Introduction of Aromatic and Heteroaromatic Groups in the 2- and 8-Positions of the Tröger's Base Core by Suzuki, Stille and Negishi Cross-Coupling Reactions – A Comparative Study

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A comparative study on the bis(functionalization) of the Tröger's base core by aromatic and heteroaromatic groups using palladium-catalyzed cross-coupling reactions is presented. Three different reactions, the Suzuki, Stille, and Negishi couplings, were investigated using Tröger's base analogues equally substituted in the 2,8-positions with $(HO)_2B$, Bu_3Sn and ZnCl groups, respectively, as the metallated component. Six aryl halides with different electronic and steric properties were employed as coupling partners. The presence of the bulky and electron-rich phosphane $P(tBu)_3$ as co-catalyst was found to play an important role. In addition, the palladium source, $[Pd(PPh_3)_4]$ or $[Pd_2(dba)_3]$, was also found to be an important factor for the yield of the reactions. The Suzuki coupling was found to be the best method in general, giving excellent yields for most aryl halides, whereas the Stille and Negishi couplings gave moderate to good yields. Finally, the crystal structures of the 4-nitrophenyl- and the 2-pyridyl-appended analogues of Tröger's base, **7d** and **7f**, are presented in the Supporting Information.

Introduction

Tröger's base, 2,8-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (**1**)[1] (Figure 1), is a preeminent molecule with a notable history[2] and remarkable properties. These properties stem mainly from its chiral rigid aromatic cleft (Figure 1). Due to these properties, the foremost applications of Tröger's base have been in the field of molecular recognition[3–6] although qualified for extensive usage in many other fields.[7–10] Since the synthesis of Tröger's base itself in 1887, more than 150 derivatives and analogues have been synthesized using various methods. The scope of this fascinating molecule could be even broader having access to a greater number of general methods for the synthesis of analogues and derivatives.

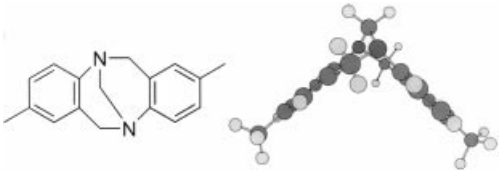

Figure 1. Tröger's base (**1**).

The synthesis of derivatives and analogues of Tröger's bases is most often accomplished by the acid-promoted condensation of anilines with formaldehyde or another methylene synthon. This reaction is limited in scope because of the harsh reaction conditions and because it works best with anilines carrying an electron-donating group.[11] However, we recently showed that halo-substituted anilines could be employed as starting materials by performing the reaction in TFA at room temperature and using paraformaldehyde as the methylene synthon, giving access to 2,8-dihalo-substituted Tröger's base analogues in high to excellent yields.[12,13] In addition, 2- and 3-bromoanilines containing methyl substituents were successfully condensed to Tröger's base analogues in moderate to good yields using the above protocol.[14] Having access to 2,8-dibromo and -diiodo analogues of Tröger's base, we carried out the first transition-metal-catalyzed cross-coupling reaction involving a Tröger's base analogue, the Curriu-Kumada cross-coupling.[12] In this way we could synthesize 2,8-dialkynyl analogues of Tröger's base and later we could develop a general protocol for the introduction of terminal alkynes into the Tröger's base core by the Sonogashira reaction.[15] We were also able to further functionalize the 2,8-position of Tröger's base by single and double halogen/lithium exchange followed by quenching with various electrophiles. In this way C_1- and C_2-symmetric analogues of Tröger's base could be prepared in good to high yields.[16] During the progress of the present investigation, Lützen published the first Suzuki-coupling involving the Tröger's base system.[17]

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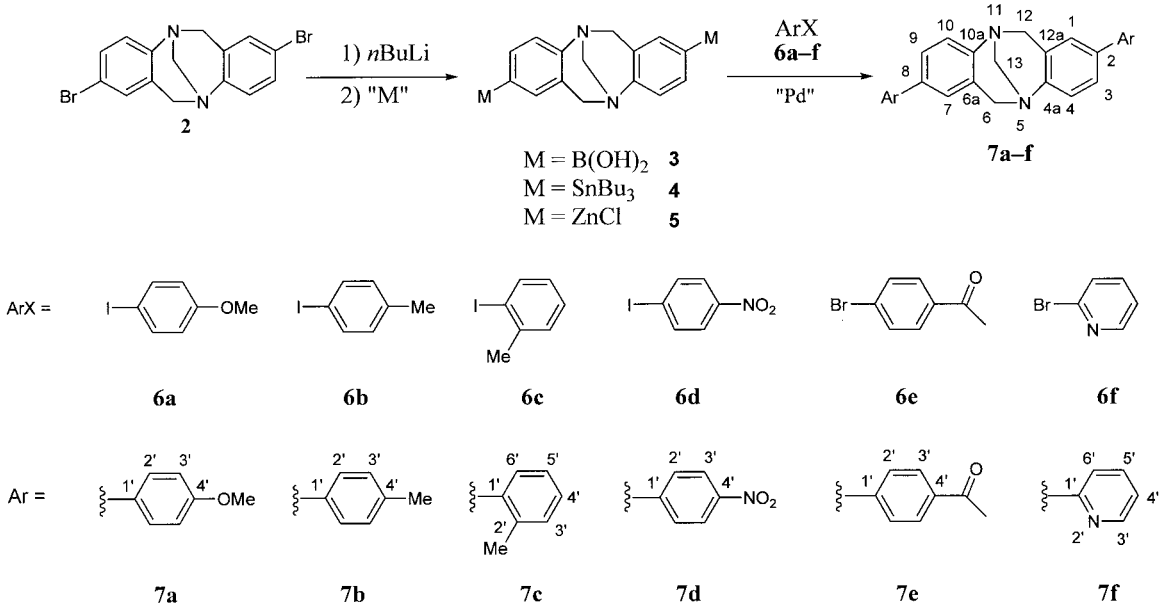
We now want to report a study of the direct introduction of aromatic and heteroaromatic groups into the 2- and 8-position of Tröger's base core leading to analogues possessing a biaryl structural unit. This is important in the field of supramolecular chemistry: For instance: (1) The placement of rigid linkers, such as aromatic groups, between units containing the Tröger's base core is a means for the formation of extended aromatic clefts. (2) Being able to place aromatic groups in the Tröger's base framework will allow for the introduction of functional groups in specific spatial positions to interact with complementary functionalities of guest molecules.

There are examples of biaryl analogues of Tröger's base; those are, however, synthesized from the corresponding anilines in the process of forming the Tröger's base framework. The yields are highly dependent on the aromatic substituents.[10,18–20] A methodology based on first constructing the Tröger's base framework and then introducing the aryl groups as we propose in the present work, leads to greater synthetic flexibility, the tolerance to acid-sensitive groups on the aryl moiety and in general much higher yields.

