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Solvent and Base Dependence of Copper-Free Palladium-Catalyzed Cross-Couplings between Terminal Alkynes and Arylic Iodides: Development of Efficient Conditions for the Construction of Gold(III)/Free-Base Porphyrin Dimers

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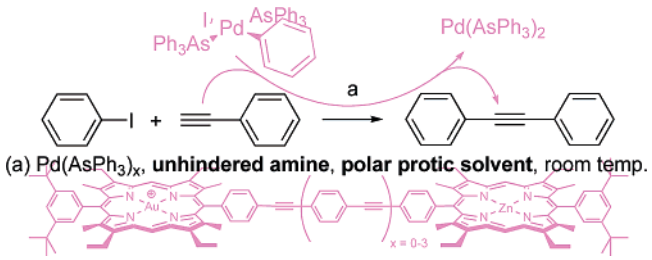

In this paper, our attempts to optimize the Heck alkynylation (copper-free Sonogashira) reaction are presented. An efficient copper-free coupling protocol was needed for the synthesis of gold/zinc porphyrin dimers because previous methods had failed. Previous studies have usually focused on ligands, whereas this work focuses on the choice of solvent and base. The catalytic system throughout the investigation was formed from the stable precursor [$Pd_2(dba)_3$·$CHCl_3$] together with the ligand triphenylarsine, an easy-to-handle, air-stable ligand. A model study was conducted to examine the dependence of the Heck alkynylation on the solvent and base. The most successful modification proved to be the addition of methanol, as a cosolvent, in combination with a nucleophilic tertiary base. The success of the methanol additive is hypothesized to be caused by the presence of a rate-determining deprotonation step featuring a charge-separated transition state. Finally, the very high yielding and successful synthesis of a series of porphyrin systems using these new conditions is presented. For the first time, gold porphyrin substrates could efficiently be coupled in Heck alkynylation reactions.

Introduction

The palladium-catalyzed couplings of terminal alkynes with vinyl and aryl halides, in the presence of cuprous iodide, are generally known as a Sonogashira reaction.[1,2] It is a powerful tool in the synthesis of conjugated carbon skeletons. Since its discovery by Sonogashira in 1975, it has found wide applications in the synthesis of such diverse areas as natural products,[3] molecular wires,[4] and nonlinear optics.[5] However, in some instances, the substrates to be coupled are sensitive to the presence of copper and alternative variants of the coupling procedure have had to be developed. In our case, modifications were necessary because of the problems associated with metalation/transmetalation of porphyrins in the presence of copper under basic conditions.[6] Copper porphyrins are non-

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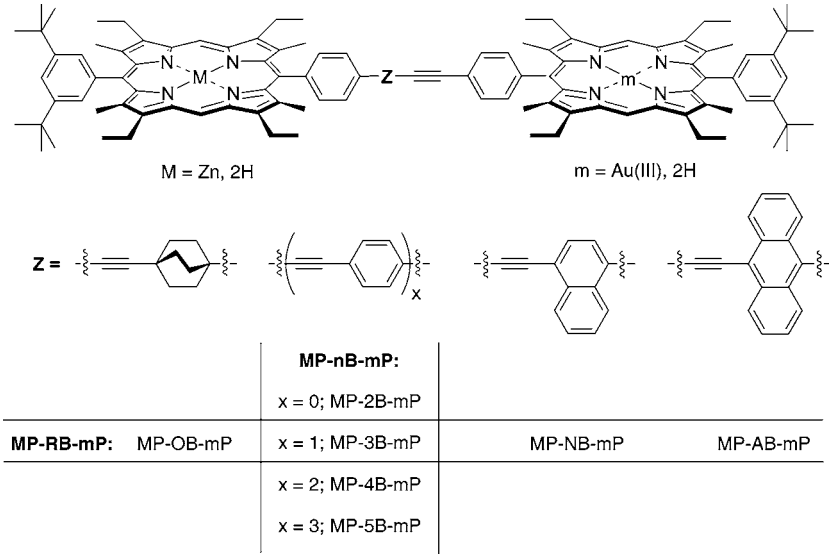
CHART 1. Overview of Our Porphyrin-Based D−B−A Series Designed for EET and ET Studies with the System ZnP−nB−AuP$^+$, Featuring the Repeating Phenylethynyl Unit, Being the Topical Series



fluorescent and have the ability, even in trace amounts, to quench the fluorescence of the systems which we intended to study photophysically. This forced us to completely exclude copper from the reaction mixture.

A number of copper-free Sonogashira protocols have been published throughout the years, most of which have been focused on the rate enhancement of the oxidative addition step of the catalytic cycle. The objective, in many instances, has been to enable the use of more readily available but less reactive substrates, such as unactivated arylic bromides or even activated arylic chlorides.[7−12] Other recently published procedures cover reactions in water under aerobic conditions,[13] recyclable zeolite-supported catalysts,[14] and ionic liquids as the reaction medium.[15] However, when the arylic iodide is easily accessible and the problem is instead the poor reactivity of the alkyne, the number of copper-free alternative reaction conditions drops significantly. For this scenario, the Linstrumelle conditions using excess piperidine or pyrrolidine have been the most widely used.[16] Alkynylation of aryl and vinyl halides using palladium catalysis in the absence of any cocatalysts, such as cuprous iodide, was first explored by Dieck and Heck in 1975 with amines as bases[17] and by Cassar in 1975 with alkoxides as bases.[18] The most commonly employed variant of the reaction, using amine bases, is therefore referred to as the Heck alkynylation, although it is also known as the copper-free Sonogashira reaction.

In our group, we have made extensive use of the alkyne−arylic halide cross-coupling in the assembly of porphyrin-based donor−bridge−acceptor (D−B−A) systems, designed for excitation energy transfer[19,20] (EET) and electron transfer[21,22] (ET) studies (see Chart 1).

The special problem encountered when using porphyrins as coupling partners, besides the sensitivity to copper, is that the solubility of the porphyrin (∼1−10 mM) prevents the use of the more commonly applied coupling procedures, which typically work best at concentrations above 100 mM. Furthermore, we are reluctant to increase the temperature to more than 40 °C because high temperatures tend to degrade the porphyrins. In the assembly of porphyrin-based donor−acceptor systems such as these, the conditions introduced by Wagner and Lindsey et al. in 1995 have been the most frequently used.[23] The Lindsey conditions rely on a large catalyst loading coupled with the use of the dative ligand triphenylarsine in toluene/triethylamine. In our synthetic work on porphyrins, we have previously relied on both the Lindsey and Linstrumelle conditions. They have produced acceptable yields for systems involving free-base and zinc porphyrins. However, when applied to the current synthetic targets, involving gold porphyrins, the yields were exceedingly low with massive byproduct formation and reaction times sometimes in the order of days. The nature of the byproducts in these kinds of reactions has to some extent been investigated by Wagner and Lindsey et al.[24] The failure of the common Sonogashira/Heck alkynylation conditions in our efforts to

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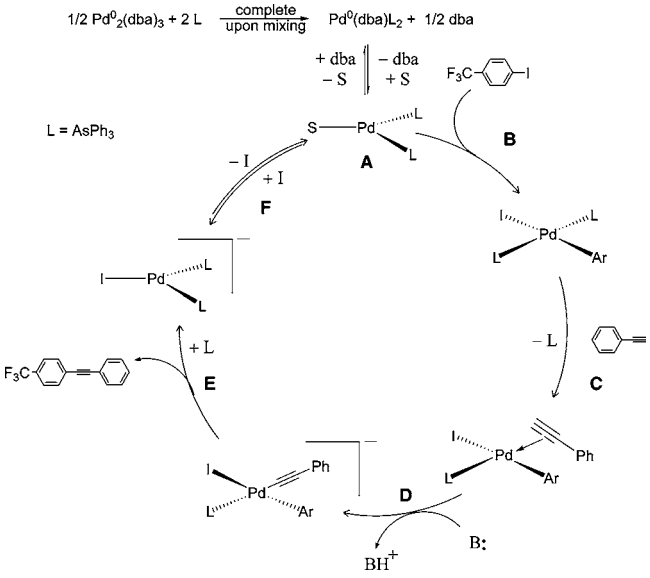

FIGURE 1. Tentative catalytic cycle of the Heck alkynylation reaction.

obtain the gold porphyrin systems led us to try a new approach toward the optimization of the Heck alkynylation reaction. Instead of focusing on the catalyst, the choice of solvent and base was scrutinized using a model reaction.

The paper is organized as follows. First, a hypothesis for a plausible rate-determining step and its transition-state structure for the Heck alkynylation reaction are presented (catalytic cycle for the cross-coupling in the absence of CuI). Then, the design of the studied model reaction is discussed on the basis of the above hypothesis. The experimental results from the study of this model reaction are presented together with a discussion on their implication to the reaction mechanism. The synthetic part is rounded off by illustrating the usefulness of the developed reaction conditions, through application to the assembly of porphyrin-based donor−bridge−acceptor, D−B−A, systems.

Results and Discussion

In our optimizations of the Heck alkynylation, very sensitive precatalysts and ligands were avoided, as the objective was to develop very simple and robust conditions. Therefore, the catalyst throughout the investigation was consistently the air-stable $[Pd_2(dba)_3{\cdot}CHCl_3]$ with triphenylarsine as a dative ligand. Triphenylarsine is a relatively cheap, easy-to-handle, air-stable substance known to show promising results in copper-free couplings.[23] The major drawback of triphenylarsine is of course its toxicity. We are, however, also undertaking ligand optimization experiments, where the phosphites are showing some promising results (vide infra), but extensive ligand screening is outside the scope of this article.

