ORGANOMETALLICS

Article

pubs.acs.org/Organometallics

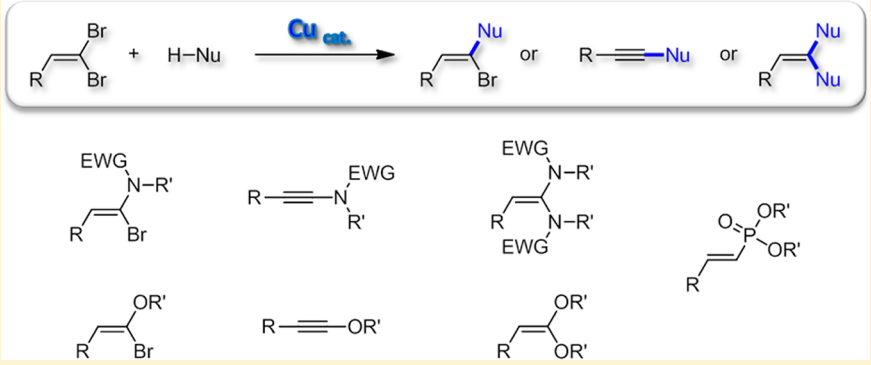
Copper-Mediated Selective Cross-Coupling of 1,1-Dibromo-1-alkenes and Heteronucleophiles: Development of General Routes to Heterosubstituted Alkynes and Alkenes

Kévin Jouvin,[†] Alexis Coste,[†] Alexandre Bayle,[†] Frédéric Legrand,[†] Ganesan Karthikeyan,[†] Krishnaji Tadiparthi,[†] and Gwilherm Evano*[,‡]

[†]Institut Lavoisier de Versailles, UMR CNRS 8180, Université de Versailles Saint-Quentin en Yvelines, 45 Avenue des Etats-Unis, 78035 Versailles Cedex, France

[‡]Laboratoire de Chimie Organique, Service de Chimie et PhysicoChimie Organiques, Université Libre de Bruxelles, Avenue F. D. Roosevelt 50, CP160/06, 1050 Brussels, Belgium

Supporting Information



ABSTRACT: Efficient and general procedures for the cross-coupling of 1,1-dibromoalkenes and N-, O-, and P-nucleophiles are reported. Fine-tuning of the reaction conditions allows for either site-selective, double, or alkynylative cross-coupling, therefore providing divergent and straightforward entries to numerous building blocks such as bromoenamides, ynamides, ketene *N*,*N*-acetals, bromoenol ethers, ynol ethers, ketene *O*,*O*-acetals, or vinylphosphonates and further expanding the copper catalysis toolbox with useful and versatile processes.

INTRODUCTION

Over the last 10 years or so, the use of copper-based catalytic systems has enabled the design of efficient and general reactions, especially for the formation of carbon−heteroatom bonds.[1] The introduction of simple, readily available, and inexpensive chelating ligands, the most common ones being diamines[2] or amino acids,[3] has allowed the dramatic softening of the reaction conditions compared to the classical Ullmann[4] and Goldberg[5] ones and the broadening of the scope of these cross-coupling reactions as well. Indeed, most heteronucleophiles can now participate in these reactions, provided that the right combination of ligand, base, and solvent is used, and the nature of the halide coupling partner has also been extensively studied. While the first developments mostly focused on the use of aryl halides, the catalytic systems designed for these coupling partners were then quickly adapted for vinyl and alkynyl halides, therefore greatly expanding the scope of copper-mediated cross-coupling reactions and solving some long-standing problems at the same time. They also provided the chemical community with highly efficient tools that have found numerous academic and industrial applications for the preparation of an impressive array of compounds, ranging from the simplest building blocks to complex natural and/or biologically relevant compounds.[1] An overview of most representative Ullmann/Goldberg-like copper-mediated cross-coupling available to date is shown in Figure 1. A simple glance at this gross picture and extreme simplification reveals that there is one key partner missing in this scheme: *gem*-dibromoalkenes.

Those reagents are easily and conveniently prepared from the corresponding aldehydes using the Ramirez dibromoolefination[6] or the more practical Lautens modification.[7] They serve as important starting materials or intermediates in an impressive number of chemical transformations, the most famous one probably being the Corey−Fuchs alkyne synthesis, where an aldehyde is converted to the dibromide, which, upon treatment with a strong base and reaction with an electrophile, gives the corresponding substituted alkyne.[8] More recently, they have been shown to be especially useful and versatile building blocks

Special Issue: Copper Organometallic Chemistry

Received: June 20, 2012

   dx.doi.org/10.1021/om3005614 | *Organometallics* XXXX, XXX, XXX−XXX

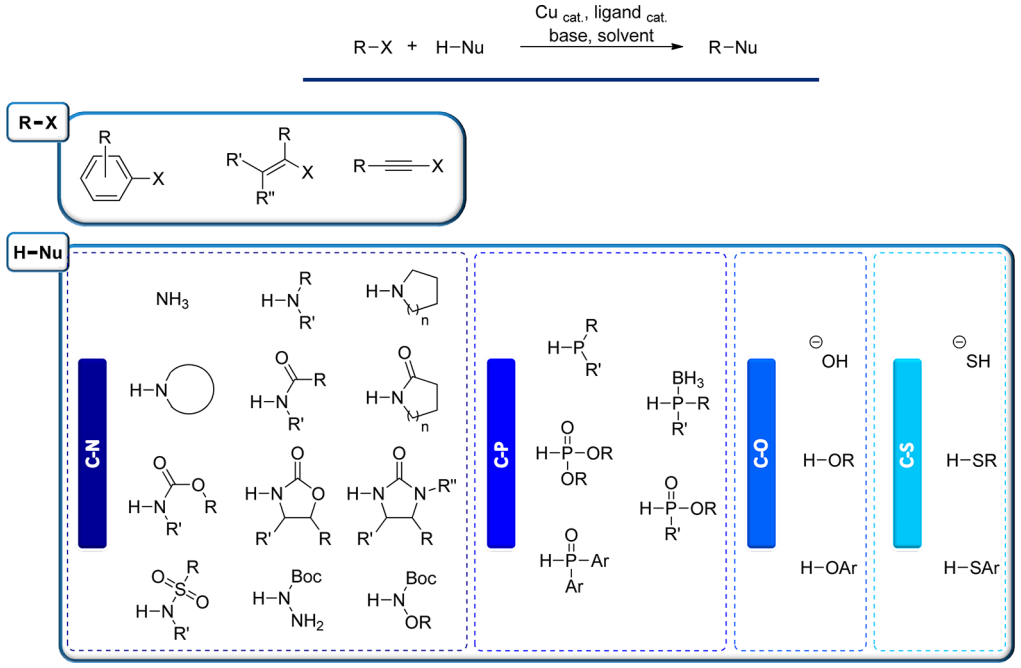
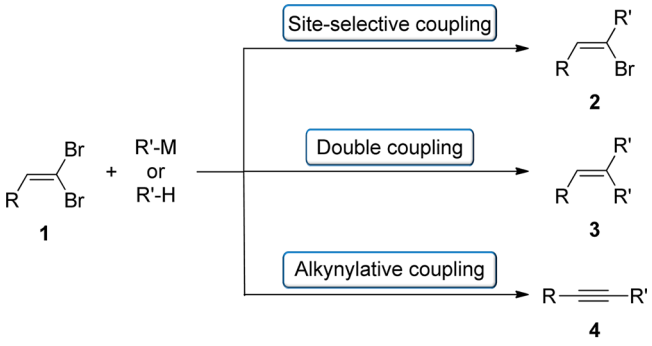


Figure 1. Overview of copper-catalyzed reactions for the formation of carbon−heteroatom bonds.