We now compare and optimize for the Tröger's base system three of the most common palladium-catalyzed cross-coupling reactions for aryl–aryl bond formation, the Suzuki,[21] Stille,[22] and Negishi[23] couplings. We also report on the solid-state structures of the 4-nitrophenyl- and the 2-pyridyl-appended analogues of Tröger's base, **7d** and **7f**, respectively.

Results and Discussion

In order to establish one single protocol for the metallation reaction, the 2,8-dibromo-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (**2**) was chosen as the moiety to be metallated (Scheme 1). Thus, compound **2** was subjected to double bromine/lithium exchange according to our previously developed protocol[16] to yield the 2,8-dilithium Tröger's base analogue. This intermediate was transmetallated using $B(OCH_3)_3$, Bu_3SnCl and $ZnCl_2$, respectively, affording the diboronic acid **3** in 92% yield after hydrolysis, the bis(tributylstannane) **4** in 70% yield,[16] and the bis(organozinc chloride) **5**, which was used in situ in the coupling reactions, respectively (Scheme 1). To determine the scope and limitations of the different cross-coupling methods, six aryl halides with different electronic and steric properties were used as coupling partners. 4-Iodoanisole (**6a**) was chosen as electron-rich aryl halide and in order to investigate the influence of steric hindrance in the coupling partner on the yield, 4-iodo- (**6b**) and 2-iodotoluene (**6c**) were also included. Two aryl halides bearing electron-withdrawing groups, 1-iodo-4-nitrobenzene (**6d**) and 4′-bromoacetophenone (**6e**), the latter having a carbonyl group susceptible to nucleophilic attack, were employed. Finally, an electron-deficient heterocyclic compound, 2-bromopyridine (**6f**), was also included. The 2,8-dibromo analogue of Tröger's base was chosen as the substrate to be metallated instead of the 2,8-diiodo analogue, because the former is synthesized in better yield.[12] Another point is that the use of the former analogue also leads to better atom economy.[24] In addition, based on the excellent yield obtained for the metallation of **2** to **3**, we can state that both analogues of Tröger's base, 2,8-dibromo and the 2,8-diiodo, undergo the halogen/lithium exchange with comparable efficiency. The yields of each of the three different coupling reactions were optimized based on palladium source, $[Pd(PPh_3)_4]$ or $[Pd_2(dba)_3]$, reaction temperature, solvent, as well as on the presence or absence of the co-catalyst $P(tBu)_3$. All the reactions were run until no further progress was observed in order to have



Scheme 1. General strategy for the palladium-catalyzed introduction of aryl groups into the 2- and 8-positions of the Tröger's base frame.

a direct comparison between the three different methodologies.

Suzuki Cross-Coupling Reactions

The Suzuki–Miyaura coupling reaction has proven to be one of the most efficient methods to produce biaryl compounds. The key advantages of this method are the mild reaction conditions, the thermal stability of boronic compounds combined with the fact that these compounds are inert to water and oxygen.[25] In addition, the handling and removal of boron-containing side-products are easy when compared with other organometallic reagents. We started our investigation by coupling **3** with **6a**, using 10 mol-% of [Pd(PPh_3)$_4$] as catalyst (Scheme 1). After 24 h at room temperature, the latter in an ambition to have as mild reaction conditions as possible, the bis(coupled) product **7a** could not be detected, neither in 1,4-dioxane nor in 1,2-dimethoxyethane as solvents, and neither with $NaHCO_3$(aq) nor with Cs_2CO_3(aq) as bases. We had previously experienced that the catalyst [Pd(PPh_3)$_4$] was not active enough when developing the Sonogashira coupling for the Tröger's base system.[15] The solution, inspired by Fu et al., was to use P(tBu)$_3$ as co-catalyst. Fu et al. used the sterically demanding and electron-rich trialkylphosphane P(tBu)$_3$ as co-catalyst in palladium-catalyzed cross-couplings to obtain a highly reactive system for the coupling of otherwise unreactive aryl chlorides.[26] In the presence of this additive and under the above-mentioned conditions, product was detected but the yields were not satisfactory. The problem was finally overcome by rising the reaction temperature to 85 °C. In the extended investigation, **3** was coupled with **6a**–**f** in dioxane at 85 °C using [Pd(PPh_3)$_4$] or [Pd_2(dba)$_3$] as catalyst, and P(tBu)$_3$ as co-catalyst and $NaHCO_3$(aq) as base, (Table 1). With a remarkably low catalyst loading, 1.5 mol-% relative to **3**, fast reactions, no more than 4 h, were achieved giving excellent yields of the desired double bis(coupled) products **7a**–**f**. In addition, $Pd(OAc)_2$ was investigated as a less expensive palladium source. Thus, substituting [Pd_2(dba)$_3$] for $Pd(OAc)_2$ in the attempted coupling of **3** with **6b** and **6e**, respectively, using the optimized conditions above, resulted in the formation of metallic palladium within minutes.

Of the two Pd^0 catalysts employed in the presence of P(tBu)$_3$, [Pd_2(dba)$_3$] turned out to be the one providing the higher yields, 69–85%, in all the coupling reactions (Table 1). That lower yields were observed when [Pd(PPh_3)$_4$] was employed as catalyst is not surprising because PPh_3 will compete with P(tBu)$_3$ as ligand to the palladium atom. However, in some other Entries in the cross-coupling reactions using the Stille and Negishi methodologies, the [Pd(PPh_3)$_4$]/P(tBu)$_3$ system gave higher yields (Table 2, Table 3, conditions D and E). The finding that [Pd_2(dba)$_3$]/P(tBu)$_3$/$NaHCO_3$ is an efficient catalyst in the present system is also in agreement with the recent results by Lützen, using Pd(PtBu$_3$)$_2$/CsF for the coupling of some aryl halides and a Tröger's base 2,8-bis[$(HO)_2$B] analogue similar to ours.[17] Even if several reactions gave the corresponding products in a comparable yield by either of the two catalysts, an appreciable increase in the yields of **7a** and **7f** in the coupling of **3** with **6a** and **6f**, respectively, were observed when [Pd_2(dba)$_3$] was used (Table 1, Entries 1 and 6). For the coupling of **3** with **6a**, a phenyl group of PPh_3 was incorporated in the 2- and 8-positions of the Tröger's base core when [Pd(PPh_3)$_4$] was employed as catalyst, thus reducing the yield of the desired coupling product (Table 1, conditions A, Entry 1). Such a phenomenon has previously been reported when one or both components in the Suzuki coupling are electron-rich, just as in **6a**.[27] For the coupling of **3** with **6f**, formation of the desired product was accompanied by protodeboronation of **3** when [Pd(PPh_3)$_4$] together with P(tBu)$_3$, was used as catalyst. Both problems were overcome by the use of [Pd_2(dba)$_3$] and P(tBu)$_3$ instead. To further demonstrate the importance of P(tBu)$_3$, the coupling between **3** and **6b** was repeated in the absence of P(tBu)$_3$ and using [Pd_2(dba)$_3$] as palladium source. This resulted in a doubled reaction time to obtain complete consumption of **3** and, in addition, the yield of bis(coupled)

Table 1. Suzuki cross-couplings of **3** and different aryl halides.