Heck Alkynylation Reaction: Mechanistic Considerations. The literature specifically discussing the mechanisms of the Sonogashira reaction is rather limited.[25] Mechanistic discussions covering the Sonogashira reaction performed in the absence of CuI or other cocatalysts, i.e., the Heck alkynylation, occur even less frequently. Therefore, a schematic catalytic cycle has been derived from the literature covering other similar processes (Figure 1).

The approach to the improvement of the reaction conditions for the Heck alkynylation in this paper is based on the apparent nature of these hypothetical intermediates. The cycle drawn in Figure 1 is merely an illustration of one of several possible cycles. However, according to our reasoning, regardless of their exact nature, they should all share several important features that strongly affect their response to the nature of the solvent and base. The cycle in Figure 1 is based on the following reasoning:

(A) Active catalyst: Two major species, $Pd^0(dba)L_2$ and $Pd^0(solvent)L_2$, exist in solution when the precatalyst is $[Pd_2(dba)_3{\cdot}CHCl_3]$ and $AsPh_3$ is the ligand in a coordinating solvent.[26] The only proven effect of copper on the equilibrium and nature of the species is a ligand scavenging effect to produce more reactive palladium species. However, it has been shown to play a minor role for the readily dissociating ligand $AsPh_3$.[27] In fact, Amatore et al. have shown that the Pd^0 equilibrium in this system is virtually insensitive to arsine excess, at least up to 10 equiv.[26] Furthermore, the use of very reactive substrates, such as activated arylic iodides, ensures that any small effect on the equilibrium of the Pd^0 species will play a negligible role in the overall rate.

(B) Oxidative addition: After oxidative addition, a square planar, neutral, trans complex is formed, possibly from a transient cis complex.[28] This assumption is only valid if the total salt concentration is kept relatively low, i.e., if the requirements for the Jeffery conditions[29] are not fulfilled. This is at least true for the beginning of the reaction, before the liberation of any significant amount of iodide ions.[30]

(C) Alkyne coordination probably takes place through dissociative pathways, to form a square planar uncharged complex. This assumption is based on the alkynes weak coordination ability to Pd^{II} complexes, the alkyne probably being unable to induce substitution through associative pathways.[31] In fact, the reactive species in the transmetalation in the Stille reaction with the same catalyst system has been shown to be $PhPd^{II}I(AsPh_3)(solvent)$ in coordinating solvents.[32] This indicates that one important feature of the arsine ligand that makes it a favorable choice in copper-free alkynylations could be the ease with which the ligand dissociates to form this reactive complex. The square planar complex that is formed has one loosely coordinated solvent molecule that could be replaced by the poorly nucleophilic alkyne. Substitution of the solvent with an alkyne would then produce a neutral square planar Pd^{II} complex.

(D) The mechanism originally suggested by Dieck and Heck for Heck alkynylations involved carbometalation of the alkyne followed by β-hydride elimination (see Scheme 1),[17] instead of alkyne coordination/deprotonation (see Figure 1). However, Dieck and Heck also suggested the existence of a different mechanism including a deprotonation step when the strong base piperidine was used. This concept was further developed by Linstrumelle et al. who concluded that when neat piperidine or

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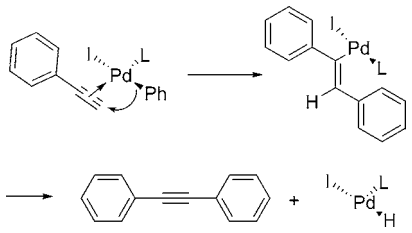
SCHEME 1. Proposed Carbometalation and β-Hydride Elimination of a Heck Alkynylation



pyrrolidine was used a deprotonation pathway was likely to be present.[16] Given that the β-hydride elimination in the Heck mechanism would have to be from a vinylpalladium species in a trans geometry, we hypothesized that this pathway could be disfavored at room temperature compared to a deprotonation mechanism. We therefore focused our attention on a catalytic cycle for the Heck alkynylation starting from the assumption of a deprotonation pathway. It was suggested in the original article by Dieck and Heck that deprotonation occurred on the uncoordinated alkyne, followed by an attack on the palladium complex formed through oxidative addition. However, we believe that deprotonation is most likely to occur after coordination of the alkyne to a Pd^{II} complex, given the very large difference in pK_a between alkylammonium ions and terminal alkynes. The assumption of coordination prior to deprotonation has been made before.[7] A deprotonation of the alkyne on the neutral Pd^{II} complex would then produce a negatively charged palladate complex, assuming that concomitant expulsion of iodide does not take place. If this did occur, a coordinatively unsaturated T-shaped complex should be formed instead. However, regardless of the exact nature of the palladium species formed, the transition state of the deprotonation step should feature a substantial charge separation.

(E) Reductive elimination takes place from the cis isomer of the complex to regenerate the active catalyst. This process is usually rapid in the case of alkynes.[25] Copper can enhance the rate of reductive elimination by facilitating cis−trans isomerism.[25,33] It is, however, unclear if it will have any bearing on the reaction rate in this case, although it could be wise to use a polar coordinating solvent because this would facilitate the formation of the more polarized cis complexes.[34]

(F) The uncharged $[Pd^0(AsPh_3)_2]$ is the active catalyst in the oxidative addition of arylic iodides when the catalyst is $[Pd(dba)_2]/AsPh_3$ in THF and DMF.[26] The final step in our tentative cycle is therefore depicted as the expulsion of the iodide, although $[Pd^0(AsPh_3)_2I]^-$ would be in equilibrium with the other Pd^0 species. If the deprotonation in step (D) is taking place under concomitant iodide expulsion, the uncharged $[Pd^0(AsPh_3)_2]$ will be formed directly upon reductive elimination and coordination to an arsine ligand.

On the basis of this hypothetical catalytic cycle, we made the following assumptions: In the absence of copper, the rate-determining step was likely to be the deprotonation of the alkyne (D, Figure 1). The absence of ligand scavenging effects in the equilibrium between the Pd^0 species (A) and negative effects on the reductive elimination (E), due to decelerated cis−trans isomerization, seem unlikely to explain the huge decline in reaction rate upon removal of copper. Furthermore, in polar solvents, the cis−trans isomerization is usually rapid even in the absence of copper. If all of these assumptions were to be correct, the coupling reaction should show two distinctive features:

(1) The reaction should be faster in solvents of higher polarity because of the charge-separated transition state in the rate-determining deprotonation step. Protic solvents could prove to be beneficial if the developing negative charge is open for solvent stabilization through hydrogen bonding. Furthermore, a polar solvent should prevent any cis−trans isomerization in the reductive elimination step from becoming rate determining.

(2) The base is directly involved in the rate-determining transition state, and the reaction rate should thus depend on its concentration and its electronic and steric properties. A higher concentration of the base and electronic factors that could contribute to stabilizing the transition state should accelerate the reaction, whereas large steric hindrance should impede it.

Solvent Polarity and Base Reactivity Estimations. The polarities of the solvents used in the model reactions were estimated from their $E_T(30)$ value according to the scale developed by Reichardt and Dimroth.[35,36] The steric hindrance of the bases studied was estimated from values of their cone angles (θ). The factors governing the reactivity of the substrates in a number of different reactions have successfully been interpreted in terms of the "curve crossing model".[37−39] Applying this model to a series of reactions, in which the electrophilic substrate is kept the same throughout the series, it has been possible to reduce the parameters determining the relative reactivity among the similar but different nucleophilic reagents to the vertical ionization potential, IE_v; the lower the ionization potential, the more reactive the nucleophilic reagent. To predict the reactivity of the different bases, we therefore chose to use the vertical ionization potential, IE_v. The result of the dependence on electronic factors should be, in the case of common aliphatic amines, that tertiary amines are superior because of the greater stabilization of the transition state. This correlates well with the values of IE_v in Table 1. The pK_a values could also be good measures of the base efficiency in the deprotonation step. However, because this is a thermodynamic quantity, quantifying the extent of deprotonation in an acid−base equilibrium, it is not necessarily a good measure of the kinetic performance of the base in the transition state under scrutiny. The structure of the transition state may reduce the opportunity for solvation, thus making the thermodynamic base strength concept, including very large solvation factors, inadequate.

