	**2a**[b] [%]	**4a**[b] [%]
1	15	3	140	5	10	>99	85	10
2	15	3	160	8	10	>99	79	16
3	15	3	180	11	10	>99	81	15
4	15	3	200	15	10	>99	86 (81)[c]	13

[a] Reaction conditions: **1a** (0.26 mmol), benzene (4 mL), argon atmosphere, SiC vial. [b] Determined by GC-FID using dodecane as internal standard. [c] Isolated yield.

Table 2. Optimization of the catalyst and base concentration on the direct arylation of benzene with 4-bromoanisole (**1a**).[a]



1a **2a** **4a**

	Co(acac)$_3$ [mol%]	LiHMDS [equiv]	*T* [°C]	*t* [min]	Conv.[b] [%]	**2a**[b] [%]	**4a**[b] [%]
1	15	3	140	10	>99	85	10
2	5	2	140	10	40	13	6
3	5	2	140	30	72	49	12
4	5	2	160	10	76	55	12
5	5	2	160	30	86	71	11
6	5	2	180	10	89	75	12
7	5	2	180	20	>99	87	12
8	5	1.5	180	10	81	43	11
9	5	2	200	5	>99	88 (83)[c]	9
10	5	2	200	5	>99	91[d]	10
11	5	1.5	200	10	90	44	12
12	5	2	220	5	>99	84	8
13	5	1.5	220	10	87	65	11

[a] Reaction conditions: **1a** (0.26 mmol), benzene (4 mL), argon atmosphere, SiC vial. [b] Determined by GC-FID using dodecane as internal standard. [c] Isolated yield. [d] Performed in a Pyrex reaction vessel.

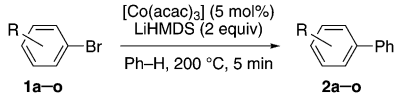
remaining substrate was still detected, even after extended reaction times at higher temperatures (entries 3–6). When the arylation with this catalyst/base loading was performed at 180 °C, 20 min were necessary to achieve full conversion of the aryl bromide **1a** (entry 7). Gratifyingly, we discovered that with only 5 mol % of [$Co(acac)_3$] and two equivalents of LiHMDS, full conversion was attained after 5 min at 200 °C, which clearly constitutes a remarkable improvement compared to the published 80 °C/24 h conditions that use three times the amount of catalyst and a higher base loading (entry 9).[7] In terms of catalyst turnover numbers (TON) and frequencies (TOF), the high-*T*/*p* processing allowed a dramatic improvement of efficiency (compare a TOF of $3.3 \times 10^{-5}\ s^{-1}$ for the 80 °C experiment[7] with a TOF of $5.5 \times 10^{-2}\ s^{-1}$ for the 200 °C run).

The same result was obtained when a standard Pyrex vessel was used, demonstrating that the results are not influenced by the vessel material or microwave dielectric heating (entry 10, see Figure S2 in the Supporting Information for further details). However, a further reduction of the catalyst or the base was not feasible because complete conversions could not be obtained, neither by applying higher reaction temperatures nor by extended reaction times (entries 11–15).

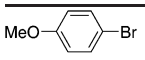
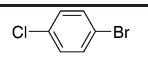
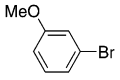
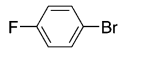
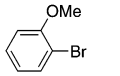
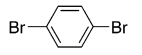
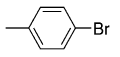
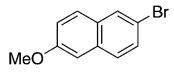
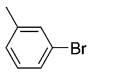
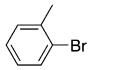
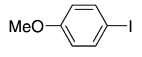
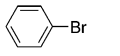
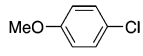
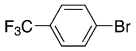
To compare the reaction speed and the selectivity of the new high-*T*/*p* direct arylation protocol conducted at 200 °C with the conventional approach at 80 °C, oil-bath experiments were carried out following the literature protocol as close as possible (catalyst (15 mol %), LiHMDS (3 equiv), 80 °C, 48 h).[7] Thereby, a 100 °C internally monitored reaction temperature was necessary to achieve complete consumption of the aryl bromide **1a** within the reported reaction time of 48 h (see Figure S4 in the Supporting Information). When using our reduced catalyst/base loading at the moderate 100 °C temperature region, not more than 50 % conversion was obtained, even after 200 h (Figure S4). These results highlight the advantages of operating in a high-*T*/*p* process window for this particular transformation: the catalytic system can tolerate the extreme temperatures very well and is not thermally deactivated or undergoing nonproductive events. Most importantly, the selectivity for the 100 °C experiment [catalyst (15 mol %), base (3 equiv)] was nearly identical compared to the one of the 200 °C run [catalyst (5 mol %), base (2 equiv)], as evidenced by a comparison of the crude GC-traces resulting from both experiments (see Figure S5 in the Supporting Information).