Entry	Aryl halide	Product	Conditions A[a] Yield (%)[b]	Conditions B[a] Yield (%)[b]
1	**6a**	**7a**	50	81
2	**6b**	**7b**	81	85[c]
3	**6c**	**7c**	74	82
4	**7d**	**7d**	81	85
5	**6e**	**7e**	69	69
6	**6f**	**7f**	58	75

[a] Conditions A: 0.16 mmol of **3** in 1,4-dioxane, 2.4 equiv. of ArX, 1.5 mol-% of [Pd(PPh_3)$_4$], 3.6 mol-% of P(tBu)$_3$ as 10 wt.-% solution in hexanes and $NaHCO_3$ 10% w/v in water. Reaction under Ar at 85 °C for 4 h. Conditions B: 0.16 mmol of **3** in 1,4-dioxane, 2.4 equiv. of ArX, 1.5 mol-% of [Pd_2(dba)$_3$], 3.6 mol-% of P(tBu)$_3$ as 10 wt.-% solution in hexanes and $NaHCO_3$ 10% w/v in water. Reaction under Ar at 85 °C for 4 h. [b] Yields after chromatography. [c] A 72% yield was obtained in the absence of P(tBu)$_3$ as 10 wt.-% solution in hexanes.

Table 2. Stille cross-couplings of **4** and different aryl halides.[a]

Entry	Aryl halide	Product	Conditions A Yield(%)	Conditions B Yield(%)
1	**6a**	**7a**	25	18
2	**6b**	**7b**	63[b]	25
3	**6c**	**7c**	66[c]/55[d]	0[e]
4	**6d**	**7d**	60	45
5	**6e**	**7e**	53	40
6	**6f**	**7f**	10/64[d]	0[e]

[a] Yields after chromatography. Conditions A: 0.30 mmol of **4**, 2.4 equiv. of ArX, 2.6 equiv. of CsF, 1.5 mol-% of [Pd(PPh_3)$_4$], 3.5 mol% of P(tBu)$_3$ as 10 wt.-% solution in hexanes. Reaction under Ar in refluxing 1,4-dioxane. Conditions B: 0.30 mmol of **4**, 2.4 equiv. of ArX, 2.6 equiv. of CsF, 1.5 mol-% of [Pd_2(dba)$_3$], 3.5 mol-% of P(tBu)$_3$ as 10 wt.-% solution in hexanes. Reaction under Ar in refluxing 1,4-dioxane.[b] A 40% yield was obtained when the reaction was run without P(tBu)$_3$.[c] A 28% yield was obtained by using CuI instead CsF.[d] In the presence of 2.6 equiv. of CsF and 8 mol-% of CuI. [e] Additional 1.5 mol-% of [Pd_2(dba)$_3$] and 3.5 mol-% of P(tBu)$_3$ as 10 wt.-% solution in hexanes were added after 40 h.

Table 3. Negishi cross-couplings of **5** and different aryl halides.[a]

Entry	Aryl halide	Product	Conditions A Yield [%]	Conditions B Yield [%]	Conditions C Yield [%]	Conditions D Yield [%]	Conditions E Yield [%]	Conditions F Yield [%]
1	**6a**	**7a**	55	40	32[b]	37	42	0[c]
2	**6b**	**7b**	62	45	51[b]	51	54	0[c]
3	**6c**	**7c**	55	44	27[b]	40[b]	46	0[c]
4	**6d**	**7d**	20[b]	60	42	23[b]	69	0[d]
5	**6e**	**7e**	20[b]	39	24	37[b]	21	–
6	**6f**	**7f**	45[b]	38	22	28	58	42

[a] Yields after chromatography. Conditions A: 1.0 mmol of **2** in THF, 2.4 equiv. of *n*BuLi, 6.0 equiv. of $ZnCl_2$, 3.0 equiv. of ArX, 5 mol-% of $[Pd(PPh_3)_4]$. Reaction at room temperature under Ar for 4–16 h. Conditions B: 1.0 mmol of **2** in THF, 2.4 equiv. of *n*BuLi, 6.0 equiv. of $ZnCl_2$, 3.0 equiv. of ArX, 5 mol-% of $[Pd(PPh_3)_4]$, 12 mol-% $P(tBu)_3$ as 10 wt.-% solution in hexanes. Reaction at room temperature under Ar for 16 h. Conditions C: 1.0 mmol of **2** in THF, 2.4 equiv. of *n*BuLi, 6.0 equiv. of $ZnCl_2$, 3.0 equiv. of ArX, 5 mol-% of $[Pd(PPh_3)_4]$, 12 mol-% $P(tBu)_3$ as 10 wt.-% solution in hexanes. Reaction at reflux under Ar for 16 h. Conditions D: 1.0 mmol of **2** in THF, 2.4 equiv. of *n*BuLi, 6.0 equiv. of $ZnCl_2$, 3.0 equiv. of ArX, 5 mol-% of $[Pd_2(dba)_3]$, 12 mol-% $P(tBu)_3$ as 10 wt-% solution in hexanes. Reaction at reflux under Ar for 16 h. Conditions E: 1.0 mmol of **2** in THF, 2.4 equiv. of *n*BuLi, 6.0 equiv. of $ZnCl_2$, 3.0 equiv. of ArX, 5 mol-% of $[Pd(PPh_3)_4]$. Reaction at reflux under Ar for 16 h. Conditions F: 3.0 mmol of ArX in THF, 1.2 equiv. of *n*BuLi, 6.0 equiv. of $ZnCl_2$, 0.33 equiv. of **2**, 5 mol-% of $[Pd(PPh_3)_4]$. Reaction at reflux under Ar for 16 h. [b] Additional recrystallization was needed after chromatography. [c] No efficient iodine/lithium exchange took place at –78 °C or at 0 °C. [d] Compound **6d** was not soluble at –78 °C.

product **7b** dropped from 85% to 72% compared to when $P(tBu)_3$ was present.