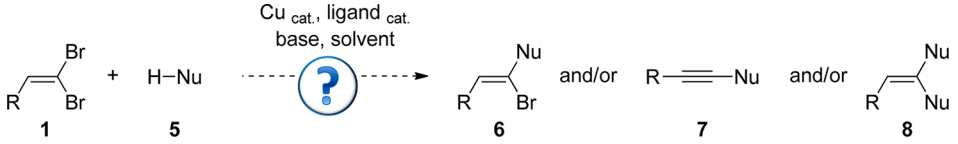
in transition-metal-mediated reactions, mostly with palladium-based catalytic systems.[9] The great advantage inherent to the nature of these reagents **1** is that they are typically more reactive than the corresponding monobromides, therefore rendering the cross-coupling quite facile, and their reactivity can be finely tuned depending on the reaction partner and conditions. Indeed, they can participate in site-selective cross-coupling reactions,[10] where only the sterically less hindered *trans* C−Br bond is involved in the transformation (Scheme 1),[11] yielding with excellent stereoselectivity vinyl bromides **2**, in which the remaining bromine atom can be involved in a second cross-coupling, a strategy that has been especially successful and reliable for the preparation of stereodefined olefins, even on complex substrates. Slight modifications of the reaction conditions and/or the stoichiometry of the reactions usually allow driving the reaction to the formation of products **3**, resulting from a double cross-coupling, where the two halogen atoms are formally substituted. In addition, *gem*-dibromoalkenes have also proven to be especially suitable precursors of alkynyl−transition metal complexes or synthetic equivalents of electrophilic alkynyl residues, yielding substituted alkynes **4** after cross-coupling. In all of these transformations, all reaction partners typically involved in palladium-catalyzed cross-coupling reactions have been used with vinyl dibromides for the formation of carbon−carbon bonds (Grignard or organozinc reagents, stannanes, boronic acids, terminal alkynes, etc.), which clearly demonstrated the versatility of these reagents in palladium-catalyzed processes.

Scheme 1. 1,1-Dibromo-1-alkenes in Metal-Catalyzed Cross-Coupling Reactions



In sharp contrast, and apart from Hayes'[12] and Bisseret's[13] reports on the palladium-catalyzed intermolecular cross-coupling with dialkylphosphites yielding alkynylphosphonates and intramolecular cross-coupling from the Lautens group[14] and others,[13,15] the use of *gem*-dibromoalkenes in carbon−heteroatom bond-forming reactions has been less studied, despite the enormous potential of these reactions. They would indeed potentially provide efficient entries to a wide range of heteroatom-substituted alkenes and alkynes, highly valuable building blocks in organic synthesis, depending on the coupling mode and the nature of the heteronucleophile used in the process. On the basis of our experience in copper-catalyzed reactions,[16] we felt that the use of copper catalysis might provide

Scheme 2. Envisioned Copper-Mediated Cross-Coupling between 1,1-Dibromo-1-alkenes and Heteronucleophiles



dx.doi.org/10.1021/om3005614 | *Organometallics* XXXX, XXX, XXX−XXX

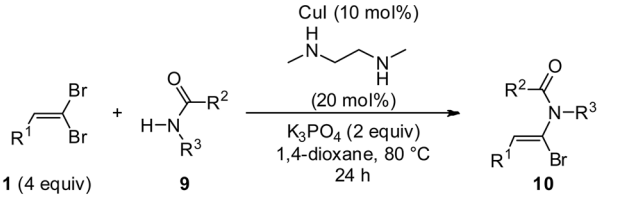
efficient systems to perform either site-selective, double, or alkynylative cross-coupling with various heteronucleophiles (Scheme 2). They indeed provided efficient routes to nitrogen-,[17] oxygen-,[18] and phosphorus[19]-substituted alkenes and alkynes of general structures **6**, **7**, and **8**. We report here a full account of the development of these reactions as well as extensions of our studies that broaden the scope of these procedures as well as insights into the mechanism of these reactions.

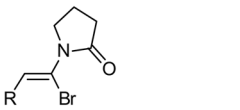
RESULTS AND DISCUSSION

Selective Cross-Coupling with Nitrogen Nucleophiles: Divergent Synthesis of 1-Bromoenamides, Ketene *N,N*-Acetals, and Ynamides. We initiated our studies with the cross-coupling between 1,1-dibromo-1-alkenes and nitrogen nucleophiles, a reaction that could provide straightforward entries to 1-bromoenamides, ketene *N,N*-acetals, or ynamides depending on the coupling mode and provided that high levels of selectivity between all reaction pathways could be achieved.

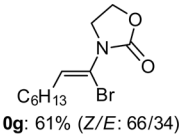
The selective monocoupling was actually one of the most difficult one to optimize, mostly because of the fast elimination of hydrobromic acid from *Z*-1-bromoenamides **10** in the presence of a base and the ease of the second cross-coupling yielding competitive formation of ketene *N,N*-acetals. However, using an excess of vinyl dibromides **1** in the presence of catalytic amounts of copper(I) iodide and *N,N′*-dimethylethylenediamine and 2 equivalents of potassium phosphate in 1,4-dioxane at 80 °C cleanly promoted the formation of **10**, which could be obtained in reasonable yields as 2:1 mixtures of stereoisomers (Chart 1),

Chart 1. Site-Selective Cross-Coupling with N-Nucleophiles to 1-Bromoenamides

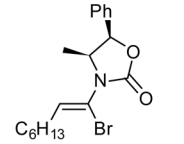




10a: R = C_6H_{13} 61% (*Z*/*E*: 64/36)
10d: R = CH_2CH_2Ph 19% (*Z*/*E*: 62/38)
10e: R = *p*-Cl-C_6H_4 30% (*Z*/*E*: 75/25)
10f: R = *p*-MeO-C_6H_4 56% (*Z*/*E*: 75/25)



10g: 61% (*Z*/*E*: 66/34)



10h: 70% (*Z*/*E*: 81/19)

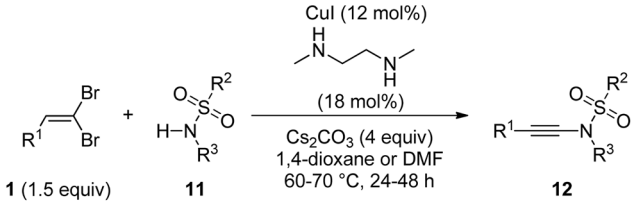
the *Z*-olefin being the major one in all cases, as demonstrated by NOE experiments. Besides the need for an excess of **1** to ensure the selective formation of 1-bromoenamides **10**, the number of equivalents of potassium phosphate was found to be the key parameter in this selective mono-cross-coupling: while the use of a single equivalent of the base resulted in low conversion, increasing this number to three dramatically favored the elimination since only traces of **10** could be detected in crude reaction mixtures. A major practical advantage of this procedure is that no workup is required since a simple filtration allows for the removal of both the heterogeneous base and the catalyst. A brief survey of the scope of this transformation showed that it can successfully be applied to aryl- and alkyl-substituted dibromides **1**, with more or less efficiency however, and that lactams and oxazolidinones perform equally well, yielding the corresponding 1-bromoenamides with similar efficiency. It does therefore provide a straightforward and practical entry to these useful building blocks, in which the remaining bromide atom could serve as an anchor for further functionalization, and nicely complements the most efficient synthesis of these compounds reported to date relying on the hydrobromination of the corresponding ynamides using magnesium dibromide in wet dichloromethane, a process in which the *E*-bromoenamides are predominantly formed.[20]