Choice of Model Reaction. To investigate the validity of the hypotheses, we designed a model reaction. As oligo(phenyleneethynylene) was our target structural motif, the tolan scaffold was selected as a suitable product for the model reaction. To isolate the effects of the conditions on the deprotonation/insertion step, we used 4-iodobenzotrifluoride as one of the two coupling partners (Scheme 2). The high intrinsic reactivity of aryl iodides and the activating effect of the trifluoromethyl group in oxidative addition should prevent this

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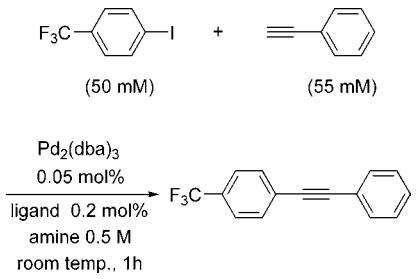
TABLE 1. Yields[a] of 4-Trifluoromethyltolane after One Hour for the Model Reaction[b] with Different Solvent/Amine Combinations

					solvents: by decreasing polarity			
no.	amines	pK_a[c]	cone angle[d]	IE$_v$[e]	MeOH	DMF	THF	PhCH$_3$
1	quinuclidine	11.3	132	8.05	35	45	4	4
2	DABCO[f]	8.8	132[g]	7.52, 8.59[h]	16	20	n.d.[i]	4
3	triethylamine	10.9	150	8.08	16	4	3	3
4	DIPEA	11.4	205	7.7	4	1	n.d.	1
5	piperidine	11.1	121	8.66	9	n.d.	n.d.	n.d.
6	diethylamine	11.0	125	8.63	n.d.	n.d.	n.d.	n.d.
7	DIPA	11.1	137	8.40	8	n.d.	n.d.	n.d.
8	butylamine	10.8	108	9.40	n.d.	n.d.	n.d.	n.d.
9	DMAP	9.7	91.9[j]	9.1, 7.82, 9.3[k]	n.d.	n.d.	n.d.	n.d.
10	DBU	11.6		7.81, 8.73, 10.18[l]	n.d.	n.d.	n.d.	n.d.

[a] The yields were determined by ^{19}F NMR. [b] Reaction conditions: 4-iodobenzotrifluoride (50 mM), phenylacetylene (55 mM), 0.05 mol % [$Pd_2(dba)_3$·$CHCl_3$], 2 equiv $AsPh_3$ per Pd, 10 equiv amine, room temperature. [c] Refers to pK_a of the corresponding conjugate acid in H_2O at 25 °C and taken from ref 41. [d] The angles are in degrees and are taken from ref 42. [e] All values are in electronvolts and are taken from ref 43. [f] Included in the table as a potential quinuclidine surrogate. [g] Estimated to be equal to quinuclidine. [h] The second value is an average of the IE$_v$'s of the first two bands caused by splitting of the two nitrogen lone pairs, and the first value is the maximum of the first band. [i] n.d. means a product formation below the detection limit, i.e., below 1%. [j] Estimated to be equal to pyridine. [k] The three ionization potentials given for DMAP correspond to n, π_S, and π_A, respectively (ref 44). [l] The three ionization potentials given for DBU correspond to n_N, n_{CN}, and π_{CN}, respectively (ref 45).

SCHEME 2. Model Reaction



step from becoming rate determining, thus allowing us to focus more on the deprotonation/insertion step.

Furthermore, the presence of the trifluoromethyl group offered a convenient means of determining the yield because of the high resolution of trifluoromethyl singlets in ^{19}F NMR. Phenylacetylene, the simplest possible coupling partner to obtain the tolan skeleton, was chosen as the second reactant. Four solvents were selected as representatives for the four solvent categories: apolar, low-polarity aprotic, high-polarity aprotic, and high-polarity protic solvents. The selected representative for each of these categories was toluene (PhCH$_3$, $E_T(30) = 33.9$), tetrahydrofurane (THF, $E_T(30) = 37.4$), dimethylformamide (DMF, $E_T(30) = 43.8$), and methanol (MeOH, $E_T(30) = 55.4$), respectively.[40]

The concentration of the substrates was fixed at 50 mM with the very low catalyst loading of 0.05 mol % (0.1 mol % Pd) to intentionally produce a low to moderate yield for the reactions in 1 h. The catalyst loading was adjusted so as to give a conversion of around 50% for the most efficient reaction. By stopping the reaction at moderate conversion rather than at high conversion, a larger difference in yields is observed between the faster and more interesting reactions, thus giving a more reliable indication of the relative rates. Therefore, the yields presented for the model reaction in Table 1 to Table 5 should by no means be taken as maximum conversion under realistic conditions. Instead, they should illustrate the relative difference in rate among different protocols to give information about solvent and base dependence. The reproducibility of the experiments was very good; for a detailed description of the experimental procedure for a typical base and solvent set, see Supporting Information.

Studies of the Solvent, Base, and Ligand Dependence. The structure of this part of the paper is as follows: First, the effects of steric bulk and solvent polarity are explored together with a comparative study of the performance of tertiary, secondary, and primary amines in the model reaction. The results are discussed in terms of basicity, inductive stabilization, and steric bulk. Following this, the effect of the σ- and π-donating ability of the ligand is briefly explored, and a comparative study between the optimum reaction conditions found for the model reaction and the reaction conditions for established protocols is made. Finally, the new reaction protocol is applied to the assembly of porphyrin-based D−B−A systems.

Solvent and Base Dependence. The first experiments were designed to study two variables simultaneously: the effect of steric bulk and solvent polarity when using tertiary amines. Three different bases were chosen to represent different levels of steric hindrance (ordered by increasing steric bulk): quinuclidine, triethylamine, and diisopropylethylamine (DIPEA). These three bases are all tertiary, and their stabilizations of the transition state, as judged from their IE$_v$, are in the same order of magnitude (7.7−8.08 eV), thereby allowing us to minimize the effect of properties other than the steric bulk. Each of these three bases was tried in the four different solvents selected for this investigation, PhCH$_3$, THF, DMF, and MeOH (entries 1, 3, and 4, Table 1).

On examination of the results from the first experiments on tertiary amines in Table 1, it became clear that the choice of base as well as the choice of solvent were of crucial importance to the outcome of the reaction. It unambiguously supports the hypothesis that reaction rates increase as the steric bulk of the tertiary amine decreases, regardless of solvents used.

The trend of increasing reaction rate with increasing ability of the solvent to stabilize charges was also quite clear. Methanol, the most polar solvent in the study according to the $E_T(30)$ scale, was superior in the reactions when relatively hindered amine nucleophiles were used. This most likely indicates the presence of a stabilizing effect of the solvent on the developing charge separation in the rate-determining transition state. When highly nucleophilic tertiary bases were used, however, the order was reversed for methanol and DMF. One possible explanation is a counteracting pacifying effect of methanol on the quinuclidine

(40) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*; 3rd ed.; Wiley-VCH: Weinheim, Germany, 2004.

reactivity due to solvation of the very exposed nitrogen atom. However, the twelve reactions did seem to support the general solvent and base dependence indicated by the proposed catalytic cycle in Figure 1.

We also conducted the same experiments with 1,4-diazabicyclo-[2.2.2]octane (DABCO) as a quinuclidine surrogate, to test whether quinuclidine could be replaced by the far less expensive and readily available DABCO in our further work (entry 2, Table 1). The lower reaction rate was surprising, given the lower IE_v of DABCO compared to that of quinuclidine. The effect of having two interacting nitrogens in the same base gives two different values of IE_v that make a direct comparison with a normal aliphatic amine difficult. Nevertheless, the results were encouraging with a trend very similar to that of quinuclidine, with the optimum solvent being the polar aprotic DMF. Although less efficient than quinuclidine, it proved to be superior to all other bases screened and was therefore a good surrogate for quinuclidine (vide infra).

The experiments were repeated with secondary bases. The purpose was to investigate the difference between secondary and tertiary bases. Therefore, the bases that were investigated were the closest secondary analogues of quinuclidine, triethylamine, and diisopropylethylamine, viz., piperidine, diethylamine, and diisopropylamine (DIPA) (entries 5, 6, and 7, Table 1). The IE_v values of these bases are also in the same order of magnitude (8.40−8.66 eV) and are all substantially higher than that of any of their tertiary counterparts. As Table 1 shows, the secondary bases were, in all cases but one, inferior to the corresponding tertiary bases (DIPA was more effective than DIPEA) and only in the case of methanol as solvent was there any detectable product formation after 1 h. The slower reaction with DIPEA than with DIPA could be a result of the very low IE_v of DIPEA not compensating for its extreme bulk ($\theta = 205°$). The inferiority of the secondary amines in all other cases could be contributed to the significantly reduced electron-donating capability in the transition state when going from tertiary to secondary bases. Furthermore, the reduced bulk and the presence of a hydrogen on secondary amines make their deprotonation ability much more dependent on solvation,[46,47] which is reflected by detectable product formation being observable only in methanol, the strongest solvating agent. The small difference in yield between piperidine and DIPA in methanol is probably due to the reduced significance of steric bulk when using secondary amines. The secondary amines are all relatively unhindered with a much narrower spread in cone angles compared to that for tertiary amines. The lower IE_v of DIPA will therefore have a much larger impact on the reaction rate than that in the case of the analogous tertiary bases. The reaction with diethylamine in methanol failed inexplicably to produce any product.

The pronounced reactivity drop on going from tertiary to secondary amines indicated that reactions employing primary amines were not likely to be high yielding. The positive effect of their very small cone angles did not seem likely to be able to compensate for their poor electron-donating capabilities (see butylamine, entry 8, Table 1). In fact, the primary amine, butylamine, failed to participate in any productive reaction, even in methanol.