Stille Cross-Coupling Reactions

The popularity of this reaction stems from the fact that tributylstannanes have a high stability to air and moisture and that they are compatible with most functional groups.[26] All this prompted us to include the Stille coupling in our comparative study (Scheme 1). Based on our experience from the Suzuki coupling of **3** with each of **6a–f**, that a co-catalyst must be present to obtain a respectable yield, we directly turned our attention to the protocol developed by Fu et al. using the system $[Pd_2(dba)_3]/P(tBu)_3/CsF$ in 1,4-dioxane with a catalyst loading of 1.5 mol-% for the Stille coupling of aryl halides.[28] However, low yields were obtained under original Fu conditions (Table 2, conditions B) for the coupling of **4** with **6a–f**, with the highest being a modest 45% yield of **7d** in the series for the coupling of **4** with electron-poor **6d**. Notably, no product at all could be detected for the coupling of **4** with **6c** and **6f**, respectively, not even after refluxing the reaction mixture for 3 d. Better results were obtained by using $[Pd(PPh_3)_4]$ instead of $[Pd_2(dba)_3]$ as palladium source. Thus, by employing the system $[Pd(PPh_3)_4]/P(tBu)_3/CsF$ in 1,4-dioxane with a catalyst loading of 1.5 mol-% for the coupling of **4** with moderate electron-donating coupling partners **6b** and **6c**, and with electron-withdrawing coupling partners **6d** and **6e**, yields in the range of 53–66% of the desired bis(coupled) products **7b–e** (Table 2, conditions A, Entries 2–5) were obtained. These results might be explained by the fact that triphenylphosphane-based palladium catalysts are stable on prolonged heating compared to the tri(*tert*-butyl)phosphane-based palladium catalyst, thus keeping the former catalytic system active for a longer time. Under these former conditions the lowest yields of bis(coupled) products were obtained for the coupling of **4** with **6a** and **6f**, respectively (Table 2, conditions A, Entries 1 and 6).

Some common features were found for the two catalytic systems, $[Pd_2(dba)_3]/P(tBu)_3/CsF$ and $[Pd(PPh_3)_4]/P(tBu)_3/CsF$: The mono(coupled) product turned out to be the main side-product in all the reactions. For example, when using $[Pd_2(dba)_3]$, a 25% yield of the stannylated mono(coupled) product was isolated in the reaction of **4** with each of **6b** and **6e**, together with the bis(coupled) products **7b** and **7e**, respectively. Moreover, longer reaction times compared to the Suzuki coupling were also needed in all cases. Due to the fact that no further progress in the reaction was observed, even when both the stannylated mono(coupled) products and their respective aryl halide coupling partner were present in the reaction mixture, we suggest that thermal decomposition of the catalyst had occurred before complete conversion of the stannylated Tröger's base analogue had taken place.

Replacing CsF by CuI did not lead to a more active system[29] for the test reaction, the coupling of **4** with **6c** (Table 2, Entry 3). However, using both additives together[30] led to a remarkable increase in yield for the coupling of **4** with **6f**, affording a 64% yield for the bis(coupled) product under the same reaction time (Table 2, Entry 6). A likely explanation to the remarkable increase in yield in this case is that Cu^I coordinates to the pyridine moiety, thus hampering the deactivating effect of the pyridine moiety previously exercised by coordination to the catalyst. In contrast, applying this combination of additives to the coupling of **4** with **6c** was not so fruitful; a yield of 55% was obtained which is lower than when only CsF was used as an additive (Table 2, Entry 3).

The importance of $P(tBu)_3$ was clearly demonstrated in the coupling of **4** with **6b** using $[Pd(PPh_3)_4]$ as the catalyst in the absence of $P(tBu)_3$, where the yield of **7b** dropped from 63% to 40% and that a longer reaction time was needed until no further progress in reaction was observed.

Negishi Cross-Coupling Reactions

The synthesis of unsymmetrical biaryl compounds by palladium-catalyzed coupling of arylzinc derivatives was

first reported more than 20 years ago by Negishi.[23] While the Suzuki and Stille cross-couplings have found several applications and are widely used for the formation of $C(sp^2)$–$C(sp^2)$ bonds due to their high functional group compatibility and the inherent stability of the organoboron and organotin reagents, the Negishi coupling has been employed to a lesser extent due to the instability towards water and air of most organozinc species. On the other hand, the halogen/lithium exchange and the following transmetallation of the substrate and the subsequent palladium-catalyzed coupling can be performed in a one-pot procedure, without isolating the metallated species.

In the first reactions, 5 mol-% of $[Pd(PPh_3)_4]$ was used as catalyst and the couplings of **5** and each of **6a**–**f** were run at room temperature in 1,4-dioxane for 16 h affording each of **7a**–**f** in low to moderate yields (Scheme 1 and Table 3, conditions A). Low yields of each of **7d**–**e** were also observed for the coupling of each of electron-poor **6d**–**e** (Table 3, Entries 4 and 5). The best results were achieved in the coupling of **5** with electron-rich **6a**–**c** affording **7a**, **7b**, and **7c** in 55, 62 and 55% yield, respectively. The previous low yields of **7d** and **7e** in the coupling of **6d**–**e** were notably improved by performing the reactions in the presence of $P(t\mathrm{Bu})_3$, without affecting much the yields for the coupling of the other aryl halides (Table 3, conditions B). This increase in the yield for the bis(coupled) products when **5** was coupled with **6d** and **6e**, respectively, disappeared when the reaction was repeated in refluxing THF (Table 3, conditions C, Entries 4 and 5). Similar conditions to those employed by Fu et al. for the coupling of unreactive aryl chlorides using the Negishi methodology were also investigated.[31] Thus, using $[Pd_2(dba)_3]$ as catalyst and $P(t\mathrm{Bu})_3$ as co-catalyst resulted in one of the highest yields for the Negishi coupling of **5** with 4′-bromoacetophenone (**6e**), affording **7e** in 37% yield (Table 3, conditions D, Entry 5).

The best conditions for the Negishi coupling, resulting in moderate to good yields in general, were observed when $[Pd(PPh_3)_4]$ was used without co-catalyst $P(t\mathrm{Bu})_3$ in refluxing THF (Table 3, conditions E). Under these conditions, compound **5** was coupled with **6d** affording **7d** in 69% yield, the highest yield obtained for all the different substrates and conditions in the Negishi coupling of our components. Beside the bis(coupled) products, mono(reduced) mono(coupled) products were obtained in an average yield of 10%. This makes the purifications of the reaction mixtures difficult using chromatography because of the similar R_f values and in some cases, purification by recrystallization after chromatography was employed to obtain pure products.

In an attempt to obtain higher yields for the Negishi coupling, a reverse addition approach was undertaken. Each of the aryl halides **6a**–**f** were subjected to halogen/lithium exchange followed by transmetallation to the corresponding organozinc chloride, after which the 2,8-dibromo Tröger's base analogue **2** was added as the coupling partner (Table 3, conditions F). In this new approach, the only successful coupling was the coupling of the 2-pyridinylzinc chloride, formed in situ from **6f**, with **2**, yielding the desired bis(coupled) product **7f**, in a reasonable 42% yield. There were several practical obstacles with the reverse-addition approach: Compound **6d** could not be employed due to its limited solubility at –78 °C, and for **6e** nucleophilic addition to the carbonyl group took place instead of the desired bromine/lithium exchange. For compounds **6b** and **6c**, the iodine/lithium exchange was not efficient, neither at –78 °C nor at room temperature and the isolation of the homocoupled product of **6b** and **6c**, respectively, strongly indicates that the reason for the low yields is not the coupling of the dihalo analogue of the Tröger's base unit with arylzinc chloride, but instead the poor formation of the arylzinc chloride from the corresponding aryl halide.