Encouraged by the results obtained in the above described optimization experiments, the direct arylation of benzene with several aryl halides was investigated by using the optimized high-*T*/*p* protocol (Table 3). The *para*-, *meta*-, and *ortho*-substituted aryl bromides, containing different functionalities, were suitable electrophiles in this coupling protocol. In agreement with the published data,[7] no significant difference between electron-donating and electron-withdrawing substituents was found when using the high-*T*/*p* methodology. As expected, it was also possible to carry out the coupling of 4-iodoanisole (**1n**) in high yields, whereas the chloride analog **1o** showed less efficiency in this reaction. A comparison with the results published by Lei and co-workers using 80 °C[7] demonstrates that most of the *meta*- and *para*-substituted bromides react in similar yields under both sets of conditions. The reaction appeared to be less efficient when *ortho*-substituted halides were used (**1c**, **1f**, and **1m**), and, indeed, the published protocol reports very low yields (< 10 %) for 2-bromoanisole (**1c**) and 2-bromotoluene (**1f**) at 80 °C.[7] For the 200 °C procedure, an increase of the reaction time to 25 min for these substrates allowed complete consumption of the aryl bromide and isolation of the desired biaryls in moderate yields (Table 3). The

Table 3. Substrate scope of the high-speed Co-catalyzed direct arylation of benzene with different aryl halides.[a]



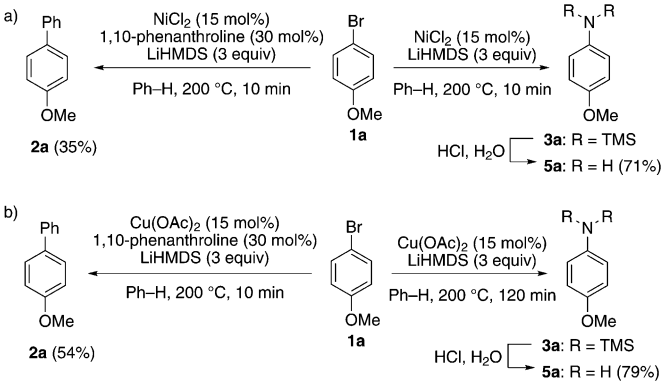
1a–o 2a–o

Aryl halide	1	Yield [%]	Lit. yield[b] [%]	Aryl halide	1	Yield [%]	Lit. yield[b] [%]
	**1a**	83	85		**1i**	82	89
	**1b**	73	88		**1j**	71	49
	**1c**	39[c]	< 5		**1k**	68[e]	–
	**1d**	76	80		**1l**	62	–
	**1e**	80	–		**1m**	34[c]	–
	**1f**	51[c,d]	10		**1n**	84	86
	**1g**	77	86		**1o**	< 10[f]	–
	**1h**	70	55				

[a] Reaction conditions: **1** (0.26 mmol), benzene (4 mL), argon atmosphere, 200 °C, 5 min, SiC vial. For detailed conditions, see Table 2, entry 9. [b] Data from ref. [7]. Reaction conditions: 80–100 °C, 48 h, catalyst (15 mol %), base (3 equiv). [c] Reaction time: 25 min. [d] GC-purity: 90 %. [e] Catalyst (5 mol %) and base (3 equiv) for each Br atom to obtain diarylation. [f] Yield (7 %) determined by GC-FID with *n*-dodecane as internal standard.