Another very nucleophilic but weakly basic amine is (dimethylamino)pyridine (DMAP). This was also included as a representative of unhindered but weak bases (entry 9, Table 1). The three different ionization energies for DMAP represent the contribution of different orbitals to the ionization of the base. As in the case of DABCO, it is difficult to categorize DMAP from its IE_v's, given that there are two interacting nitrogen atoms and several ionization potentials associated with these. However, the IE_v value of 9.1 eV in the reference article is attributed to the nitrogen lone pair of the pyridine moiety and could thus possibly serve as a guideline to its electron-donating capability.[44] This puts it between the primary and the secondary amines and should, if this IE_v value was a correct representation, electronically be a poor base in this reaction. For the same reason, it is not unambiguous which IE_v value to use in the quantitative comparison for diazabicyclo[5.4.0]undec-7-ene (DBU), which was included to represent the other extreme, a very bulky amine coupled with a superior electron-donating capability (entry 10, Table 1). Although we have been unable to find a θ value for DBU, it is generally considered to be very bulky and nonnucleophilic in almost all types of reactions.[48,49] Both DMAP and DBU failed to induce any detectable product formation. The blank results show that neither a small cone angle (DMAP) nor powerful electron-donating capabilities (DBU) are alone sufficient for a fast reaction.

Despite a difference by a factor of 10^3 in the acid constant for the different amines used in this study, no obvious correlation or clear trend can be discerned between the cross-coupling yield and the pK_a values. The pK_a values for amines show a strong solvent dependence, especially when comparing tertiary with secondary or primary amines. However, the acid constants for the various amines in methanol are in general very similar to the ones obtained for water. Therefore, because the pK_a values given in Table 1 refer to aqueous solutions, a correlation of the cross-coupling efficiency with these values should only be expected for the results obtained from the experiments run in methanol. However, it was apparent from the results of the cross-couplings performed in methanol that no such correlation existed. Comparing the bases of highest and lowest basicity of

(41) pK_a values are taken from: (a) (quinuclidine) Grob, C. A. *Helv. Chim. Acta* **1985**, *68*, 882−886. (b) (DABCO) Hine, J.; Kaufmann, J. C.; Cholod, M. S. *J. Am. Chem. Soc.* **1972**, *94*, 4590−4595. (c) (TEA) Kuna, S.; Pawlak, Z.; Tusk, M. *J. Chem. Soc., Faraday Trans. 1* **1982**, *78*, 2685−2692. (d) (DIPEA) Faltin, C.; Fleming, E. M.; Connon, S. J. *J. Org. Chem.* **2004**, *69*, 6496−6499. (e) (piperidine, diethylamine, and butylamine) Heo, C. K. M.; Bunting, J. W. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2279−2290. (f) (DIPA) Tamres, M.; Searles, S.; Leighly, E. M.; Mohrman, D. W. *J. Am. Chem. Soc.* **1954**, *76*, 3983−3985. (g) (DMAP) Heo, C. K. M.; Bunting, J. W. *J. Org. Chem.* **1992**, *57*, 3570−3578. (h) (DBU) Ivanova, G.; Bratovanova, E.; Petkov, D. *J. Pept. Sci.* **2002**, *8*, 8−12.

(42) Cone angles are taken from: (a) (all except DIPEA and pyridine) Seligson, A. L.; Trogler, W. C. *J. Am. Chem. Soc.* **1991**, *113*, 2520−2527. (b) (DIPEA) Fox, A.; Hartman, J. S.; Humphries, R. E. *J. Chem. Soc., Dalton Trans.* **1982**, 1275−1283. (c) (pyridine) Marques, H. M.; Bradley, J. C.; Campbell, L. A. *J. Chem. Soc., Dalton Trans.* **1992**, 2019−2027.

(43) IE_v values are taken from: (a) (quinuclidine, DABCO, TEA, diethylamine, DIPA, and piperidine) Aue, D. H.; Webb, H. M.; Bowers, M. T. *J. Am. Chem. Soc.* **1976**, *98*, 311−317. (b) (butylamine) Katsumata, S.; Iwai, T.; Kimura, K. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3391−3395. (c) (DMAP) Ramsey, B. G.; Walker, F. A. *J. Am. Chem. Soc.* **1974**, *96*, 3314−3316. (d) (DIPEA) de Meijere, A.; Chaplinski, V.; Gerson, F.; Merstetter, P.; Haselbach, E. *J. Org. Chem.* **1999**, *64*, 6951−6959. (e) (DBU) Novak, I.; Wei, X.; Chin, W. S. *J. Phys. Chem. A* **2001**, *105*, 1783−1788.

(44) Ramsey, B. G.; Walker, F. A. *J. Am. Chem. Soc.* **1974**, *96*, 3314−3316.

(45) Novak, I.; Wei, X.; Chin, W. S. *J. Phys. Chem. A* **2001**, *105*, 1783−1788.

(46) Hall, H. K. *J. Am. Chem. Soc.* **1957**, *79*, 5441−5444.

(47) Pearson, R. G.; Williams, F. V. *J. Am. Chem. Soc.* **1954**, *76*, 258−260.

(48) Ghosh, N. *Synlett* **2004**, 574−575.

(49) Oediger, H.; Möller, F.; Eiter, K. *Synthesis* **1972**, 591−598.

TABLE 2. Yields of 4-Trifluoromethyltolane after One Hour for the Model Reaction[a] in Different MeOH/CH_2Cl_2 Mixtures

	% v/v MeOH in CH_2Cl_2				
	0	10	20	50	100
yield[b]	6	7	7	14	16

[a] Reaction conditions: 4-iodobenzotrifluoride (50 mM), phenylacetylene (55 mM), 0.05 mol % [$Pd_2(dba)_3$·$CHCl_3$], 2 equiv $AsPh_3$ per Pd, 10 equiv NEt_3, room temperature. [b] The yields were determined by ^{19}F NMR.

all the bases explored in this study, we found that the strongest base, DBU, gave no coupling products under the reaction conditions applied, whereas the weak base, DABCO, showed excellent performance. DABCO was only second to quinuclidine, which in contrast to DABCO is a very strong base, further refuting any correlation. The best tools for prediction were instead the vertical ionization energy, IE_v, of the base in combination with its cone angle.

Quinuclidine and DABCO, although being excellent bases, are not a very appealing choice when it comes to routinely performing couplings. This is due to the cost and purification problems associated with 10 equiv or more of these nonvolatile bases. Therefore, the most promising solvent/base combination seemed to be triethylamine in methanol. Both components are cheap and easy to remove during purification, and the reaction rate is comparatively fast. The only drawback of using this combination is solubility issues encountered when using hydrophobic substrates. In our synthetic work, we are regularly using porphyrin systems exhibiting low solubility in polar solvents. The obvious question that arises from this is: how does the reaction respond to solvent mixtures, i.e., how much of the methanol additive is needed to get a fast reaction in suitable nonpolar solvents?

To answer this question, we carried out four reactions in the very versatile and relatively unpolar solvent dichloromethane (CH_2Cl_2). The ratio between CH_2Cl_2 and MeOH was successively decreased from pure CH_2Cl_2 to a 1:1 mixture. We considered the mixture of equal amounts of CH_2Cl_2 and MeOH to be the limit for our applications; a larger amount of methanol would render our porphyrin system too insoluble. The results, as shown in Table 2, were encouraging. A 1:1 mixture produced a yield of 14%, almost reaching the 16% obtained in pure methanol. The 1:1 mixture of CH_2Cl_2 and MeOH with triethylamine therefore seemed to be a viable alternative for the coupling of the porphyrin systems.

Ligand Dependence: σ-Donating vs π-Accepting Properties. Triphenylarsine was chosen as the ligand in the above series of experiments on the basis of the literature precedent for its performance in Heck alkynylation reactions.[23] Its excellent performance under copper-free conditions, compared to the analogous phosphine ligands, has been ascribed to its fast dissociation, a property that was pointed out as beneficial in our hypothesis. To test the relative effectiveness of triphenylarsine under the most promising conditions for the Heck alkynylation developed, a comparison with a few other readily available ligands seemed appropriate. The ligands chosen were the stable triphenylphosphine (PPh_3) and triethyl phosphite ($P(OEt)_3$) together with the more sensitive but, nowadays, often employed tri-*tert*-butylphosphine ($P(t\text{-}Bu)_3$). The choice of the more sensitive trialkylphosphine was based on the reported effectiveness of it in copper-free cross-couplings. The effectiveness of tri-*tert*-butylphosphine is generally attributed to its strong σ-donating power and its large cone angle. These properties combined induce the formation of a coordinatively highly unsaturated Pd^0 species that readily undergoes oxidative addition. However, the oxidative addition in the model reaction is not thought to be rate determining, which is the reason this ligand may not necessarily be an optimal choice. Triethyl phosphite was selected because of its low σ-donating capacity and stronger π-accepting ability, compared to the other ligands. Conceivably, the π-accepting ability could contribute to dispersal of the negative charge developing on the coordinated alkyne in the transition state upon proton removal. Thus, the stabilizing effect of the developing negatively charged complex of this ligand should increase the rate for proton removal and formation of the palladium alkynide. The final ligand, triphenylphosphine, was chosen because of its frequent use in palladium chemistry and for comparative studies of established protocols (vide infra).

TABLE 3. Yields[a] of 4-Trifluoromethyltolane after One Hour for the Model Reaction[b] Using Four Different Ligands in Combination with Two Different Bases in Two Different Solvents

		solvent	
ligand	amine	MeOH	DMF
$AsPh_3$	DABCO	16	20
$AsPh_3$	triethylamine	16	4
$P(OEt)_3$	DABCO	3	18
$P(OEt)_3$	triethylamine	n.d.[b]	1
PPh_3	DABCO	6	1
PPh_3	triethylamine	8	4
$P(t\text{-}Bu)_3$	DABCO	10	8
$P(t\text{-}Bu)_3$	triethylamine	1	2

[a] The yields were determined by ^{19}F NMR. [b] Reaction conditions: 4-iodobenzotrifluoride (50 mM), phenylacetylene (55 mM), 0.05 mol % [$Pd_2(dba)_3$·$CHCl_3$], 2 equiv ligand per Pd, 10 equiv amine, room temperature. [c] n.d. means a product formation below the detection limit, i.e., below 1%.