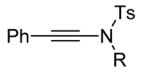
After demonstrating that *gem*-dibromides can participate in selective mono-cross-coupling with N-nucleophiles, we next moved to their use in alkynylative cross-coupling, which might provide an original and efficient entry to ynamides, building blocks whose chemistry has considerably expanded over the past five years[21] due to the development of new and efficient copper-mediated methods for their synthesis. Among all methods available for their preparation, the most efficient ones rely on the use of bromoalkynes,[22] terminal alkynes,[23] potassium alkynyl trifluoroborates,[16g] propiolic acids,[24] and copper acetylides[25] as alkynylating agents, and the use of 1,1-dibromo-1-alkenes would therefore provide an interesting and practical alternative to these procedures. Due to the easy elimination from 1-bromoenamides **10**, the optimization of this alkynylative cross-coupling with sulfonamides as test substrates was relatively simple, and changing the base to cesium carbonate together with increasing the number of equivalents of this base from two to four smoothly allowed for the production of the desired ynamides **12**, which were virtually formed as the sole products of the reactions (Chart 2).[17] The choice of the base/solvent couple turned out to be a critical parameter for this cross-coupling since the use of potassium phosphate in toluene in place of cesium carbonate in 1,4-dioxane completely modified the outcome of the reaction, ketene *N,N*-acetals resulting from a second cross-coupling being isolated as the major products in this case (see below). Due to the growing potential of ynamides in organic synthesis, the scope of this cross-coupling was extensively studied with a wide range of dibromides **1** and sulfonamides **11** possessing representative substitution patterns. While the nature of the substituents on the starting sulfonamide **11** had virtually no effect on the outcome of the reaction, the substitution patterns of the dibromides had a marked influence on the yields due to a slower elimination step with *gem*-dibromoolefins substituted with an alkyl group, a shortcoming that could be easily overcome by running the reaction in DMF at 70 °C instead of in 1,4-dioxane at 60 °C with these substrates. Using these optimized conditions, all *N*-sulfonyl-ynamines **12** could be obtained in yields ranging from 64% to 97%, except in the case of methyl-substituted ynamide **12j**, the low yield (25%) obtained with this substrate being certainly due to its high sensitivity to basic conditions and its extremely fast rate of hydrolysis. A wide range of substituents are tolerated on both reaction partners since the reaction conditions were shown to be compatible with bulky alkyl groups, electron-donating as well as -withdrawing substituents, or heteroaromatics. Notably, the presence of an aromatic chloride was also shown to be compatible since no competitive amination or reduction was observed.

To further test the efficiency of this alkynylation of sulfonamides, the synthesis of a bis-ynamide from bis-

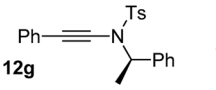
dx.doi.org/10.1021/om3005614 | *Organometallics* XXXX, XXX, XXX−XXX

Chart 2. Alkynylative Cross-Coupling with Sulfonamides to *N*-Sulfonyl-ynamines

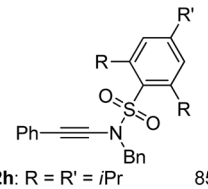




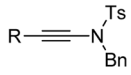
12a: R = Pr 94%
12b: R = Bn 83%
12c: R = allyl 81%
12d: R = CH_2CH_2Ph 93%
12e: R = cyclopropyl 79%
12f: R = adamantyl 77%



12g 83%

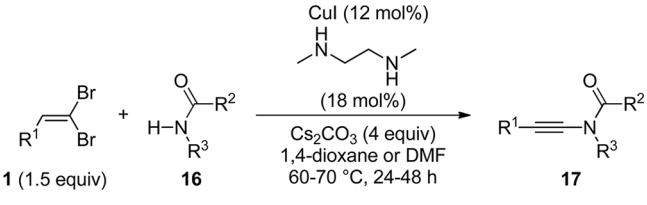


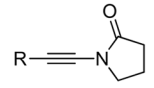
12h: R = R' = *i*Pr 85%
12i: R = H, R' = NO_2 82%



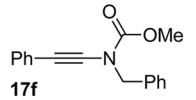
12j: R = Me 25%
12k: R = Et 67%
12l: R = C_5H_{11} 70%
12m: R = C_8H_{17} 86%
12n: R = $CH_2OTBDPS$ 64%
12o: R = (*E*)-CH=CHPh 84%
12p: R = *p*-F-C_6H_4 94%
12q: R = *p*-Cl-C_6H_4 77%
12r: R = *p*-MeO-C_6H_4 86%
12s: R = *o*-MeO-C_6H_4 93%
12t: R = *p*-NC-C_6H_4 75%
12u: R = *o*-NC-C_6H_4 82%
12v: R = *m*-NO_2-C_6H_4 94%
12w: R = *p*-*i*Pr-C_6H_4 93%
12x: R = *o*,*o*'-Me_2-C_6H_3 87%
12y: R = naphthalen-2-yl 97%
12z: R = anthracen-9-yl 86%
12aa: R = furan-2-yl 88%
12ab: R = thiofuran-2-yl 66%
12ac: R = pyridin-2-yl 92%
12ad: R = pyridin-3-yl 96%

Chart 3. Alkynylative Cross-Coupling with Pyrrolidinone, Carbamates, and Oxazolidinones

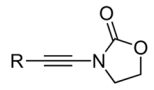




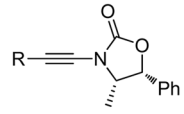
17a: R = C_8H_{17} 43%
17b: R = *t*Bu 34%
17c: R = Cy 43%
17d: R = Ph 80%
17e: R = *p*-MeO-C_6H_4 66%



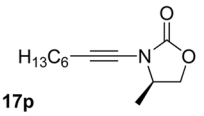
17f 67%



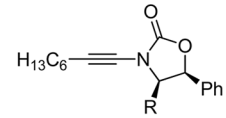
17g: R = Et 68%
17h: R = Ph 84%



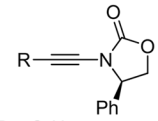
17i: R = Et 65%
17j: R = C_8H_{17} 69%
17k: R = *t*Bu 80%
17l: R = Cy 70%
17m: R = (*E*)-CH=CHPh 77%
17n: R = Ph 35%
17o: R = *p*-F-C_6H_4 80%



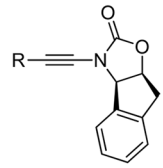
17p 71%



17q: R = Me 72%
17r: R = Ph 87%



17s: R = C_6H_{13} 77%
17t: R = Ph 82%
17u: R = *p*-MeO-C_6H_4 55%
17v: R = *m*-NO_2-C_6H_4 58%



17w: R = C_6H_{13} 72%
17x: R = Ph 85%

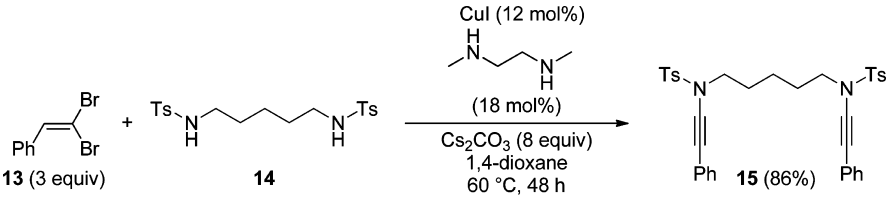
sulfonamide **14** was evaluated. Under our standard conditions and using 3 equivalents of (2,2-dibromovinyl)benzene **13**, the desired product **15** resulting from a double alkynylation could be isolated in 86% yield after 48 h at 60 °C in 1,4-dioxane (Scheme 3).

The synthesis of ynamides from other representative N-nucleophiles commonly used in the chemistry of ynamides was next envisioned. The reactivity of pyrrolidinone, carbamates, and oxazolidinones **16** was therefore assayed with various dibromides **1** possessing representative substituents: the alkynylation was found to be a little less efficient with these N-nucleophiles compared to the one involving sulfonamides, which is mostly due to the lower acidity of these substrates (pK_a values in DMSO of 24 and 20−21 for pyrrolidinone and oxazolidinones, respectively, vs 16−18 for sulfonamides), but still gave the corresponding ynamides **17** in good to excellent yields (Chart 3). Importantly, the presence of bulky substituents around the nitrogen, which can dramatically lower the yields with other procedures, had no detrimental effect on the cross-coupling, therefore enabling the alkynylation of a wide range of chiral ynamides. Here again, the reaction from alkyl-substituted 1,1-dibromo-1-alkenes was best performed in DMF at 70 °C rather than in 1,4-dioxane at 60 °C to avoid the formation of 1-bromoenamides, which are extremely difficult to separate from the corresponding ynamides, and facilitate the elimination step.