In summary, for the Negishi couplings applied to the Tröger's base system, there is no procedure that in general gives high yields of bis(coupled) products. Instead, for each desired coupling partner, specific reaction conditions must be employed to obtain the highest yield. It was also concluded that for several reasons, a reverse-addition protocol was not a good approach.

X-ray Diffraction Studies

The solid-state structures of racemic 2,8-bis(4-nitrophenyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (**7d**) and racemic 2,8-di(pyridin-2-yl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (**7f**) were determined by X-ray diffraction analysis.[32] This investigation is presented in the Supporting Information (see also the footnote on the first page of this article).

Conclusions

Of the three different palladium-catalyzed cross-coupling reactions, the Suzuki coupling was found to be the most successful for the attachment of aromatic and heteroaromatic moieties to the Tröger's base core. The generality of the method was demonstrated by employing aryl halides with different electronic and steric properties as coupling partners, resulting in excellent yields of the bis(coupled) products in most of the Entries. Moderate to good yields were obtained for the Stille coupling with reaction times longer than the ones required for the Suzuki coupling. In contrast to the Suzuki coupling, where higher yields were achieved using $[Pd_2(dba)_3]$ as catalyst, $[Pd(PPh_3)_4]$ was found to be the best catalyst for the Stille couplings. Moreover, for both the Suzuki and the Stille couplings, the presence of $P(t\mathrm{Bu}_3)$ as co-catalyst in the reaction mixture resulted in faster coupling reactions leading to high substrate conversion before the decomposition of the catalyst took place, thus resulting in higher yields of the desired bis(coupled) products. For these two coupling reactions the reaction temperature was found to strongly affect not only the reaction time but also the yields of coupled products. Moderate yields were found for the Negishi couplings. The Negishi couplings were not strongly influenced by the choice of the catalyst, the presence of co-catalyst, or the reaction temperature.

However, using $[Pd(PPh_3)_4]$ as only catalyst in refluxing THF seems to give slightly higher yields. In this case, similar yields were observed in the Stille and Negishi couplings but purification of the reaction mixture turned out to be more difficult in the latter case.

Experimental Section

General Remarks: All reactions were performed under argon using syringe-septum cap techniques and after flame drying all glassware prior to use. All the chemicals and solvents were used as received from commercial sources without further purification, except for THF which was distilled from sodium benzophenone ketyl. 2,8-Dibromo-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (**2**)[12] as well as 2,8-bis(tributylstannyl)-6*H*,12*H*-5,11-methanodibenzo-[*b*,*f*][1,5]diazocine (**4**)[16] were prepared as described previously. $P(tBu)_3$ was used as commercially available 10 wt.-% solution in hexanes (Strem Chemicals). A $ZnCl_2$ solution was prepared prior to use by melting $ZnCl_2$ under vacuum (0.2 Torr) and cooling under argon. The sequence was repeated three times before dry THF was added, resulting in a 0.68 M solution. All reactions were run until no further progress was observed as demonstrated by TLC. TLC analyses (Merck 60 F_{254} sheets) were visualized under UV light (254 nm). Column chromatography was performed on silica gel (Matrex 0.063–0.200 mm). Typically columns of diameter = 4 and length = 6–12 cm were used. Melting points (m.p.) were determined in capillary tubes and were uncorrected. Chemical shift are given in ppm relative to TMS using the residual $CHCl_3$ peaks δ = 7.27 (^{1}H NMR) and 77.16 (^{13}C NMR) ppm in $CDCl_3$ and the residual CD_3OD peaks at δ = 3.31 (^{1}H NMR) and 40.00 (^{13}C NMR) ppm in CD_3OD as internal standards. The assignments were accomplished by two-dimensional NMR spectroscopic experiments (COSY, HMQC, HMBC). For numbering of atoms see Scheme 1. The experimental procedures that proved not to be the best are reported in the Supporting Information.

2,8-(6*H*,12*H*-5,11-Methanodibenzo[*b*,*f*]diazocineylene)diboronic Acid (3): To a stirred solution of 2,8-dibromo-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (**2**) (1.67 g, 4.39 mmol) in dry THF (15 mL) was added dropwise 2.5 M *n*BuLi in hexane (4.20 mL, 10.5 mmol) over 5 min. After stirring at –78 °C for 10 min, trimethyl borate (2.10 mL, 12.3 mmol) was added and the reaction mixture was allowed to reach room temperature. The reaction mixture was stirred for additional 1 h. After this time, H_2O (20 mL) was added to the reaction mixture and the mixture was extracted with dichloromethane (3 × 15 mL). The aqueous phase was acidified with 6 M HCl and the obtained precipitate was filtered off and washed with water to afford 1.08 g of **3** (92%) as a white solid after drying in vacuo. M.p. 235 °C (dec). ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ = 4.25 (d, *J* = 16.8 Hz, 2 H, 6*endo*-H), 4.27 (s, 2 H), 4.69 (d, *J* = 16.8 Hz, 2 H, 6*exo*-H), 6.98 (d, *J* = 8.6 Hz, 2 H), 7.04 (d, *J* = 2.2 Hz, 2 H), 7.18 (dd, *J* = 8.6, 2.3 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 60.21 (2 C), 68.44 (1 C), 118.52 (2 C), 128.85 (2 C), 131.61 (2 C), 132.30 (2 C), 132.42 (2 C), 148.89 (2 C) ppm. $C_{15}H_{16}B_2N_2O_4$ (309.92): calcd. C 58.13, H 5.20, N 9.04; found C 58.20, H 5.29, N 9.15.

Suzuki Cross-Coupling Using $[Pd_2(dba)_3]$. Conditions B: To a suspension of **3** (50 mg, 0.16 mmol) in 1,4-dioxane (2.0 mL) was added the aryl halide (1.2 equiv.), $[Pd_2(dba)_3]$ (2.2 mg, 1.5 mol-%), 10 wt.-% $P(tBu_3)$ in hexanes (14 μL, 3.6 mol-%) and 10% w/v aqueous solution of $NaHCO_3$ (1 mL, 1.2 mmol). The reaction mixture was stirred at 85 °C until completion of the reaction. The reaction mixture was diluted with water (10 mL) and extracted with dichloromethane (3 × 15 mL), the combined organic phases were dried (Na_2SO_4), the solvent removed under vacuum and the residue was adsorbed on SiO_2 prior to column chromatography.