The results from this study were hard to interpret, although they clearly show how sensitive the reaction is to changes in the composition of the ligand, base, and solvent (Table 3). The only obvious conclusion was that triphenylarsine was generally better than the other ligands. In contrast to the positive effect of protic solvents found in the study of base dependence, protic solvents were shown to be inferior when $P(OEt)_3$ was used, possibly because of solvation effects of the phosphite ligand. In DMF, however, it was more or less as effective as triphenylarsine. On the other hand, when $P(t\text{-}Bu)_3$ was used, MeOH and DMF seemed to be about equally effective with respect to reaction rate. In the reactions where triphenylphosphine was used, a marked reaction rate increase was seen when switching from DMF to MeOH, again suggesting a pronounced beneficial effect of the protic solvent.

Comparative Studies with Established Protocols. To draw conclusions about the usefulness of the reaction, it had to be compared to the rate of a standard Sonogashira-type coupling and a coupling under the Linstrumelle conditions while keeping all other parameters unchanged. This meant that the bases triethylamine and piperidine were used as solvents, and cuprous iodide was added to the triethylamine reaction to give a Linstrumelle- and Sonogashira-type reaction (Table 4). The ligands were in both cases triphenylphosphine, as this was the ligand originally used for these reactions.

Apparent from these data is that the standard Sonogashira cross-coupling gave a much lower yield after 1 h than the best copper-free solvent/base combination, and the reaction under Linstrumelle conditions failed to deliver any detectable product altogether. This could of course be due to the specific substrates

TABLE 4. Yields of 4-Trifluoromethyltolane after One Hour under Sonogashira- and Linstrumelle-Type Conditions[a]

ligand	solvent = base	yield[b]
PPh_3	triethylamine/CuI[c] (Sonogashira)	10
PPh_3	piperidine (Linstrumelle)	n.d.[d]

[a] Reaction conditions: 4-iodobenzotrifluoride (50 mM), phenylacetylene (55 mM), 0.05 mol % [$Pd_2(dba)_3$·$CHCl_3$], 2 equiv PPh_3 per Pd, room temperature. [b] The yield was determined by ^{19}F NMR. [c] A Pd/Cu ratio of 1:2 was used. [d] n.d. means a product formation below the detection limit, i.e., below 1%

TABLE 5. Yields[a] of 4-Trifluoromethyltolane after One Hour for the Model Reaction[b] with Different Solvent/Amine Combinations

		solvents			
ligand	amines	MeOH	DMF	THF	$PhCH_3$
PPh_3	piperidine	8	n.d.[c]	n.d.	n.d.
PPh_3	diethylamine	n.d.	n.d.	n.d.	n.d.
PPh_3	DIPA	6	n.d.	n.d.	n.d.

[a] The yields were determined by ^{19}F NMR. [b] Reaction conditions: 4-iodobenzotrifluoride (50 mM), phenylacetylene (55 mM), 0.05 mol % [$Pd_2(dba)_3$·$CHCl_3$], 2 equiv PPh_3 per Pd, 10 equiv secondary amine, room temperature. [c] n.d. means a product formation below the detection limit, i.e., below 1%.

used in the model coupling and/or the catalyst type and loading. Nevertheless, it does indicate that in a lot of couplings large gains in reaction rate can be made by just excluding the cuprous iodide and changing the solvents and bases used.

However, because the Linstrumelle conditions use the secondary amines piperidine and pyrrolidine as bases and are known to produce high yields when $Pd(PPh_3)_4$ is used as the catalyst, we performed another set of reactions with the three secondary amines in the four selected solvents, changing only the ligand from $AsPh_3$ to PPh_3. This was done to make sure that the poor result of the secondary amines was not ligand dependent. As Table 5 shows, there was no dramatic change. The same two solvent/base combinations turned out to be productive with only a slight decrease in the yield. It also shows that it could be better to run the piperidine/PPh_3 reaction with only 10 equiv of the base in methanol rather than in piperidine as the sole solvent (compare Table 4).

Of interest, after the base and solvent studies, was to test whether this protocol was applicable to the coupling of phenylacetylene with common arylic iodides under more normal concentrations (200 mM) and catalyst loadings (1%). We therefore tested the coupling of three substrates, 4-iodobenzotrifluoride, iodobenzene, and 4-iodotoluene, with phenylacetylene in methanol using 10 equiv of triethylamine at room temperature. The yield of the reactions after 1 h was determined by HPLC (see Table 6). For a typical experimental procedure, see Supporting Information. It was also of interest whether these conditions would hold up at the low concentration, high catalyst loading, and solvent mixture needed for the couplings involving porphyrins. One reaction included in Table 6 (entry 4) was therefore performed at 5 mM of the arylic iodide in CH_2Cl_2/methanol (1:1). For this entry, the simplest possible reactant, iodobenzene, was chosen to simulate the arylic iodide moiety of the porphyrin. To compensate for the overall lower concentrations, the reaction was performed at elevated temperature (40 °C) and increased catalyst and base concentrations ([$Pd_2(dba)_3$·$CHCl_3$], 15 mol %; NEt_3, 100 equiv). The highest temperature we thought appropriate for the porphyrin reactants was 40 °C in subsequent applications.

The reactions gave good to excellent yields for the tested arylic iodides at 200 mM and room temperature. A very good yield was also observed for the highly diluted reaction, as seen for the coupling of iodobenzene at 5 mM and 40 °C. Therefore, these conditions seemed suitable for the cross-coupling of the porphyrin substrates.

Butadiynes, formed through homocoupling, can be of concern when synthesizing large hydrophobic porphyrin systems[23] because chromatography cannot always separate the product from the butadiyne. We therefore checked for butadiyne formation in the test reactions monitored by HPLC. In the 200 mM reactions (entries 1−3, Table 6), small amounts of 1,2-diphenylbutadiyne were detected in the range of 0.01−0.05% yield. For the highly diluted reaction (entry 4, Table 6), no butadiyne was detected.

Application of the Modified Heck Alkynylation Conditions to the Assembly of Donor−Bridge−Acceptor Systems. The larger structures comprising one or more porphyrin moieties were assembled using the modified Heck alkynylation protocol to avoid metalation/transmetalation problems associated with the presence of copper.[6] The synthetic strategy for the construction of the systems was based on a building block approach and is described in detail in our earlier work on excitation energy transfer in the analogous zinc/free-base systems.[50] All of the gold porphyrins carry a positive charge and tetrafluoroborate as a counterion, but the counterion is, for simplicity, left out of the abbreviations in the text. The assembly of the series of D−B−A systems, **ZnP−nB−AuP$^+$**, began with palladium-catalyzed cross-couplings between the arylic iodide moiety of the free-base porphyrin and the terminal alkyne moieties of the monoprotected diethynyl functionalized bridge building blocks (see Scheme 3). The remaining triisopropylsilyl protective group was subsequently cleaved off by fluoride ions, forming a new terminal alkyne available for the final cross-coupling with the gold porphyrin. Finally, zinc insertions afforded the **ZnP−nB−AuP$^+$** systems in a precise state of metalation.

The shortest dimer, **ZnP−2B−AuP$^+$** ($x = 0$, Scheme 3), was prepared from the cross-coupling of the functionalized porphyrin building blocks **AuP$^+$−1B−I** and **H$_2$P−1B−ethynyl** using the same modified Sonogashira protocol. The building blocks **AuP$^+$−1B−I**, **H$_2$P−1B−I**, **H$_2$P−1B−ethynyl**, and **H$_2$P−4B−ethynyl** together with the dimer **ZnP−3B−AuP$^+$** ($x = 1$, Scheme 3) were available from our previous work on donor−bridge−acceptor systems.[22,50,51]

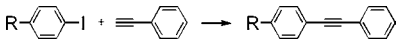
The reference compounds, **AuP$^+$−nB**, were produced by gold insertion into the corresponding free-base porphyrin (Scheme 4). However, the reference compound **AuP$^+$−3B** was synthesized in our previously published work on D−B−A systems and is not included in this Experimental Section. The free-base porphyrins **H$_2$P−2B**, **H$_2$P−4B**, and **H$_2$P−5B** were either directly available from previous work or obtained by demetalation of the available zinc porphyrin.[50] The free-base porphyrins **H$_2$P−4B** and **H$_2$P−5B** produced by demetalation were exceedingly insoluble and were therefore directly subjected to gold insertion without further purification or characterization, using a [$Au(tht)_2$]BF_4^- disproportionation method based on a literature procedure.[52]

(50) Ljungdahl, T.; Pettersson, K.; Albinsson, B.; Mårtensson, J., submitted for publication.

(51) Kajanus, J.; van Berlekom, S. B.; Albinsson, B.; Mårtensson, J. *Synthesis* **1999**, 1155−1162.

(52) Chambron, J.-C.; Heitz, V.; Sauvage, J.-P. *New J. Chem.* **1997**, *21*, 237−240.