Finally, the alkynylation of π-excessive nitrogen nucleophiles **18** with vinyl dibromides **1** was examined. Compared to the synthesis of other classes of ynamides, their preparation, mostly relying on the copper-catalyzed cross-coupling with bromoalkynes, is typically more difficult due to competing direct nucleophilic addition of the nitrogen nucleophile to the alkynyl bromide, yielding heterocyclic 2-bromoenamines.[22c,26] The use of 1,1-dibromo-1-alkenes **1** might therefore be a good alternative since the formation of these byproducts is not possible with these reagents.

Benzimidazole was first chosen as a model substrate to initiate those studies: if the reaction turned out to be a bit more sluggish

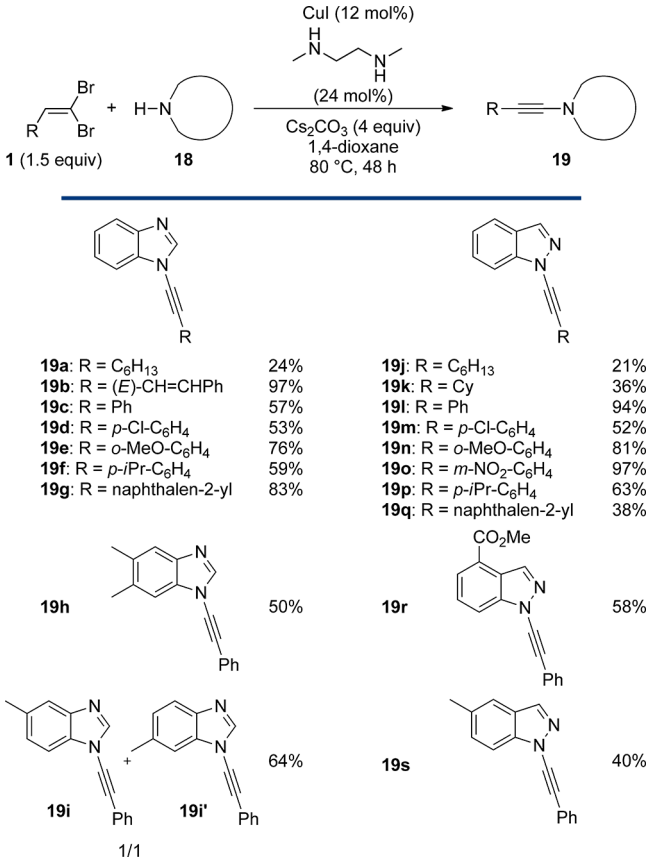
Scheme 3. Double Alkynylation of a Bis-sulfonamide Using a Vinyl Dibromide



dx.doi.org/10.1021/om3005614 | *Organometallics* XXXX, XXX, XXX−XXX

compared to the one involving standard N-nucleophiles such as sulfonamides, oxazolidinones, or secondary amides, a simple increase of the reaction temperature to 80 °C allowed for a smooth alkynylation. The reaction was found to be compatible with a variety of aromatic groups, and the presence of electron-withdrawing or -donating substituents had virtually no effect on the reaction (Chart 4). Cinnamaldehyde-derived dibromide was

Chart 4. Alkynylative Cross-Coupling with Conjugated N-Heterocycles

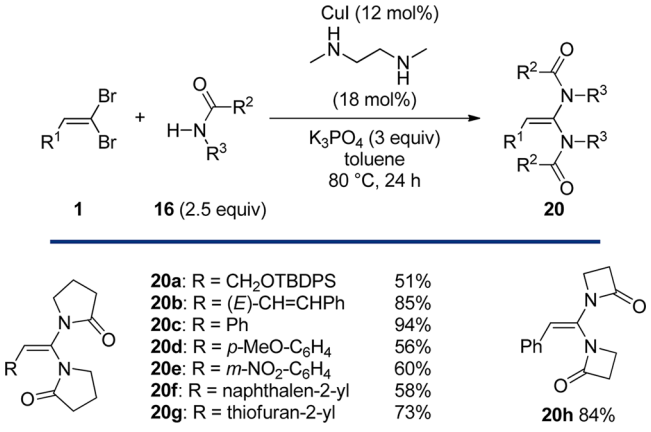


also found to be an excellent reaction partner, providing the corresponding styryl-substituted alkynylbenzimidazole **19b** in excellent yield. The slower alkynylation with alkyl-substituted dibromoalkenes turned out to be more pronounced with benzimidadoles, and the corresponding products, such as **19a**, could be isolated only in low yields, while the cross-coupling involving substituted benzimidazoles was found to be equally efficient. Extending this chemistry to include indazoles as substrates proved to be quite successful, which is particularly noteworthy since the corresponding stable alkynylated products might provide excellent platforms for molecular diversity and drug discovery. A number of *N*-alkynylindazoles can be readily prepared using our reaction conditions with excellent regioselectivity for the N1 alkynylation product, and, as with benzimidazoles, a variety of functional groups are tolerated.[17d] This procedure was later extended by other groups to the use of indazoles using TMEDA as the ligand,[27] which seems to be superior to DMEDA in some cases, and to the alkynylation of imidazoles and pyrazoles using a preformed soluble copper catalyst, [Cu(Phen)(PPh_3)Br].[28]

After demonstrating that 1,1-dibromo-1-alkenes can participate in site-selective and alkynylative cross-coupling with N-nucleophiles and extensively studying the scope and potential of these transformations, we focused our attention on the optimization of the third and last possible coupling mode with these reagents: the double cross-coupling. Provided that a combination of the proper catalytic system, base, solvent, and temperature could allow for a selective double cross-coupling and suppress the competitive mono-cross-coupling and elimination pathways, this could provide an interesting entry to stabilized ketene *N,N*-acetals **20**, useful intermediates in organic synthesis that combine two enamines in one functional group and exhibit significant nucleophilicity at C-2 due to the delocalization of the lone pairs of both nitrogen atoms into the double bond. Due to the lack of general methods for their preparation,[29] this might bring a practical procedure for their synthesis as well as provide additional insights into the reactivity of vinyl dibromides in copper catalysis.

On the basis of results obtained during the optimization of the alkynylative cross-coupling, where we had noticed that considerable amounts of products resulting from a double cross-coupling **20** were formed when potassium phosphate was used instead of cesium carbonate, regardless of the reaction stoichiometry used (1.5 equivalents of the dibromide **1** compared to the nitrogen nucleophile **16** in order to try to avoid the second cross-coupling), the optimized conditions were relatively easy to obtain, and we found that toluene was slightly more efficient than 1,4-dioxane for this transformation, which was best performed using 2.5 equivalents of the nitrogen nucleophile with respect to the *gem*-dibromoolefin **1**. The scope and limitations of the ketene aminal synthesis was briefly evaluated using our optimized conditions, and the reaction was found to be best performed with lactams, which gave the corresponding products in reasonable to good yields, the reaction being again more efficient with aryl- or alkenyl-substituted dibromoalkenes **1** (Chart 5).[17b] In this case, the

Chart 5. Double Cross-Coupling with Lactams to Ketene *N,N*-Acetals



use of other N-nucleophiles such as sulfonamides or conjugated N-heterocycles did not give the corresponding ketene acetals, and the alkynylative cross-coupling was preferred with these reagents, which might be due to a faster elimination from these substrates and to an unfavorable second cross-coupling due to the steric bulk associated with these nucleophiles. As a note, the use of carbamate-protected 1,2-diamines did not yield the formation of the expected cyclic ketene *N,N*-acetals but tetrahydropyrazine derivatives resulting from an alkynylative

dx.doi.org/10.1021/om3005614 | *Organometallics* XXXX, XXX, XXX−XXX

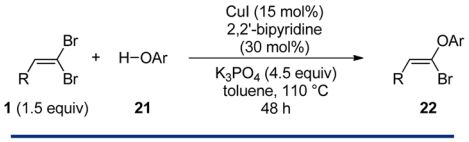
cross-coupling followed by a 6-*endo*-*dig* cyclization, which is in accordance with similar results from the Urabe group.[30]

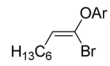
We have therefore been able to demonstrate that 1,1-dibromo-1-alkenes can participate in copper-catalyzed cross-coupling reactions with a variety of nitrogen nucleophiles and that all possible coupling mode are possible with these reagents, provided that the right stoichiometry is used. A fine-tuning of the reaction conditions and the nature of the base and the solvent, which are key parameters in these coupling reactions, as well as the nature of the nitrogen-nucleophile, therefore allows for divergent preparations of 1-bromoenamides, ynamides, or ketene *N*,*N*-acetals, useful reagents in organic synthesis that are now readily available from simple starting materials and inexpensive copper-based catalytic systems. A logical extension of this work was the application of these procedures to other nucleophiles commonly used in copper catalysis, alcohols being especially attractive coupling partners due to the high potential of the products that might arise from their selective cross-coupling with vinyl dibromides. The development of the corresponding procedures is described in the following section.