2,8-Di(4-anisyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (7a): Compound **7a** was prepared applying conditions B using **6a** (90 mg, 0.38 mmol). After 6 h reaction time, column chromatography of the crude product [EtOAc (30%) in heptane] afforded 56 mg (81%) of **7a** as a white solid. R_f = 0.26 (10% heptane in EtOAc). M.p. 230–232 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 3.83 (s, 6 H, MeO–H), 4.29 (d, *J* = 16.6 Hz, 2 H, 6*endo*-H), 4.40 (s, 2 H, 13-H), 4.79 (d, *J* = 16.6 Hz, 2 H, 6*exo*-H), 6.94 (dd, *J* = 9.2, 2.0 Hz, 4 H, 3′-H), 7.11 (d, *J* = 2.0 Hz, 2 H, 1-H), 7.22 (d, *J* = 8.4 Hz, 2 H, 4-H), 7.37 (dd, *J* = 8.4, 2.0 Hz, 2 H, 3-H), 7.43 (d, *J* = 9.2 Hz, 4 H, 2′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.48 (2 C, MeO–C), 59.02 (2 C, 6-C), 67.22 (1 C, 13-C), 114.31 (4 C, 3′-C), 125.25 (2 C, 1-C), 125.56 (2 C, 4-C), 126.03 (2 C, 3-C), 128.02 (4 C, 2′-C), 128.25 (2 C, 6a-C), 133.46 (2 C, 4′-C), 136.90 (2 C, 2-C), 147.05 (2 C, 4a-C), 159.09 (2 C, 1′-C) ppm. IR (KBr): $\tilde{\nu}$ = 1246 cm^{-1} (C–O–C). HRMS (FAB+): *m*/*z* calcd. for $C_{29}H_{26}N_2O_2$ [M] 434.1994; found 434.1990. $C_{29}H_{26}N_2O_2$ (434.53): calcd. C 80.16, H 6.03, N 6.45; found C 79.97, H 5.99, N 6.37.

2,8-Di(4-tolyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (7b): Compound **7b** was prepared applying conditions B using **6b** (82 mg, 0.38 mmol). After 3 h reaction time, column chromatography of the crude product [EtOAc (25%) in heptane] afforded 55 mg (85%) of **7b** as a white solid. R_f = 0.24 (50% EtOAc in heptane). M.p. 213–214 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.38 (s, 6 H, Me-H), 4.30 (d, *J* = 16.6 Hz, 2 H, 6*endo*-H), 4.40 (s, 2 H, 13-H), 4.80 (d, *J* = 16.6 Hz, 2 H, 6*exo*-H), 7.15 (d, *J* = 1.9 Hz, 2 H, 1-H) 7.20–7.24 (m, 6 H, 3′-H and 4-H), 7.39–7.42 (m, 6 H, 4′-H and 3-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.27 (2 C, Me-C), 59.02 (2 C, 6-C), 67.21 (1 C, 13-C), 125.51 (2 C, 1-C), 125.59 (2 C, 4-C), 126.27 (2 C, 3-C), 126.87 (4 C, 2′-C), 128.26 (2 C, 6a-C), 129.62 (4 C, 3′-C), 136.92 (2 C, 4′-C), 137.22 (2 C, 2-C), 138.01 (2 C, 1′-C), 147.38 (2 C, 4a-C) ppm. HRMS (FAB+): *m*/*z* calcd. for $C_{29}H_{26}N_2$ [M] 402.2096; found 402.2087. $C_{29}H_{26}N_2$ (402.53): calcd. C 86.53, H 6.51, N 6.96; found C 86.45, H 6.49, N 6.88.

2,8-Di(2-tolyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (7c): Compound **7c** was prepared applying conditions B using **6c** (49 μL, 0.38 mmol). After 3 h reaction time, column chromatography of the crude product [EtOAc (20%) in heptane] afforded 53 mg (82%) of **7c** as a white solid. R_f = 0.31 (50% EtOAc in heptane). M.p. 202–203 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.32 (s, 6 H, Me-H), 4.32 (d, *J* = 16.6 Hz, 2 H, 6*endo*-H), 4.39 (s, 2 H, 13-H), 4.84 (d, *J* = 16.6 Hz, 2 H, 6*exo*-H), 6.97 (s, 2 H, 1-H), 7.22–7.31 (m, 12 H, 3-H, 4-H, 3′-H, 4′-H, 5′-H, and 6′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.76 (2 C, Me-C), 58.81 (2 C, C-6), 67.08 (1 C, 13-C), 124.89 (2 C), 125.93 (2 C), 127.30 (2 C), 127.73 (2 C), 127.76 (2 C), 128.52 (2 C), 129.97 (2 C), 130.53 (2 C), 135.47 (2 C), 137.85 (2 C), 141.52 (2 C), 147.09 (2 C) ppm. HRMS (FAB+): *m*/*z* calcd. for $C_{29}H_{26}N_2$ [M] 402.2096; found 402.2085. $C_{29}H_{26}N_2$ (402.53): calcd. C 86.53, H 6.51, N 6.96; found C 86.69, H 6.47, N 6.96.

2,8-Bis(4-nitrophenyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (7d): Compound **7d** was prepared applying conditions B using **6d** (95 mg, 0.38 mmol). After 4 h reaction time, column chromatography of the crude product [EtOAc (60%) in heptane] afforded 62 mg (85%) of **7d** as a yellow solid. R_f = 0.32 (10% heptane in EtOAc). M.p. 154–157 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.33 (d, *J* = 16.6 Hz, 2 H, 6*endo*-H), 4.40 (s, 2 H, 13-H), 4.83 (d,

J = 16.6 Hz, 2 H, 6*exo*-H), 7.22 (d, *J* = 2.1 Hz, 2 H, 1-H), 7.29 (d, *J* = 8.4 Hz, 2 H, 4-H), 7.46 (dd, *J* = 8.4, 2.1 Hz, 2 H, 3-H), 7.63 (d, *J* = 8.9 Hz, 4 H, 2′-H), 8.24 (d, *J* = 8.9 Hz, 4 H, 3′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 59.00 (2 C, 6-C), 67.07 (1 C, 13-C), 124.30 (4 C, 3′-C), 126.02 (2 C, 1-C), 126.19 (2 C, 4-C), 126.71 (2 C, 3-C), 127.48 (4 C, 2′-C), 128.69 (2 C, 6a-C), 134.68 (2 C, 2-C), 147.00 (2 C, 4′-C), 147.10 (2 H, 1′-C), 149.18 (2 C, 4a-C) ppm. IR (KBr): $\tilde{\nu}$ = 1514, 1344 cm^{-1} (N–O). HRMS (FAB+): *m*/*z* calcd. for $C_{27}H_{20}N_4O_4$ [M] 464.1485; found 464.1477. $C_{27}H_{20}N_4O_4$ (464.47): calcd. C 69.82, H 4.34, N 12.06; found C 69.74, H 4.31, N 11.97.