yields for fluorinated substrates (**1h** and **1j**) were also higher when the high-*T*/*p* conditions were applied without any reoptimization. In the case of the original 80 °C conditions, the catalyst loading had to be increased from 15 to 30 mol % to improve the reaction of 4-bromofluorobenzene (**1j**), which resulted in 75 % yield.[7] Apart from simple monoarylation reactions, it was also possible to obtain a controlled diarylation, as exemplified by the formation of *p*-terphenyl from 1,4-dibromobenzene (**1k**). More base-sensitive substrates (not discussed in the original work by Lei and coworkers),[7] including 4-bromobenzonitrile, 4-bromoacetophenone, and ethyl 3-bromobenzoate, did not yield the desired biaryl products. This is likely to be a result of the base-sensitivity of these functionalities under the chosen reaction conditions.

Ni versus Cu catalysis—the ligand makes the difference: Based on the surprising results in terms of reaction selectivity in the catalyst screenings described above (Scheme 1), a more comprehensive set of experiments, employing Ni and Cu catalysts, was subsequently carried out. As shown in Figure 2, different screening results were obtained when these reactions were performed either in the presence of a ligand (arylation pathway) or with the metal catalyst alone (amination pathway). $NiCl_2$ and $Cu(OAc)_2$ were chosen as representative metal species and 1,10-phenanthroline as ligand for the high-*T*/*p* experiments. In the case of $NiCl_2$, both reactions were carried out by using the same reaction conditions (200 °C, 10 min). In the presence of 30 mol % of the 1,10-phenanthroline ligand, the desired biaryl **2a** was isolated in moderate yield (>99 % GC-conversion, only trace amounts of amination product were formed) by preparative column chromatography (Scheme 2 a). In contrast, the experiment without ligand provided high selectivity (>90 %) for the amination pathway. In agreement with the results published by Hartwig and co-workers, we found that an isolation/purification of the silylamine **3a** was not possible, owing to inadvertent hydrolysis during chromatography.[29a] Thus, the corresponding 4-methoxyaniline (**5a**) was isolated after treatment with aqueous HCl and subsequent neutralization in a good overall yield.



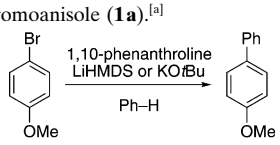
Scheme 2. Ligand-mediated switch in selectivity between arylation and amination in Ni- and Cu-catalyzed reactions of 4-bromoanisole (**1a**) with LiHMDS in benzene.

When $Cu(OAc)_2$ was used as catalyst, similar results were obtained, as shown in Scheme 2 b, although the required reaction time for the amination was significantly higher. Apparently, the direct arylation pathway using Cu seems to be more efficient than in the Ni-catalyzed variation. It is worth noting that previous investigations have found that, when using DMEDA and KO*t*Bu in combination with these catalysts, Ni is the more effective metal for arylation.[25] This indicates that, in addition to the chosen ligand, the base also plays an important role in the reactivity of different arylation catalysts.

Transition-metal-free direct arylations: To complete our study, further analysis of the screening results shown in Figure 2, involving the transition-metal-free organocatalytic direct arylation using 1,10-phenanthroline, was carried out. While an optimization of the so far undisclosed catalytic system using LiHMDS is of interest in its own right, a comparison with the already published reaction system using KO*t*Bu as base[16] can be expected to reveal additional effects of the utilized base for these unusual metal-free direct arylations.

Initially, both experiments were carried out by using 40 mol % of 1,10-phenanthroline in combination with three equivalents of the respective base using traditional oil-bath heating at 100 °C, as described in literature by Shi and coworkers.[16] Full conversion was obtained after 18 h when KO*t*Bu was employed, whereas the reaction with LiHMDS required at least 44 h (Table 4, entries 1 and 2), but was significantly cleaner and provided higher product selectivity. A detailed GC-MS analysis revealed significant differences in the two resulting reaction mixtures (see Figure S6 in the Supporting Information). In both instances, trace amounts of biphenyl, resulting from homocoupling of the benzene solvent, as well as minor amounts of the dehalogenated substrate **4a** were obtained. Interestingly, when KO*t*Bu in combination with 1,10-phenanthroline was used, we also observed various terphenyl species, as a result of benzene ho-