Selective Cross-Coupling with Oxygen Nucleophiles: Straightforward Synthesis of 1-Bromoenol Ethers, Ketene Acetals, and Ynol Ethers. Phenols were chosen as substrates for these studies since they would provide products resulting either from a site-selective, alkynylative, or double cross-coupling that would be much more stable than the one obtained with aliphatic alcohols, the corresponding ynol ethers and ketene acetals being well known for their instability. As with N-nucleophiles, we initiated our studies with the site-selective cross-coupling using a slight excess of **1**. While the nature of the base was found to be the key parameter with N-nucleophiles, the ligand appeared to be of crucial importance in this case. As expected, the cross-coupling was much more sluggish and the suppression of the competing dimerization of the starting dibromides to the corresponding diynes[31] turned out to be quite challenging. The use of aromatic N,N-bidentate ligands such as 1,10-phenanthroline, 3,4,7,8-tetramethyl-1,10-phenanthroline, or 2,2′-bipyridine however allowed for a clean site-selective cross-coupling, and the optimized conditions relied on the use of 15 mol % copper(I) iodide, 30 mol % 2,2′-bipyridine, and 4.5 equivalents of potassium phosphate in toluene at 110 °C.

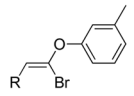
With the optimized conditions in hand, we examined the reactivity of various 1,1-dibromo-1-alkenes **1** and phenols **21** possessing representative substituents and substitution patterns (Chart 6).[18] *Para*-, *meta*-, and *ortho*-substituted phenols were all readily transformed to the corresponding bromoenol ethers **22**, although the cross-coupling was slowed down in the last case. The presence of electron-withdrawing or -donating groups had virtually no effect on the outcome of the reaction, and even the challenging 4-bromophenol could be smoothly transformed to the corresponding enol-ether **22g**, without competing cross-coupling or reduction. In this case, the nature of the substituent on the starting dibromides **1** was found to have little influence on the reaction time and yields, and the corresponding alkyl- (**22a-s**), alkenyl- (**22t**), and aryl- (**22u-v**) substituted bromoenol ethers were obtained in comparable yields and efficiency. In all cases, a site-selective cross-coupling favoring the formation of the *Z*-isomers occurred with synthetically useful levels of stereoselectivity, which nicely complements the synthesis of their *E*-isomers by hydrobromination of the corresponding ynol ethers with bromotrimethylsilane in methanol, a reaction that we found to be nonselective in the case of phenol-derived ynol ethers.[32] Compared to the analogous coupling involving N-nucleophiles,

Chart 6. Site-Selective Cross-Coupling with Phenols to 1-Bromoenol Ethers





22a: Ar = *m*-Me-C_6H_4	81% (*Z*/*E*: 91/9)
22b: Ar = *o*-Me-C_6H_4	47% (*Z*/*E*: 93/7)
22c: Ar = Ph	77% (*Z*/*E*: 88/12)
22d: Ar = *m*-MeO_2C-C_6H_4	76% (*Z*/*E*: 90/10)
22e: Ar = *p*-F-C_6H_4	72% (*Z*/*E*: 88/12)
22f: Ar = *p*-Cl-C_6H_4	69% (*Z*/*E*: 93/7)
22g: Ar = *p*-Br-C_6H_4	54% (*Z*/*E*: 92/8)
22h: Ar = *p*-^{i}Pr-C_6H_4	64% (*Z*/*E*: 88/12)
22i: Ar = *p*-^{t}Bu-C_6H_4	73% (*Z*/*E*: 85/15)
22j: Ar = *p*-Ph-C_6H_4	52% (*Z*/*E*: 91/9)
22k: Ar = *m*-^{t}Bu-C_6H_4	75% (*Z*/*E*: 88/12)
22l: Ar = *m*-Ph-C_6H_4	67% (*Z*/*E*: 89/11)
22m: Ar = 3,5-Me_2-C_6H_3	65% (*Z*/*E*: 90/10)



22n: R = ^{i}Bu	79% (*Z*/*E*: 96/4)
22o: R = ^{t}Bu	63% (*Z*/*E*: 95/5)
22p: R = Et	54% (*Z*/*E*: 87/13)
22q: R = Cy	64% (*Z*/*E*: 92/8)
22r: R = cyclopropyl	62% (*Z*/*E*: 91/9)
22s: R = CH_2CH_2Ph	58% (*Z*/*E*: 85/15)
22t: R = (*E*)-CH=CHPh	45% (*Z*/*E*: 74/26)
22u: R = 2-pyridyl	49% (*Z*/*E*: 94/6)
22v: R = 2-naphtyl	66% (*Z*/*E*: 78/22)

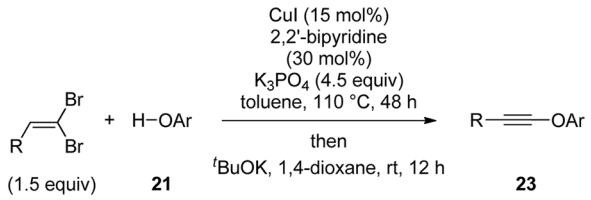
higher levels of selectivity were obtained in all cases with phenols (typically 9:1 with phenols compared with 7:3 with lactams and oxazolidinones), which might be due to the slower cross-coupling with phenols, that would imply a better differentiation of the two C–Br bonds and ensure a greater selectivity for the least hindered *trans* C–Br bond. Due to the very different nature of the ligands used for the site-selective cross-coupling involving N- and O-nucleophiles, distinct reaction mechanisms might also be operating and could account for the nucleophile-dependent selectivities. Indeed, on the basis of computational studies by Buchwald and Houk[33] and by Fu,[34] the use of N- and O-nucleophiles as well as the use of different chelating ligands might result in either a different activation mode of the 1,1-dibromoalkene (oxidative addition, atom transfer, or single-electron transfer) or a shift in the rate-limiting step depending on the coordination of the nucleophile before or after the oxidative addition.

The alkynylative cross-coupling was next envisioned with the hope of providing a useful alternative to the existing routes to O-substituted alkynes relying on either the use of lengthy stepwise sequences[35] or alkynylation with alkynyl hypervalent iodonium salts,[36] which has strongly hampered the development of these most useful building blocks. With this goal in mind, we spent a considerable amount of time trying to optimize all reaction parameters in order to find a system that would allow direct alkynylative cross-coupling, and most of the possible combinations of ligands, bases, solvents, and temperatures were evaluated. We were, however, unfortunately unable to cleanly isolate the expected ynol ethers **23** in decent yields, mostly because of the much slower elimination step from the intermediate bromoenol ethers **22** compared to their nitrogen analogues. We therefore decided to slightly modify our strategy and found that exposure of the crude reaction mixtures obtained after the site-selective cross-coupling described above to potassium *tert*-butoxide after dilution with 1,4-dioxane triggered a rapid and clean β-elimination and allowed for the isolation of the long-sought-after ynol ethers **23** in a one-pot, two-step process and in good yields.[18] The elimination being an especially clean process, the scope of our ynol ether synthesis is basically the same as that of the site-selective cross-coupling, and ynol ethers **23** with representative substitution patterns could be obtained with high efficiency (Chart 7), which nicely comple-

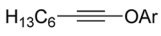
dx.doi.org/10.1021/om3005614 | *Organometallics* XXXX, XXX, XXX–XXX

ments their classical synthesis involving the procedures cited above.