2,8-Bis(4-acetylphenyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (7e): Compound **7e** was prepared applying conditions B using **6e** (76 mg, 0.38 mmol). After 3 h reaction time, column chromatography of the crude product [EtOAc (20%) in heptane] afforded 51 mg (69%) of **7e** as a white solid. R_f = 0.26 (10% EtOAc in heptane). M.p. 237–239 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.61 (s, 6 H, Me-H), 4.31 (d, *J* = 16.6 Hz, 2 H, 6*endo*-H), 4.39 (s, 2 H, 13-H), 4.81 (d, *J* = 16.6 Hz, 2 H, 6*exo*-H), 7.21 (d, *J* = 2 Hz, 2 H, 1-H), 7.26 (d, *J* = 8.3 Hz, 2 H, 4-H), 7.46 (dd, *J* = 8.3, 2.0 Hz, 2 H, 3-H), 7.57 (d, *J* = 8.4 Hz, 4 H, 2′-H), 7.97 (d, *J* = 8.4 Hz, 4 H, 3′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.79 (2 C, Me-C), 59.01 (2 C, 6-C), 67.11 (1 C, 13-C), 125.80 (2 C, 4-C), 125.95 (2 C, 1-C), 126.55 (2 C, 3-C), 126.95 (4 C, 2′-C), 128.47 (2 C, 6a-C), 129.07 (4 C, 3′-C), 135.78 (4 C, 2-C and 4′-C), 145.28 (2 C, 1′-C), 148.52 (2 C, 4a-C), 197.84 (2 C, CO–C) ppm. IR (KBr): $\tilde{\nu}$ = 1682 cm^{-1} (C=O) cm^{-1}. HRMS (FAB+): *m*/*z* calcd. for $C_{31}H_{26}N_2O_2$ [M] 458.1994; found 458.1992. $C_{31}H_{26}N_2O_2$ (458.55): calcd. C 81.20, H 5.72, N 6.11; found C 81.08, H 5.66, N 6.03.

2,8-Di(pyridin-2-yl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (7f): Compound **7f** was prepared applying conditions B using **6f** (37 μL, 0.38 mmol). After 6 h reaction time, column chromatography of the crude product (EtOAc) afforded 45 mg (75%) of **7f** as a white solid. R_f = 0.47 (10% MeOH in dichloromethane). M.p. 201–202 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.35 (d, *J* = 16.6 Hz, 2 H, 6*endo*-H), 4.40 (s, 2 H, 13-H), 4.81 (d, *J* = 16.6 Hz, 2 H, 6-H), 7.16 (m, 2 H, 4′-H), 7.24 (d, *J* = 8.4 Hz, 2 H, 4-H), 7.60–7.63 (m, 4 H, 1-H and 6′-H,), 7.68 (dt, *J* = 7.8, 1.9 Hz, 2 H, 5′-H), 7.74 (d, *J* = 1.9 Hz, 2 H, 3-H), 8.61 (d, *J* = 4.6 Hz, 2 H, 3′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 59.15 (2 C, 6-C), 67.25 (1C, 13-C), 120.28 (2 C, 6′-C), 121.95 (2 C, 4′-C), 125.48 (2 C, 4-C), 125.80 (2 C, 1-C), 126.11 (2 C, 3-C), 128.34 (2 C, 6a-C), 135.34 (2 C, 2-C), 136.88 (2 C, 5′-C), 149.14 (2C, 4a-C), 149.72 (2 C, 3′-C), 157.12 (2 C, 1′-C) ppm. HRMS (FAB+): *m*/*z* calcd. for $C_{25}H_{20}N_4$ [M] 376.1688; found 376.1699. $C_{25}H_{20}N_4$ (376.45): calcd. C 79.76, H 5.35, N 14.88; found C 79.85, H 5.37, N 14.43.

Stille Cross-Coupling Using [Pd(Pph$_3$)$_4$]. Conditions A: A 5-mL sealed flask containing compound **4** (240 mg, 0.300 mmol) was evacuated and refilled with argon three times. 1,4-Dioxane (1.0 mL) was added followed by the aryl halide (1.2 equiv.), [Pd(PPh$_3$)$_4$] (5 mg, 1.5 mol-%), 10 wt.-% P(*t*Bu$_3$) in hexanes (27 μL, 3.6 mol-%) and finally CsF (118 mg, 0.780 mmol). The suspension was heated at reflux. After 10–20 min of heating, plenty of white precipitate was formed. After stirring at reflux for 40 h, the reaction was diluted with dichloromethane (5 mL). The precipitate was filtered off and washed with additional dichloromethane (5 mL). The combined organic phases were washed with water (2 × 10 mL), dried (Na_2SO_4), the solvent was removed in vacuo and the residue was adsorbed on SiO_2 prior to column chromatography.

2,8-Di(4-anisyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (7a): Compound **7a** was prepared applying conditions A using **6a** (168 mg, 0.718 mmol). Column chromatography [EtOAc (65%) in heptane] afforded 35 mg (25%) of **7a** as a white solid. $C_{29}H_{26}N_2O_2$ (434.53): calcd. C 80.16, H 6.03, N 6.45; found C 80.24, H 6.08, N 6.37.

2,8-Di(4-tolyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (7b): Compound **7b** was prepared applying conditions A using **6b** (160 mg, 0.734 mmol). Column chromatography [EtOAc (40%) in heptane] afforded 77 mg (63%) of **7b** as a white solid. $C_{29}H_{26}N_2$ (402.53): calcd. C 86.53, H 6.51, N 6.96; found C 86.36, H 6.43, N 6.86.

2,8-Di(2-tolyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (7c): Compound **7c** was prepared applying conditions A using **6c** (96 μL, 0.72 mmol). Column chromatography [EtOAc (25%) in heptane] afforded 80 mg (66%) of **7c** as a white solid. $C_{29}H_{26}N_2$ (402.53): calcd. C 86.53, H 6.51, N 6.96; found C 86.43, H 6.44, N 6.89.

2,8-Bis(4-nitrophenyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (7d): Compound **7d** was prepared applying conditions A using **6d** (181 mg, 0.726 mmol). Column chromatography [EtOAc (60%) in heptane] afforded 84 mg (60%) of **7d** as a yellow solid. $C_{27}H_{20}N_4O_4$ (464.47): calcd. C 69.82, H 4.34, N 12.06; found C 69.73, H 4.42, N 11.95.