Table 4. Optimization of the 1,10-phenanthroline-based direct arylation of benzene with 4-bromoanisole (**1a**).[a]



	1,10-phenanthroline [mol %]	Base ([equiv])	Aryl bromide **1a** [mM]	*T* [°C]	*t*	Conv.[b] [%]
1	40	LiHMDS (3)	125	100[c]	44 h	75
2	40	KO*t*Bu (3)	125	100[c]	18 h	28
3	40	KO*t*Bu (3)	65	200	10 min	32 (27)[d]
4	40	LiHMDS (3)	65	200	10 min	74 (66)[d]
5	30	LiHMDS (2)	65	200	10 min	73
6	15	LiHMDS (2)	65	200	10 min	72
7	15	LiHMDS (2)	65	200	5 min	72 (64)[d]

[a] Reaction conditions: **1a** (0.26–0.5 mmol), benzene (4 mL), argon atmosphere, SiC vial. [b] Conversion to product **2a** determined by GC-FID using dodecane as internal standard. [c] Reactions were carried out in an oil bath. [d] Isolated yield.

mocoupling. Most notably, significant amounts of by-products, derived from an apparent coupling reaction between aryl bromide **1a** with *tert*-butanolate, were additionally present in this reaction mixture.[32] Shirakawa and co-workers reported similar impurities when KO*t*Bu was used in combination with bathophenanthroline as ligand, supporting the possibility of a competing reaction pathway involving an aryne intermediate.[17] In our hands, the results with LiHMDS as base were in any event significantly better compared to the results obtained when using KO*t*Bu (Table 4, entries 1 and 2).[33]

Similar to the approach taken with the transition-metal-catalyzed arylation protocols described above, we subsequently optimized both protocols using LiHMDS and KO*t*Bu by employing a high-*T*/*p* process window. As can be seen in Table 4, for the additional optimization studies the amount of LiHMDS was successfully reduced to two equivalents. We also minimized the amount of the 1,10-phenanthroline base to 15 mol%, still being able to achieve complete conversion after 5 min at 200 °C and a moderately high product yield (Table 4, entry 7).

Conclusion

In summary, we have shown that high-*T*/*p* process windows can be used to dramatically increase the efficiency of the transition-metal-catalyzed direct arylation of benzene with aryl bromides. A high-throughput screening under these reaction conditions revealed that several metals (in particular Co complexes) are able to catalyze this arylation in the absence of a ligand, while for other metals (Cu, Ni, Cr) the presence of a ligand, such as 1,10-phenanthroline or DMEDA, is required to allow direct arylation. The high-*T*/*p* reaction screening additionally revealed a novel Ni- or Cu-catalyzed amination reaction that converts aryl bromides into the corresponding anilines when using LiHMDS as ammonia equivalent. In the presence of 1,10-phenanthroline as ligand, the selectivity in this process switches toward direct arylation and the formation of biaryls. This impressive selectivity control by a simple additive is of significant interest for further mechanistic studies. As an additional result from a comparative study, it was discovered that LiHMDS appears to be a superior base compared to KO*t*Bu in the 1,10-phenanthroline-mediated, transition-metal-free organocatalytic direct arylation of benzene with aryl bromides.

The initial results obtained from high-throughput parallel reactions screening at 160 °C were further optimized by employing a high-*T*/*p* autoclave made out of sintered SiC. At a reaction temperature of 200 °C (about 15 bar) the efficiency of the direct arylation protocols was dramatically increased, allowing, in most cases, full conversion to be achieved within 5 min, while retaining high selectivity at often much reduced catalyst loadings. This constitutes a significant improvement to the published protocols in this area and will undoubtedly contribute to the further development of this rapidly growing field of modern synthetic organic chemistry.