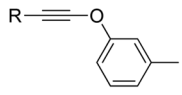
Chart 7. Synthesis of Ynol Ethers by Site-Selective Coupling/Elimination



1 (1.5 equiv) **21** **23**



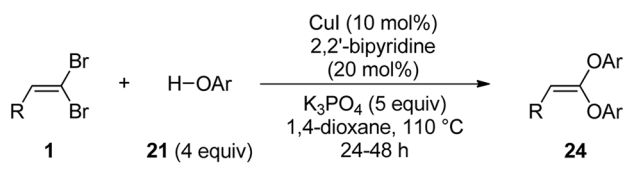
23a: Ar = *m*-Me-C_6H_4 87%
23b: Ar = *p*-Me-C_6H_4 62%
23c: Ar = Ph 46%
23d: Ar = *p*-Cl-C_6H_4 65%
23e: Ar = *p*-Br-C_6H_4 71%
23f: Ar = *p*-^{i}Pr-C_6H_4 62%
23g: Ar = *p*-^{t}Bu-C_6H_4 76%
23h: Ar = *p*-Ph-C_6H_4 38%



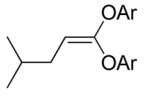
23i: R = ^{i}Bu 75%
23j: R = ^{t}Bu 65%
23k: R = Cy 71%
23l: R = cyclopropyl 45%
23m: R = CH_2CH_2Ph 84%

A reoptimization of the reaction conditions was finally performed in order to selectively promote a double cross-coupling, and this time, problems associated with the high sensitivity of the ketene acetals **24** toward hydrolysis or during their purification considerably complicated the optimization. The desired ketene acetals **24** arising from a clean double copper-catalyzed phenoxylation could however be obtained in virtually pure form by performing the reaction with excess phenol (4 equivalents) in 1,4-dioxane at 110 °C under the catalysis of copper(I) iodide (10 mol %) and 2,2′-bipyridine (20 mol %) followed by simple removal of the catalyst and base by filtration over paper filter, concentration of the crude mixture, and elimination of excess phenol by extraction of the apolar product **24** with pentane. Using this optimized procedure, a set of ketene acetals **24**, previously unknown and possessing representative substitution patterns on both the phenol and the double bond, could be obtained in good yields, as shown from the structures collected in Chart 8.

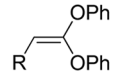
Chart 8. Double Cross-Coupling with Phenols to Ketene *O,O*-Acetals



1 **21** (4 equiv) **24**



24a: Ar = *m*-Me-C_6H_4 61%
24b: Ar = *o*-Me-C_6H_4 61%
24c: Ar = *p*-Me-C_6H_4 61%
24d: Ar = Ph 85%
24e: Ar = *p*-Cl-C_6H_4 86%
24f: Ar = *p*-^{t}Bu-C_6H_4 86%



24g: R = Et 38%
24h: R = ^{t}Bu 63%
24i: R = cyclopropyl 75%
24j: R = (*E*)-CH=CHPh 88%

While the use of aliphatic alcohols as partners in copper-catalyzed cross-coupling with *gem*-dibromoolefins mostly results in dimerization of the latter and would anyway generate products that would not be compatible with the reaction conditions, we thought that trifluoroethanol **25**, whose pK_a is relatively close to that of phenols, might participate in site-selective or double cross-couplings and therefore broaden the scope of these reactions. We were actually able to demonstrate that this was indeed the case, and a brief study summarized in Scheme 4 shows that trifluoroethanol-derived bromoenol ethers **26** and ketene acetal **28** can be readily obtained using our standard conditions with synthetically useful yields and, in the first case, reasonable levels of selectivity in favor of the *Z*-isomers, which were predominantly formed, as in the case of phenol derivatives.

In view of these results, oxygen nucleophiles can therefore participate in site-selective and double cross-coupling reactions, providing efficient entries to mono- and bis-oxygenated alkenes, and can also be alkynylated to ynol ethers with *gem*-dibromoolefins using a one-pot, two-step process. To complete these studies, we moved to the use of another class of nucleophiles commonly used in copper-catalyzed carbon–heteroatom bond-forming reactions: phosphorus nucleophiles. Results obtained with these substrates are described in the following paragraphs.

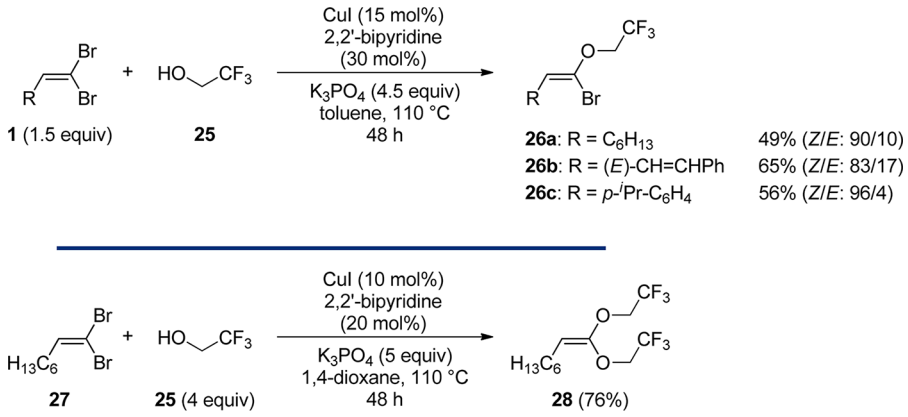
Cross-Coupling with Dialkylphosphites: New Entry to Vinylphosphonates. Copper-catalyzed reactions involving P-nucleophiles such as dialkyl/diaryl phosphines, diarylphosphine oxides, dialkylphosphites, and H-phosphinates have recently emerged as useful and efficient alternatives to the corresponding palladium-catalyzed transformations. Compared to other nucleophiles, this area has been however much less studied, despite recent progress that unambiguously demonstrated the efficiency and high potential of these reactions.

To initiate our studies on the cross-coupling between 1,1-dibromo-1-alkenes and P-nucleophiles, we initially focused on the use of diphenylphosphine as a model nucleophile. However, we were not able to promote any kind of cross-coupling with this substrate, and even after considerable experimentation on the nature of the copper source, ligand, base, solvent, and temperature, we could not suppress the dimerization of the dibromoalkenes,[31] the corresponding diynes being isolated as the major products in couple trials, or the catalyst poisoning observed in most cases. The replacement of diphenylphosphine with the corresponding phosphine borane was not more successful, and limited success was also met with diphenylphosphine oxide. To our delight, the use of diisopropylphosphite was found to be much more efficient. Indeed, upon reaction with copper iodide, *N,N*′-dimethylethylenediamine, and potassium phosphate in toluene at 120 °C for a day and provided that 2.5 equivalents of the phosphite were used (the use of less than 2 equivalents yielded the formation of complex and especially messy mixtures of products), a single product was formed, which turned out to be, quite unexpectedly, a vinylphosphonate. These compounds are especially useful small organic molecules used in polymer science as copolymers, additives, or flame-retardants, in medicinal chemistry, and as building blocks for the introduction of remote phosphonate functional groups or to prepare biologically active molecules.[37] Their preparation being still far from a trivial task,[38] we decided to study the scope of our transformation that might provide an interesting alternative to the preparation of these building blocks.