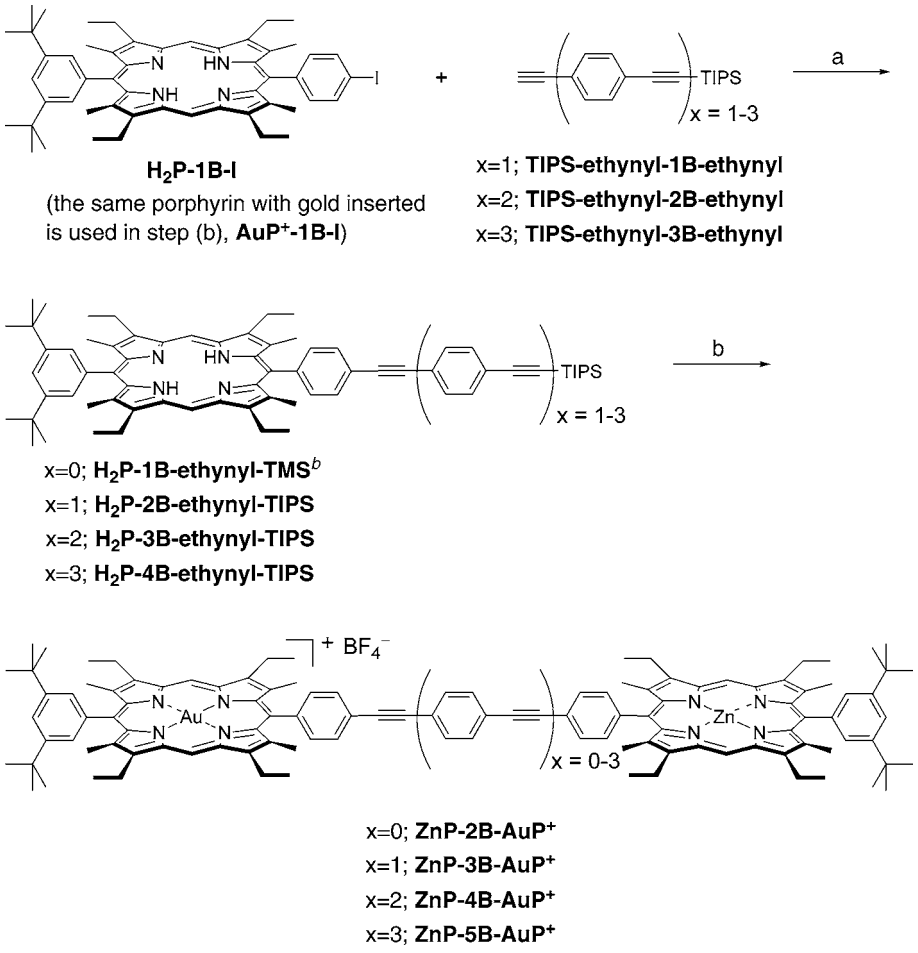
TABLE 6. Yields of Tolanes after One Hour[a]



entry	R	concd[a] (mM)	solvent	mol % catalyst	equiv NEt_3	temp (°C)	yield butadiyne (%)[c]	yield (%)[c]
1	CF_3	200	MeOH	1	10	20[d]	0.03[e]	99
2	H	200	MeOH	1	10	20[d]	0.04[e]	88
3	Me	200	MeOH	1	10	20[d]	0.05[e]	82
4	H	5	MeOH/CH_2Cl_2[f]	15	100	40	n.d.	91

[a] Reagents: [$Pd_2(dba)_3$·$CHCl_3$], $AsPh_3$ (2 equiv per Pd), NEt_3. [b] The concentration refers to the arylic iodide. 1.1 equiv of phenylacetylene was used. [c] Yields were determined by HPLC. [d] Room temperature. No temperature regulation. [e] The value was near the detection limit for the experimental setup. [f] 1:1 mixture.

SCHEME 3. Coupling−Deprotection−Coupling Approach Used to Assemble the D−B−A Systems[a]



H_2P-1B-I
(the same porphyrin with gold inserted is used in step (b), **AuP^+-1B-I**)

x=1; **TIPS-ethynyl-1B-ethynyl**
x=2; **TIPS-ethynyl-2B-ethynyl**
x=3; **TIPS-ethynyl-3B-ethynyl**

x=0; **H_2P-1B-ethynyl-TMS**[b]
x=1; **H_2P-2B-ethynyl-TIPS**
x=2; **H_2P-3B-ethynyl-TIPS**
x=3; **H_2P-4B-ethynyl-TIPS**

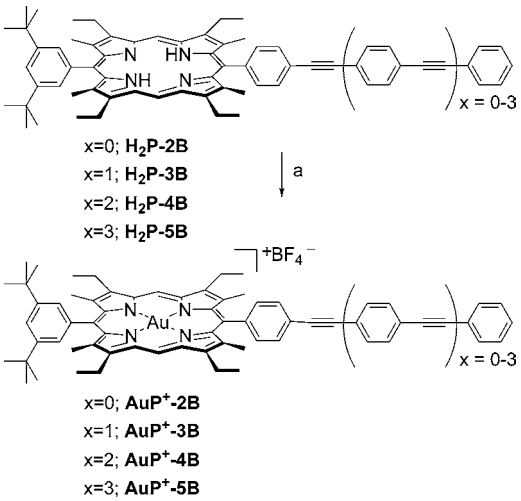
x=0; **ZnP-2B-AuP^+**
x=1; **ZnP-3B-AuP^+**
x=2; **ZnP-4B-AuP^+**
x=3; **ZnP-5B-AuP^+**

[a] Reagents and conditions: (a) 15% [$Pd_2(dba)_3$·$CHCl_3$], 10 equiv $AsPh_3$ per Pd, 100 equiv NEt_3, CH_2Cl_2/MeOH 1:1, 40 °C, 1 h; (b) (i) TBAF, THF, room temperature, 30 min, (ii) **AuP^+−1B−I**, 15% [$Pd_2(dba)_3$·$CHCl_3$], 10 equiv $AsPh_3$ per Pd, 100 equiv NEt_3, CH_2Cl_2/MeOH 1:1, 40 °C, overnight, (iii) 3 equiv $Zn(OAc)_2$·$2H_2O$/MeOH, $CHCl_3$, room temperature, 2 h. [b]**H_2P−1B−ethynyl−TMS** was produced by direct condensation of a TMS-protected *p*-ethynyl-substituted benzaldehyde in the porphyrin ring synthesis. Therefore, the protective group is different and only step (b) in the scheme is applicable to the synthesis of **ZnP−2B−AuP^+**.

For all products, except **H_2P−3B−ethynyl**, ^{13}C NMR spectra and HRMS spectra are available in the Supporting Information. The deprotected alkyne, **H_2P−3B−ethynyl**, has proven to be unstable when kept in solution for extended periods of time. Therefore, this intermediate was only characterized by ^1H NMR and HRMS (see Supporting Information). In addition to this, a thorough photophysical characterization is available in the paper covering the results from the electron-transfer studies conducted on these porphyrin systems.[21] Combined with our previous study on gold systems,[22] three main conclusions could be drawn: (1) electron transfer is the major deactivation channel for donor porphyrin emission quenching; (2) the electronic coupling between the donor and acceptor is strongly correlated to the inverse energy splitting between the singlet excited state of the donor and the bridge; (3) the electronic coupling shows exponential distance dependence with a damping factor, β, of 0.3 $Å^{-1}$. Furthermore, the steady-state and time-resolved fluorescence measurements, as well as the femtosecond transient absorption measurements, conducted in the more recent study, showed that the present gold porphyrin systems were obtained in excellent purity.

We have previously prepared the zinc/free-base systems

SCHEME 4. Gold Insertion Affording the Reference Compounds AuP$^+$−nB[a]



[a] Reagents and conditions: (a) $[Au(tht)_2]BF_4^-$, $PhCl/CHCl_3$ 3:1, 2,6-lutidine, 40 °C, overnight.

corresponding to those presented here using the conditions for the palladium-catalyzed coupling developed by Wagner and Lindsey et al.[23] These copper-free conditions feature a high loading of ($[Pd_2(dba)_3{\cdot}CHCl_3]$/4 equiv $AsPh_3$) together with toluene as solvent and triethylamine as base. For the assembly of the present gold systems, we applied our newly developed conditions (CH_2Cl_2/MeOH, 1:1; NEt_3, 100 equiv; $[Pd_2(dba)_3{\cdot}CHCl_3]$, 15 mol %; 10 equiv $AsPh_3$ per Pd). The high catalyst loading of the Lindsey method was applied to ensure fast conversion under the very dilute conditions required for the poorly soluble porphyrin substrates. Using 10 equiv of $AsPh_3$ instead of 4 equiv seemed to give less byproduct formation without seriously affecting the rate of the reaction and was therefore implemented into the new conditions.