Experimental Section

General experimental details: All reaction mixtures were prepared under argon atmosphere using an Aldrich AtmosBag. Solvents and chemicals were obtained from standard commercial vendors and were used without any further purification. Benzene (anhydrous, 99.8%), KO*t*Bu (sublimed, 99.99%), DMEDA (99%), $CoCl_2$ (97%), $Co(acac)_3$ (98%), $Fe(acac)_3$ (99.9%+), $Fe(OAc)_2$ (95%), NiI_2, $NiCl_2$ (98%), $Ni(acac)_2$ (95%), $Cr(acac)_3$ (97%), $Cu(acac)_2$ (97%), $Cu(OAc)_2$ (98%), CuI (98%), $Mn(acac)_2$, and $Mn(acac)_3$ (tech.) were purchased from Sigma–Aldrich. LiHMDS, $CoBr_2$ (anhydrous, 97%), $Co(acac)_2$, and $Co(OAc)_2$ (anhydrous, 98%) were obtained from Alfa Aesar. 1,10-phenanthroline (99+%) was purchased from Acros Organics.

^1H and ^{13}C NMR spectra were recorded on a Bruker 300 MHz instrument using $CDCl_3$ as solvent. Chemical shifts (δ) are reported in ppm downfield from TMS as internal standard. The abbreviations s, d, t, q, and m are used to indicate singlet, doublet, triplet, quadruplet, and multiplet signals, respectively. Melting points were determined on a Stuart SMP3 melting point apparatus. GC-FID analysis was performed on a Trace-GC (ThermoFisher) with a flame ionization detector using a HP5 column (30 m × 0.250 mm × 0.025 μm). After 1 min at 50 °C, the temperature was increased in 25 °C min^{-1} steps up to 300 °C and kept at 300 °C for 4 min. The detector gas for the flame ionization was H_2 and compressed air (5.0 quality). GC-MS analysis was performed on a Trace-GC Ultra–DSQ II-MS system (ThermoElectron, Waltham, USA). The GC conditions were as follows: HP-5 MS column (30 m × 0.25 mm ID, 0.25 μm film, Agilent, Waldbronn, Germany), carrier gas helium 5.0, flow 1 mL min^{-1}, temperature gradient identical to GC-FID. The MS conditions were as follows: positive EI ionization, ionization energy 70 eV, ionization source temperature 280 °C, emission current 100 μA, full-scan-mode. Silica gel flash chromatography separations were performed on a Biotage SP1 instrument by using petroleum ether/ethyl acetate mixtures as eluent.

Screening experiments were carried out in 5 mL Pyrex reaction vials with PTFE seals and screw caps in a SiC heating block with a 6×4 deep well matrix (24MG5 rotor, Anton Paar GmbH).[26] The high thermal conductivity and effusivity of silicon carbide allowed rapid heating (within 5 min) of the reaction vials in the heating block, which was preheated on a conventional hot plate with minimal deviations in temperature across the block. The actual temperature inside the vials depended on the selected temperature and the boiling point of the used solvent, but roughly corresponded to the hotplate temperature.[26] The suggested temperature/pressure limit of the vials was 200 °C/20 bar.

For experiments using 10 mL SiC vessels, a Monowave 300 single-mode microwave reactor from Anton Paar GmbH (Graz, Austria) was used (Figure S1).[31b] The reaction temperature was monitored by an external infrared sensor (IR) that was housed in the side-walls of the microwave cavity, measuring the surface temperature of the reaction vessel, as well as an internal fiber-optic (FO) temperature probe (ruby thermometer). In all instances, the temperatures recorded by the IR and FO probes were different (FO 5–25 °C higher than IR), mainly depending on IR sensor calibration. Temperature control through the internal FO probe (IR as slave) was generally a beneficial choice for Pyrex vessel experiments, in which the selected target temperature was attained by dielectric heating of the solvent. The IR sensor turned out to be superior to the FO probe when SiC vessels were used. Therefore, temperature controlling was carried out by using IR (FO as slave) after previous calibration using FO (IR as slave).

All biaryls, synthesized in this work, are known in the literature. Their structure and purity was confirmed by ^1H and ^{13}C NMR spectroscopy and GC-MS analysis. The NMR data are given in the Supporting Information.