Using our optimized conditions, which required a rather high loading of both copper(I) iodide and ligand, which is in sharp

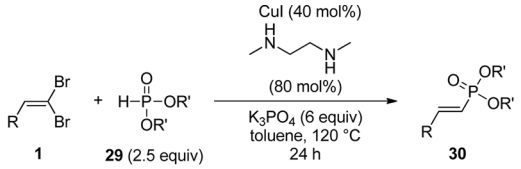
dx.doi.org/10.1021/om3005614 | *Organometallics* XXXX, XXX, XXX–XXX

Scheme 4. Site-Selective and Double Cross-Coupling with 2,2,2-Trifluoroethanol



contrast with results obtained with N- and O-nucleophiles, the cross-coupling between a set of vinyl dibromides **1** and a series of dialkylphosphites **29** was examined: results from these studies are shown in Chart 9.[19] As evidenced with these results, the reaction was found to be quite general, and 1-alkenylphosphonates **30** could be obtained in all cases with reasonable to good yields and with useful selectivities in favor of the *E*-isomer. A variety of substituents can be successfully introduced on both the phosphonate and alkene moieties, and the reaction was found to be insensitive to the presence of electron-withdrawing or -donating groups when starting from aryl-substituted dibromides **1**. We also briefly studied the cross-coupling involving the more challenging disubstituted, benzophenone- and acetophenone-derived 1,1-dibromoalkenes. Again, the reaction was found to be quite efficient since the corresponding synthesis of trisubstituted 1-alkenylphophonates **30r** and **30s** could be isolated in 58% and 78% yield. In the last case, the *E*-isomer was formed predominantly, with a selectivity similar to that observed when starting from monosubstituted *gem*-dibromoalkenes.

Chart 9. Cross-Coupling with Dialkylphosphites to Vinylphosphonates



30a: R = Et 45% (*E*/*Z*: 81/19)
30b: R = C_8H_{17} 59% (*E*/*Z*: 92/8)
30c: R = ^{t}Bu 48% (*E*/*Z*> 95/5)
30d: R = Cy 54% (*E*/*Z*: 93/7)
30e: R = (*E*)-CH=CHPh 71% (*E*/*Z*: 88/12)
30f: R = Ph 60% (*E*/*Z*: 90/10)
30g: R = *o*-MeO-C_6H_4 67% (*E*/*Z*: 89/11)
30h: R = *p*-Cl-C_6H_4 56% (*E*/*Z*: 89/11)
30i: R = *p*-F-C_6H_4 52% (*E*/*Z*: 87/13)
30j: R = *o*-MeO_2C-C_6H_4 52% (*E*/*Z*: 83/17)
30k: R = *p*-CF_3-C_6H_4 67% (*E*/*Z*: 80/20)
30l: R = 2-naphtyl 60% (*E*/*Z*: 92/8)
30m: R = anthracen-9-yl 48% (*E*/*Z*: 95/5)
30n: R = *p*-^{i}Pr-C_6H_4 58% (*E*/*Z*: 92/8)
30o: R = *m*-NO_2-C_6H_4 84% (*E*/*Z*: 88/12)

30p: R = Et 76% (*E*/*Z*: 94/6)
30q: R = Bu 57% (*E*/*Z*: 84/16)

30r: R = Ph 58%
30s: R = Me 78% (*E*/*Z*: 90/10)

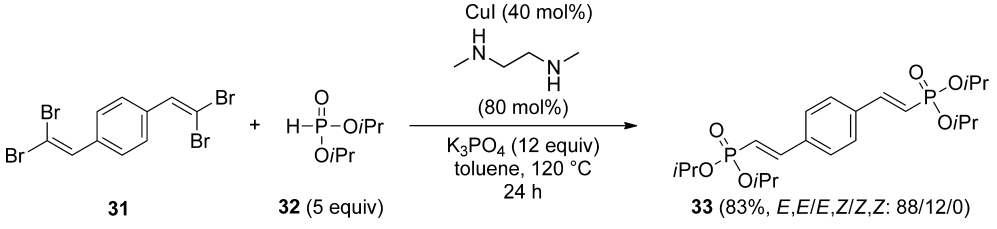
Besides all heteronucleophiles described in the previous paragraphs, whose use in combinations with *gem*-dibromoalkenes and copper-based catalytic systems was found to provide new routes to a wide range of heterosubstituted alkenes and alkynes, the reactivity of a certain number of other heteronucleophiles was also evaluated. While sulfonamides, cyclic secondary amides, carbamates, oxazolidinones, conjugated N-heterocycles, phenols, trifluoroethanol, and dialkylphosphites were in most cases readily coupled with all kinds of vinyl

To further test this procedure, a double cross-coupling was finally envisioned by reacting bis-dibromoalkene **31** with 5 equivalents of diisopropylphosphite **32** under our standard conditions. To our delight, the corresponding bis-1-alkenylphosphonate **33** could be isolated in an excellent 83% yield and with reasonable selectivity in favor of the *E*,*E*-isomer (Scheme 5).

As demonstrated with these results, phosphorus-based nucleophiles behave in a dramatically different way compared to their nitrogen or oxygen analogues: while most of them completely inhibit the catalyst, the use of dialkylphosphites gives a completely different reaction in which both bromine atoms are formally substituted, with phosphorus and hydrogen atoms, respectively. The mechanism that might be involved in this reaction will be discussed in the last section of this article.

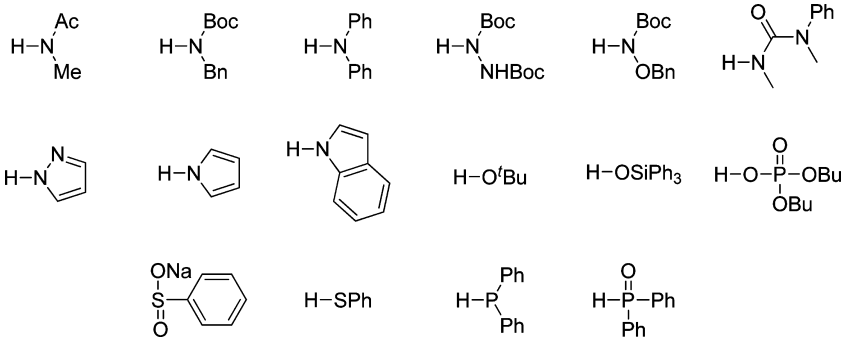
Heteronucleophiles not Participating in Copper-Catalyzed Cross-Coupling Reactions with 1,1-Dibromo-1-alkenes. Besides all heteronucleophiles described in the previous paragraphs, whose use in combinations with *gem*-dibromoalkenes and copper-based catalytic systems was found to provide new routes to a wide range of heterosubstituted alkenes and alkynes, the reactivity of a certain number of other heteronucleophiles was also evaluated. While sulfonamides, cyclic secondary amides, carbamates, oxazolidinones, conjugated N-heterocycles, phenols, trifluoroethanol, and dialkylphosphites were in most cases readily coupled with all kinds of vinyl

Scheme 5. Copper-Catalyzed Synthesis of a Bis-1-alkenylphosphonate from a Bis-dibromoalkene



dx.doi.org/10.1021/om3005614 | *Organometallics* XXXX, XXX, XXX−XXX

Chart 10. Nonparticipating Heteronucleophiles in Copper-Catalyzed Cross-Coupling Reactions with 1,1-Dibromo-1-alkenes



dibromides, the use of other substrates shown in Chart 10 was found to be more problematic. Indeed, acyclic secondary amides, Boc-protected amines, hydrazine or hydroxylamine derivatives, diphenylamine, ureas, pyrazole, pyrrole, and indole were reluctant to participate in either site-selective, alkynylative, or double cross-coupling, mostly due to either their lower basicity or their increased steric bulk, and dimerization of the starting 1,1-dibromoalkenes was observed with these substrates, as well as in the case of aliphatic alcohols, silanols, dialkylphosphates, or sulfinates. In contrast, no reaction at all occurred when starting from thiophenol, diphenylphosphine, or its oxide, which might be due to catalyst poisoning with these substrates.