2,8-Bis(4-acetylphenyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (7e): Compound **7e** was prepared applying conditions A using **6e** (139 mg, 0.698 mmol). Column chromatography [EtOAc (60%) in heptane] afforded 73 mg (53%) of **7e** as a white solid. $C_{31}H_{26}N_2O_2$ (458.55): calcd. C 81.20, H 5.72, N 6.11, O 6.98; found C 81.26, H 5.98, N 6.09.

2,8-Di(pyridin-2-yl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (7f): Compound **7f** was prepared applying conditions A using 2-bromopyridine (70 μL, 0.71 mmol); after 40 h, additional 5 mg of [Pd(PPh$_3$)$_4$] and 10 wt.-% P(*t*Bu)$_3$ in hexanes (25 μL) were added and the reaction mixture was stirred for additional 24 h. Column chromatography [EtOAc (50% to 70%) in heptane] afforded 23 mg (10%) of **7f** as a white solid. $C_{25}H_{20}N_4$ (376.45): calcd. C 79.76, H 5.35, N 14.88; found C 79.68, H 5.64, N 14.47.

2,8-Di(pyridin-2-yl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (7f): A 5-mL sealed flask containing compound **4** (240 mg, 0.300 mmol) was evacuated and refilled with argon three times. 1,4-Dioxane (1.0 mL) was added followed by **6f** (0.069 mL, 0.720 mmol), [Pd(PPh$_3$)$_4$] (5 mg, 1.5 mol-%), 10 wt-% P(*t*Bu)$_3$ in hexanes (27 μL, 3.6 mol-%), CsF (118 mg, 0.780 mmol) and CuI (4 mg, 0.02 mmol). The suspension was heated at reflux. After 10–20 min of heating, plenty of white precipitate was formed. After stirring at reflux for 40 h, the reaction mixture was diluted with dichloromethane (5 mL). The precipitate was filtered off and washed with additional dichloromethane (5 mL). The combined organic phases were washed with water (2 × 10 mL), dried (Na_2SO_4), the solvent was removed in vacuo to yield 310 mg of orange oil. The crude product was adsorbed on 1.2 g of SiO_2 and purified by column chromatography [dichloromethane (5%) in EtOAc; diameter = 3.5 cm, length = 11 cm] to obtain 72 mg (64%) of **7f** as a white solid.

Negishi Cross-Coupling. Conditions A: To a solution of **2** (0.380 g, 1.00 mmol) in THF (20 mL) at –78 °C under argon was added dropwise 2.4 M *n*BuLi in hexane (1.0 mL, 2.4 mmol) over 5 min. After stirring at –78 °C for additional 5 min, a 0.68 M solution of $ZnCl_2$ in THF (8.8 mL, 6.0 mmol) was added and the reaction mixture was allowed to reach room temperature during 30 min before the aryl halide (1.5 equiv.) and [Pd(PPh$_3$)$_4$] (60 mg, 5 mol-%) were added. The reaction mixture was stirred at room temperature for 16 h. The mixture was diluted with dichloromethane (10 mL) and washed with water (2 × 15 mL), the organic phase was dried

(Na_2SO_4) before the solvent was removed in vacuo and the residue was adsorbed on SiO_2 prior to column chromatography.

2,8-Di(4-anisyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (7a): Compound **7a** was prepared applying conditions A using **6a** (700 mg, 3.00 mmol). Column chromatography [EtOAc (60%) in heptane] afforded 239 mg (55%) of **7a** as a white solid. $C_{29}H_{26}N_2O_2$ (434.53): calcd. C 80.16, H 6.03, N 6.45; found C 79.94, H 5.88, N 6.52.

2,8-Di(4-tolyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (7b): Compound **7b** was prepared applying conditions A using **6b** (666 mg, 3.00 mmol). Column chromatography [EtOAc (40%) in heptane] afforded 249 mg (62%) of **7b** as a white solid. $C_{29}H_{26}N_2$ (402.53): calcd. C 86.53, H 6.51, N 6.96; found C 86.38, H 6.64, N 6.85.

2,8-Di(2-tolyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (7c): Compound **7c** was prepared applying conditions A using **6c** (400 μL, 3.00 mmol). Column chromatography [EtOAc (25%) in heptane] afforded 221 mg (55%) of **7c** as a white solid. $C_{29}H_{26}N_2$ (402.53): calcd. C 86.53, H 6.51, N 6.96; found C 86.53, H 6.51, N 6.96.

2,8-Bis(4-nitrophenyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (7d): Compound **7d** was prepared applying conditions A using **6d** (754 mg, 3.00 mmol). Column chromatography [EtOAc (20–50%) in heptane] followed by recrystallization from EtOAc afforded 93 mg (20%) of **7d** as a yellow solid. $C_{27}H_{20}N_4O_4$ (464.47): calcd. C 69.82, H 4.34, N 12.06; found C 69.68, H 4.31, N 12.11.

2,8-Bis(4-acetylphenyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (7e): Compound **7e** was prepared applying conditions A using **6e** (595 mg, 3.00 mmol). Column chromatography [EtOAc (20–50%) in heptane] followed by recrystallization from EtOAc afforded 93 mg (20%) of **7e** as a white solid. $C_{31}H_{26}N_2O_2$ (458.55): calcd. C 81.20, H 5.72, N 6.11, O 6.98; found C 81.08, H 5.65, N 5.94.

2,8-Di(pyridin-2-yl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (7f): Compound **7f** was prepared applying conditions A using **6f** (300 μL, 3.00 mmol). Column chromatography [EtOAc (20–100%) in heptane] followed by recrystallization from EtOAc afforded 169 mg (45%) of **7f** as a white solid. $C_{25}H_{20}N_4 \cdot 1.5H_2O$ (376.45): calcd. C 74.42, H 5.75, N 13.89, O 5.95; found C 74.73, H 5.55, N 13.56.

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[32] **7d:** Crystal data: $C_{29}H_{26}N_4O_5S$, M = 542.60, orthorhombic, a = 24.708(5), b = 9.843(2), c = 10.703(2) Å, V = 2602.8(9) Å^3, space group *Pccn*, Z = 4, 3577 reflections measured, 2143 unique (R_{int} = 0.0466) which were used in all calculations. The final w$R(F^2)$ was 0.1788 (all data) and the $R(F)$ was 0.0584 [$I > 2\sigma(I)$] using 183 parameters. **7f:** Crystal data: $C_{25}H_{20}N_4$, M = 376.46, monoclinic, a = 25.804(5), b = 5.3609(11), c = 15.300(3) Å, β = 117.75(3)°, V = 1873.1(7) Å^3, space group *C*2/*c*, Z = 4, 2530 reflections measured, 1470 unique (R_{int} = 0.0384) which were used in all calculations. The final w$R(F^2)$ was 0.2228 (all data) and the $R(F)$ was 0.0642 [$I > 2\sigma(I)$] using 133 parameters. CCDC-266952 (**7a**) and -266953 (**7f**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. See the Supporting Information for Figures and crystallographic data.

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