The porphyrin dimers, cross-coupled using the newly developed method, could be obtained in yields from 83 to 92% in 1 h when free-base porphyrins were coupled. This should be compared to our previous results using the Lindsey method, which for free-base porphyrins produced yields in the range of 59−70% with reaction times ranging from 5 to 18 h.[50,51] To further substantiate the usefulness of the new reaction conditions, a comparative coupling was performed for the free-base porphyrins. The coupling of **H$_2$P−1B−I** with **TIPS−ethynyl−3B−ethynyl** to produce **H$_2$P−4B−ethynyl−TIPS** (see Scheme 3) was selected because this had proved to be slow with a reaction time of 18 h producing 70% yield. For the same reaction under the new conditions, an isolated yield of 83% was obtained in 1 h. The marked improvement in reaction rate was obtained simply by changing the solvent from toluene to $MeOH/CH_2Cl_2$ and increasing the $AsPh_3$/Pd ratio from 4 to 10. However, even more rewardingly, the new method produced yields in the range of 81−85% in 18 h for the couplings involving gold porphyrins. Although full conversion was sometimes seen within 1−4 h as judged from NMR and worked-up yields for test reactions, the coupling of gold porphyrins appeared to generally be somewhat slower than the reactions using free-base porphyrins and was therefore allowed to run overnight. The results from the $MeOH/CH_2Cl_2/NEt_3$ solvent/base system should be compared to our previous attempts to use the Lindsey system ($toluene/NEt_3$) for the assembly of gold porphyrin systems, which gave almost no product formation after 18 h and was accompanied by massive byproduct formation. The reaction mixture was then too complex for any practical purposes. It also shows the usefulness of the new method in real synthetic applications. Although the new conditions are very useful in their current form, we are now undertaking optimization experiments and more detailed mechanistic studies to further study the nature, scope, and limitations of this protocol.

Conclusion

In the absence of a copper(I) cocatalyst, the Sonogashira-type couplings show a marked solvent and base dependence. The studies were performed using the stable $[Pd_2(dba)_3{\cdot}CHCl_3]$ precatalyst together with the dative ligand triphenylarsine. In our model studies on trifluoromethyl-tagged substrates monitored by ^{19}F NMR, we have shown that nucleophilic tertiary bases such as quinuclidine and DABCO in a polar solvent are superior in the copper-free cross-coupling of an arylic iodide and phenylacetylene when $AsPh_3$ is used as the dative ligand. Secondary and primary amines were inferior, regardless of their cone angles. No obvious correlation between the efficacy of the base and its pK_a value can be discerned. However, if the cone angle of the base is taken into account, there seems to be a good qualitative correlation between the vertical ionization potential of the base and its efficacy in the Heck alkynylation for the series of tertiary, secondary, and primary alkylamines included in the study. The best results were obtained by using the tertiary, unhindered aliphatic amines in a solvent of high polarity. It was also shown that for tertiary amines neither a small cone angle (DMAP) nor powerful electron-donating capabilities (DBU) were alone sufficient for a fast reaction. When the very nucleophilic bases were used, the aprotic DMF proved to be the best choice. If a more common and not so nucleophilic tertiary amine such as triethylamine was employed, the protic solvent methanol was instead superior. The success of the nucleophilic bases and polar solvents is hypothesized to be caused by the presence of a rate-determining deprotonation step, featuring a substantial charge separation in the transition state. For our synthetic applications, using poorly soluble hydrophobic porphyrins, the most promising solvent/base combination was triethylamine in methanol with dichloromethane as the cosolvent. All components are cheap and easy to remove during purification, and the reaction rate is comparatively fast and even faster than its cuprous iodide cocatalyzed counterpart under some of the conditions used in this article. The gold porphyrin systems, previously inaccessible by direct coupling, could be obtained in yields from 81 to 85%, showing the usefulness of the new method in real synthetic applications.

Experimental Section

[H$_2$P−2B−AuP]$^+$BF$_4^-$. $[Pd_2(dba)_3{\cdot}CHCl_3]$ (2.3 mg, 2.2 μmol) was added to a deaerated solution of **H$_2$P−1B−ethynyl** (12.5 mg, 0.016 mmol), **[AuP−1B−I]**$^+BF_4^-$ (17 mg, 0.015 mmol), $AsPh_3$ (13.5 mg, 44 μmol), and NEt_3 (207 μL, 1.48 mmol) in CH_2Cl_2/methanol (1:1, 4 mL). The reaction mixture was stirred overnight at 40 °C, and the solvent was removed in vacuo. Chromatography (Al_2O_3, neutral grade III, CH_2Cl_2 followed by 3% MeOH in CH_2Cl_2) and SEC (chlorobenzene/DMF, 3:1) gave **[H$_2$P−2B−AuP]**$^+BF_4^-$ as a red solid (22 mg, 0.012 mmol, 81%): ^1H NMR ($CDCl_3$) δ −2.44 (br s, 2H), 1.53 (s, 18H), 1.54 (s, 18H), 1.80 (m, 12H), 1.86 (m, 12H), 2.49 (s, 6H), 2.60 (s, 6H), 2.60 (s, 6H), 2.72 (s, 6H), 4.04 (m, 8H), 4.14 (m, 8H), 7.83 (t, ^4J = 2 Hz, 1H), 7.88

(d, ^4J = 2 Hz, 2H), 7.94 (d, ^4J = 2 Hz, 2H), 7.96 (t, ^4J = 2 Hz, 1H), 8.11−8.23 (m, 8H), 10.23 (s, 2H), 10.63 (s, 2H); HRMS (FAB) calcd for $[C_{106}H_{120}AuN_8]^+$ 1701.9301, found 1701.9332.

H_2P−3B−Ethynyl−TIPS. $Pd_2(dba)_3$·$CHCl_3$ (7 mg, 7 μmol) was added to a deaerated solution of **H_2P−1B−I** (40 mg, 0.046 mmol), bridge building block **TIPS−ethynyl−2B−ethynyl** (24 mg, 0.064 mmol), $AsPh_3$ (42 mg, 138 μmol), and NEt_3 (640 μL, 4.6 mmol) in CH_2Cl_2/methanol (1:1, 14 mL). The reaction mixture was stirred for 1 h at 40 °C, and the solvent was removed in vacuo. A short plug of silica gel (CH_2Cl_2 followed by 2% MeOH in CH_2Cl_2) and SEC (toluene) gave **H_2P−3B−ethynyl−TIPS** as a red solid (47 mg, 0.042 mmol, 92%): ^{1}H NMR ($CDCl_3$) δ −2.40 (br s, 2H), 1.15 (m, 21H), 1.51 (s,18H), 1.78 (m, 12H), 2.47 (s, 6H), 2.55 (s, 6H), 4.03 (m, 8H), 7.50 (m, 4H), 7.60 (d, ^3J = 8 Hz, 2H), 7.68 (d, ^3J = 8 Hz, 2H), 7.81 (t, ^4J = 2 Hz, 1H), 7.92 (d, ^4J = 2 Hz, 2H), 7.94 (d, ^3J = 8 Hz, 2H), 8.11 (d, ^3J = 8 Hz, 2H), 10.24 (s, 2H); HRMS (FAB) calcd for $[C_{79}H_{90}N_4Si]^+$ 1122.6935, found 1122.6937.

H_2P−3B−Ethynyl. A sample of **H_2P−3B−ethynyl−TIPS** (23 mg, 0.020 mmol) was dissolved in THF (3 mL). Bu_4NF (25 μmol, 25 μL of a 1.0 M solution in THF) was added, and the mixture was stirred at room temperature for 30 min, during which time the color turned darker red. Methanol was added to precipitate the porphyrin, and subsequent centrifugation gave **H_2P−3B−ethynyl** as a red solid (17 mg, 0.018 mmol): ^{1}H NMR ($CDCl_3$) δ −2.44 (br s, 1H), −2.42 (br s, 1H), 1.51 (s, 18H), 1.78 (m, 12H), 2.46 (s, 6H), 2.56 (s, 6H), 3.20 (s, 1H), 4.03 (m, 8H), 7.52 (m, 4H), 7.61 (d, ^3J = 8 Hz, 2H), 7.70 (d, ^3J = 8 Hz, 2H), 7.81 (t, ^4J = 2 Hz, 1H), 7.92 (d, ^3J = 2 Hz, 2H), 7.94 (d, ^3J = 8 Hz, 2H), 8.11 (d, ^3J = 8 Hz, 2H), 10.24 (s, 2H); HRMS (FAB) calcd for $[C_{70}H_{70}N_4]^+$ 966.5600, found: 966.5618.

$[H_2P−4B−AuP]^+BF_4^-$ was prepared from **$[AuP−1B−I]^+BF_4^-$** (15 mg, 0.013 mmol) and **H_2P−3B−ethynyl** (15 mg, 0.016 mmol), as described for **$[H_2P−2B−AuP]^+BF_4^-$**, and gave **$[H_2P−4B−AuP]^+BF_4^-$** as a red solid (22 mg, 0.011 mmol, 85%): ^{1}H NMR ($CDCl_3$) δ −2.38 (br s, 2H), 1.52 (s, 18H), 1.53 (s, 18H), 1.79 (m, 12H), 1.84 (m, 12H), 2.47 (s, 6H), 2.55 (s, 6H), 2.58 (s, 6H), 2.67 (s, 6H), 4.02 (m, 8H), 4.13 (m, 8H), 7.65 (m, 4H), 7.73 (m, 4H), 7.82 (t, ^4J = 2 Hz, 1H), 7.87 (d, ^4J = 2 Hz, 2H), 7.92 (d, ^4J = 2 Hz, 2H), 7.96 (m, 3H), 8.08 (m, 6H), 10.23 (s, 2H), 10.63 (s, 2H); HRMS (FAB) calcd for $[C_{122}H_{128}AuN_8]^+$ 1901.9927, found 1901.9935.