General procedure for parallel-screening reactions in SiC plates (Figure 2, Table S1 in the Supporting Information): LiHMDS (65 mg, 388 μmol) and the respective catalyst (19 μmol) were introduced into the 5 mL Pyrex vials under an argon atmosphere. Then, 4-bromoanisole (**1a**, 16 μL, 128 μmol), dodecane (29 μL, 128 μmol), and benzene (2 mL) were

added to the reaction mixture. For screening cycles 2 and 3, 1,10-phenanthroline (7 mg, 39 μmol) and DMEDA (4.1 μL, 38 μmol) were added under argon atmosphere, respectively. The reaction vessels were sealed using a PTFE seal and a screw cap and then placed into the SiC heating block, preheated on a hot plate at 160 °C. After heating for 1 h, the vials were cooled down to room temperature and quenched with ethyl acetate (1 mL). The reaction mixtures were filtered and washed with sufficient amounts of ethyl acetate before GC-FID analysis.

General procedure for the $Co(acac)_3$-catalyzed synthesis of biaryls 2a–o (Table 3): $Co(acac)_3$ (4.7 mg, 13 μmol), LiHMDS (87 mg, 520 μmol), the respective aryl halide (256 μmol), and benzene (4 mL) were successively added into the SiC reaction vessel under an argon atmosphere. The reaction mixture was allowed to react at 200 °C for 5 min (hold time) by microwave irradiation. After cooling, the reaction was quenched with ethyl acetate (1 mL). The mixture was filtered, washed with sufficient amounts of ethyl acetate and concentrated under vacuum. The respective biphenyls were purified by silica gel flash column chromatography using petroleum ether/ethyl acetate as eluent.

General procedure for the Cu- and Ni-catalyzed synthesis of 4-methoxyaniline (5a, Scheme 2): The SiC vessel was equipped with the respective catalyst (39 μmol), LiHMDS (130 mg, 777 μmol), 4-bromoanisole (**1a**, 32 μL, 256 μmol), and benzene (4 mL) under an argon atmosphere. The reaction mixture was allowed to react at 200 °C for 10 min [hold time for $NiCl_2$] or 120 min [hold time for $Cu(OAc)_2$]. After cooling, the reaction was quenched with ethyl acetate (1 mL), diluted with $CHCl_3$ (15 mL) and then washed with 1 M HCl (15 mL). The aqueous phase was neutralized with $NaHCO_3$ and extracted with $CHCl_3$ (2×15 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under vacuum. The obtained aniline was purified by flash column chromatography with petroleum ether/ethyl acetate as eluent.

General procedure for the Cu- and Ni-catalyzed synthesis of 4-methoxybiphenyl (2a, (Scheme 2): The SiC vessel was equipped with the respective catalyst (39 μmol), LiHMDS (130 mg, 777 μmol), phenanthroline (14 mg, 78 μmol), 4-bromoanisole (**1a**, 32 μL, 256 μmol), and benzene (4 mL) under an argon atmosphere. The reaction mixture was allowed to react at 200 °C for 10 min (hold time). After cooling, the reaction was quenched with ethyl acetate (1 mL). The mixture was filtered, washed with sufficient amounts of ethyl acetate and concentrated under vacuum. The obtained 4-methoxybiphenyl was purified by flash column chromatography using petroleum ether/ethyl acetate as eluent.

General procedure for 1,10-phenanthroline-catalyzed reactions for the synthesis of 4-methoxybiphenyl (2a): The SiC vessel was equipped with the respective amount of 1,10-phenanthroline and LiHMDS or KO*t*Bu under an argon atmosphere. Then, 4-bromoanisole (**1a**) and benzene (4 mL) were added. The reaction mixture was allowed to react at the corresponding temperature for the required reaction time (hold time) either in a preheated oil bath or in a microwave reactor (SiC vessel). After cooling, the reaction was quenched with ethyl acetate (1 mL). The mixture was filtered, washed with sufficient amounts of ethyl acetate and concentrated under vacuum. The obtained 4-methoxybiphenyl was purified by flash column chromatography using petroleum ether/ethyl acetate as eluent.

Acknowledgements

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[33] The recent literature contains several contradictory results with respect to transition-metal-free organocatalytic direct arylation protocols of this type (ref. 12, 15–17, 25). It appears likely that these catalytic systems exhibit a subtle sensitivity to external factors, reaction conditions, or impurities that are present in the reaction mixture. A careful description of all experimental parameters is therefore paramount when reporting transformations of this type.

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