$[H_2P−5B−AuP]^+BF_4^-$ was prepared from **$[AuP−1B−I]^+BF_4^-$** (18 mg, 0.016 mmol) and **H_2P−4B−ethynyl** (20 mg, 0.019 mmol), as described for **$[H_2P−2B−AuP]^+BF_4^-$**, and gave **$[H_2P−5B−AuP]^+BF_4^-$** as a red solid (27 mg, 0.013 mmol, 82%): ^{1}H NMR ($CDCl_3$) δ −2.45 (br s, 2H), 1.51 (s, 18H), 1.53 (s, 18H), 1.78 (m, 12H), 1.84 (m, 12H), 2.47 (s, 6H), 2.55 (s, 6H), 2.58 (s, 6H), 2.67 (s, 6H), 4.02 (m, 8H), 4.13 (m, 8H), 7.58 (s, 4H), 7.63 (m, 4H), 7.71 (m, 4H), 7.82 (t, ^4J = 2 Hz, 1H), 7.87 (d, ^4J = 2 Hz, 2H), 7.92 (d, ^4J = 2 Hz, 2H), 7.95 (m, 3H), 8.07 (m, 6H), 10.22 (s, 2H), 10.63 (s, 2H); HRMS (FAB) calcd for $[C_{130}H_{132}AuN_8]^+$ 2002.0240, found 2002.0251.

$[ZnP−2B−AuP]^+BF_4^-$. **$[H_2P−2B−AuP]^+BF_4^-$** (21.5 mg, 0.012 mmol) was dissolved in 10 mL of $CHCl_3$, and $Zn(OAc)_2$·$2H_2O$ (26 mg, 0.120 mmol) dissolved in MeOH (1 mL) was added. The reaction was stirred at room temperature for 3 h. The reaction mixture was washed twice with 10% $NaHCO_3$, twice with dilute aqueous KBF_4, and twice with water. Evaporation of the solvent gave **$[ZnP−2B−AuP]^+BF_4^-$** as a red solid (22.3 mg, 0.012 mmol, 100%): ^{1}H NMR ($CDCl_3$) δ 1.54 (s, 18H), 1.55 (s, 18H), 1.79 (m, 12H), 1.86 (m, 12H), 2.48 (s, 6H), 2.55 (s, 6H), 2.60 (s, 6H), 2.71 (s, 6H), 4.01 (m, 8H), 4.12 (m, 8H), 7.85 (t, ^4J = 2 Hz, 1H), 7.89 (d, ^4J = 2 Hz, 2H), 7.97 (m, 3H), 8.12 (m, 6H), 8.22 (d, ^3J = 8 Hz, 2H), 10.16 (s, 2H), 10.60 (s, 2H); HRMS (FAB) calcd for $[C_{106}H_{118}AuN_8Zn]^+$ 1763.8436, found 1763.8435.

$[ZnP−4B−AuP]^+BF_4^-$ was prepared from **$[H_2P−4B−AuP]^+BF_4^-$** (16 mg, 0.008 mmol), as described for **$[ZnP−2B−AuP]^+BF_4^-$**, and gave **$[ZnP−4B−AuP]^+BF_4^-$** as a red solid (13 mg, 0.0063 mmol, 79%): ^{1}H NMR ($CDCl_3$): δ 1.53 (s, 18H), 1.54 (s, 18H), 1.79 (m, 24H), 2.46 (s, 6H), 2.47 (s, 6H), 2.59 (s, 6H), 2.61 (s, 6H), 4.03 (m, 16H), 7.64 (m, 4H), 7.72 (m, 4H), 7.84 (t, ^4J = 2 Hz, 1H), 7.88 (d, ^4J = 2 Hz, 2H), 7.94−8.07 (m, 11H), 10.11 (s, 2H), 10.55 (s, 2H); HRMS (FAB) calcd for $[C_{122}H_{126}AuN_8Zn]^+$ 1963.9062, found 1963.9072.

$[ZnP−5B−AuP]^+BF_4^-$ was prepared from **$[H_2P−5B−AuP]^+BF_4^-$** (16 mg, 0.0077 mmol), as described for **$[ZnP−2B−AuP]^+BF_4^-$**, and gave **$[ZnP−5B−AuP]^+BF_4^-$** as a red solid (15 mg, 0.0067 mmol, 90%): ^{1}H NMR ($CDCl_3$) δ 1.53 (s, 18H), 1.54 (s, 18H), 1.78 (m, 24H), 2.45 (s, 6H), 2.46 (s, 6H), 2.59 (s, 6H), 2.60 (s, 6H), 4.02 (m, 16H), 7.56 (s, 4H), 7.61 (d, ^3J = 8 Hz, 4H), 7.71 (d, ^3J = 8 Hz, 4H), 7.84 (t, ^4J = 2 Hz, 1H), 7.88 (d, ^4J = 2 Hz, 2H), 7.92−8.06 (m, 11H), 10.09 (s, 2H), 10.54 (s, 2H); HRMS (FAB) calcd for $[C_{130}H_{130}AuN_8Zn]^+$ 2063.9375, found 2063.9361.

H_2P−nB from ZnP−nB: General Procedure. The corresponding zinc porphyrin, **ZnP−nB** (~10 μmol), was dissolved in dichloromethane and washed twice with 1 M aqueous HCl, twice with aqueous $NaHCO_3$ (10% w/w), and twice with water. The solvent was evaporated to give near quantitative yields of **H_2P−nB**. The highly insoluble products were transferred as a suspension to the reaction vessel for gold insertion without further characterization.

$[AuP−2B]^+BF_4^-$. A solution of **H_2P−2B** (10 mg, 0.012 mmol), $[Au(tht)_2]^+BF_4^-$ (0.054 mmol, 5.4 mL from a 10 mM stock solution in chlorobenzene), and 2,6-lutidine (0.036 mmol, 720 μL from a 50 mM stock solution in chlorobenzene) in chlorobenzene and chloroform (1:1, 5 mL) was stirred under argon at 40 °C overnight. After the solvent was evaporated, the residue was dissolved in CH_2Cl_2 and added to a chromatographic column (Al_2O_3, neutral, grade III). Residues of the free-base porphyrin were removed by elution with pure CH_2Cl_2. The gold porphyrin was collected by elution with 3% MeOH in CH_2Cl_2. The resulting CH_2Cl_2 solution was washed twice with dilute aqueous KBF_4 and twice with H_2O to ensure the integrity of the anion. Precipitation of the gold porphyrin from CH_2Cl_2 by addition of pentane gave **$[AuP−2B]^+BF_4^-$** as a red solid (13 mg, 0.0115 mmol, 96%): ^{1}H NMR ($CDCl_3$) δ 1.52 (s, 18H), 1.84 (m, 12H), 2.57 (s, 6H), 2.68 (s, 6H), 4.13 (m, 8H), 7.46 (m, 3H), 7.72 (m, 2H), 7.85 (d, ^4J = 2 Hz), 7.94 (t, ^4J = 2 Hz, 1H), 8.06 (m, 4H), 10.65 (s, 2H); HRMS (FAB) calcd for $[C_{60}H_{64}AuN_4]^+$ 1037.4796, found 1037.4791.

$[AuP−4B]^+BF_4^-$ was prepared from **H_2P−4B** (16 mg, 0.014 mmol), as described for **$[AuP−2B]^+BF_4^-$**, and gave **$[AuP−4B]^+BF_4^-$** as a red solid (12 mg, 0.009 mmol, 64%): ^{1}H NMR ($CDCl_3$) δ 1.53 (s, 18H), 1.84 (m, 12H), 2.57 (s, 6H), 2.68 (s, 6H), 4.13 (m, 8H), 7.36 (m, 3H), 7.53 (m, 6H), 7.59 (d, ^3J = 8 Hz), 7.69 (d, ^3J = 8 Hz, 2H), 7.85 (d, ^4J = 2 Hz, 2H), 7.95 (t, ^4J = 2 Hz, 1H), 8.07 (m, 4H), 10.65 (s, 2H); HRMS (FAB) calcd for $[C_{76}H_{72}AuN_4]^+$ 1237.5422, found 1237.5419.

$[AuP−5B]^+BF_4^-$ was prepared from **H_2P−5B** (6 mg, 0.0053 mmol), as described for **$[AuP−2B]^+BF_4^-$**, and gave **$[AuP−5B]^+BF_4^-$** as a red solid (6.8 mg, 0.0048 mmol, 91%); ^{1}H NMR ($CDCl_3$) δ 1.53 (s, 18H), 1.84 (m, 12H), 2.58 (s, 6H), 2.68 (s, 6H), 4.13 (m, 8H), 7.37 (m, 3H), 7.54 (m, 12H), 7.62 (d, ^3J = 8 Hz, 2H), 7.70 (d, ^3J = 8 Hz, 2H), 7.86 (d, ^4J = 2 Hz, 2H), 7.95 (t, ^4J = 2 Hz, 1H), 8.07 (m, 4H), 10.65 (s, 2H); HRMS (FAB) calcd for $[C_{84}H_{76}AuN_4]^+$ 1337.5735, found 1337.5747.

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Supporting Information Available: General experimental methods. General procedure and product yield determination for the reaction carousel experiments. General procedure and product yield determination for the coupling study of different arylic iodides. Proton decoupled ^{13}C NMR spectra and positive FAB HRMS spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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