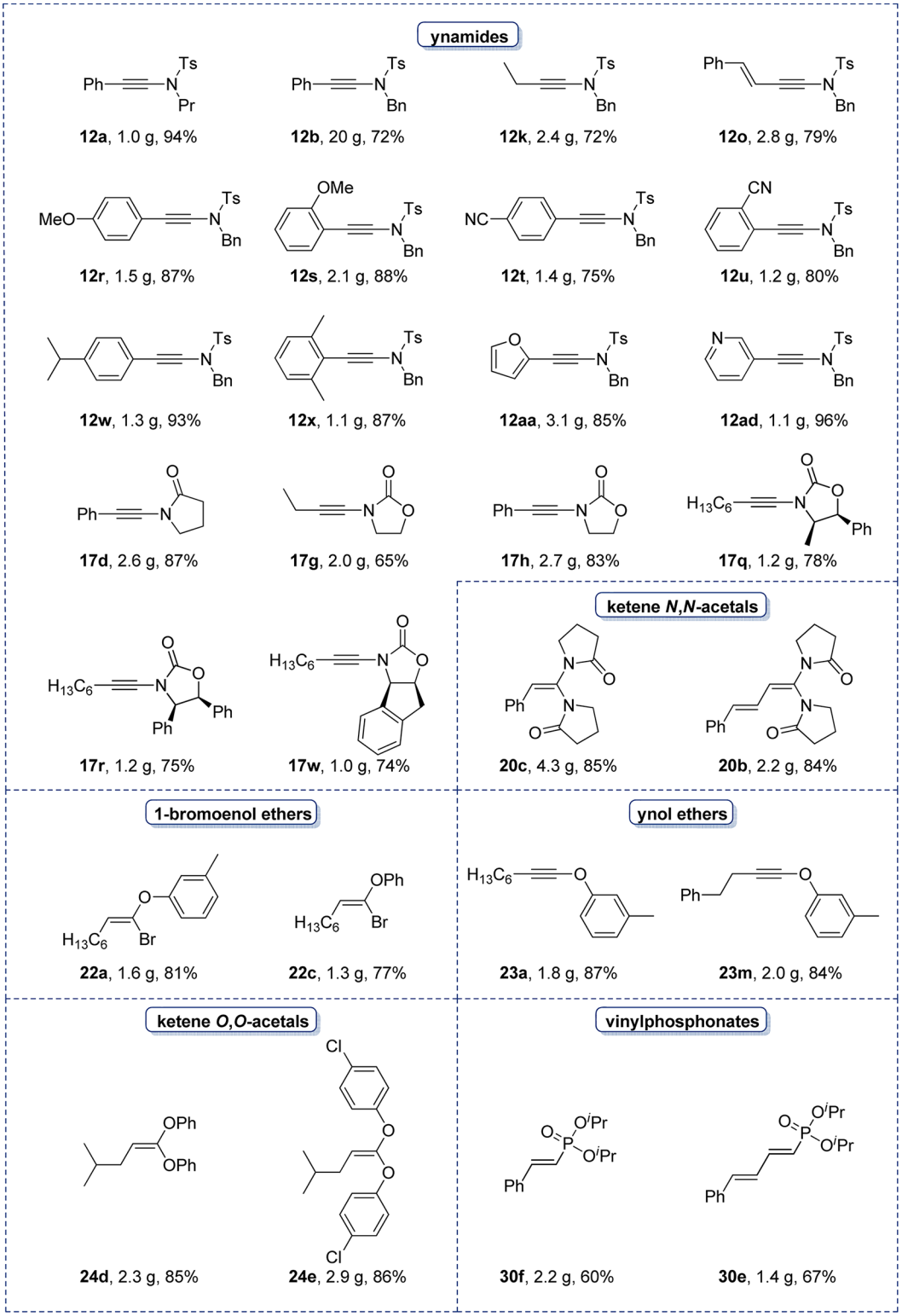
Gram-Scale Copper-Catalyzed Cross-Coupling Reactions with 1,1-Dibromo-1-alkenes. To fully assess the efficiency of our procedures and to further demonstrate the efficiency and versatility of 1,1-dibromo-1-alkenes in copper-catalyzed cross-coupling with heteronucleophiles, we decided to make sure all our procedures are not limited to the scale used during our systematic studies, i.e., 0.67 to 2.0 mmol. To this end, a series of site-selective, alkynylative, and double cross-coupling reactions were assayed on gram/multigram scales with representative N-, O-, and P-nucleophiles. Results from those studies are shown in Chart 11 and demonstrate that ynamides, ketene *N*,*N*-acetals, 1-bromoenol ethers, ynol ethers, ketene *O*,*O*-acetals, and vinylphosphonates can easily be obtained on a gram scale without noticeable change in yields. A major advantage of these procedures that is especially appreciable on a big scale is that they do not require workups after the cross-coupling reactions since simple filtrations of crude reaction mixtures over a short plug of silica allows for the elimination of the base and catalyst. The low cost of both copper source (the cost of copper iodide is typically $160 USD for a kilogram) and ligand (*N*,*N*′-dimethylethylenediamine typically costs $160 USD for 25 g) is also a real advantage of these copper-based processes, which can therefore easily be performed on large scales at reasonable costs. As a note, the purity of copper(I) iodide has virtually no influence since 99.999% purity, which we used for our studies to avoid possible cocatalysis by contaminants and ensure the reproducibility of our results, and 98% purity gave exactly the same results. All together, the development of copper-catalyzed cross-coupling between heteronucleophiles and 1,1-dibromo-1-alkenes allows for an easy and divergent synthesis of a wide range of heterosubstituted alkenes and alkynes that can, in most cases, hardly be obtained using other methods. Our syntheses are easily amenable on a gram scale, which should contribute to the development of these useful building blocks. Apart from ketene *O*,*O*-acetals and alkyl-substituted, tosyl-protected ynamines, which are quite prone to hydrolysis (they are readily hydrolyzed overnight in chloroform), all other compounds are perfectly stable and can be stored for months without noticeable degradation.

Copper-Catalyzed Cross-Coupling Reactions with 1,1-Dibromo-1-alkenes on Complex Substrates. One last point that we had to address to ensure the generality of our procedures was to test them with complex substrates. Although many chemical transformations do perform well when applied to relatively simple or commercially available molecules, it is of great importance to test them in "real life" situations, in which they are clearly challenged and pushed way beyond their limits, to ensure their robustness, compatibility, and selectivity. To this aim, a series of site-selective, alkynylative, and double cross-coupling reactions between structurally complex 1,1-dibromo-1-alkenes and nucleophiles were next envisioned, and representative examples are collected in Scheme 6. As shown by these results, the presence of various functional groups and the use of more demanding substrates did not affect the cross-coupling reactions, even if the yields were found to be lower in some cases, which are therefore suitable for the preparation of structurally complex 1-bromoenamides, ynamides, 1-bromoenol ethers, ynol ethers, and vinylphosphonates. For example, citronellal-derived dibromides **34** and **51** were readily transformed to the corresponding 1-bromoenamide **36**, 1-bromoenol ether **45**, ynol ether **48**, or vinylphosphonate **52** in reasonable to good yields, affording the corresponding monocoupled products in which the stereocenter from the starting citronellal was readily incorporated. Dibromide **37**, another readily available complex *gem*-dibromoolefin obtained by a Ramirez dibromoolefination from the corresponding prolinal derivative, was also smoothly transformed to the corresponding ynamide **39** or vinylphosphonate **50** in good yields and without epimerization, showing that structurally complex dibromoalkenes perform well in selective copper-mediated cross-coupling reactions with representative heteronucleophiles. The complexity can also arise from the use of more complex heteronucleophiles, as shown with the alkynylation of azetidinyl-sulfonamide **40**, chaetomimine-derived sulfonamide **42**, O_{17}-methylestradiol **46**, and menthol-derived phosphite **54** or with the synthesis of bromoenol ether **47**.

After carefully studying the scope of all possible modes of cross-coupling between 1,1-dibromo-1-alkenes and various heteronucleophiles using copper catalysis as well as their scale-up and the use of the optimized procedures with complex substrates, we decided to try to obtain some insights into the reaction mechanisms involved in the formation of products resulting from formal site-selective, alkynylative, or double cross-coupling reactions as well as in the synthesis of vinylphosphonates, various reaction pathways being possible to explain the formation of these products.

dx.doi.org/10.1021/om3005614 | *Organometallics* XXXX, XXX, XXX–XXX

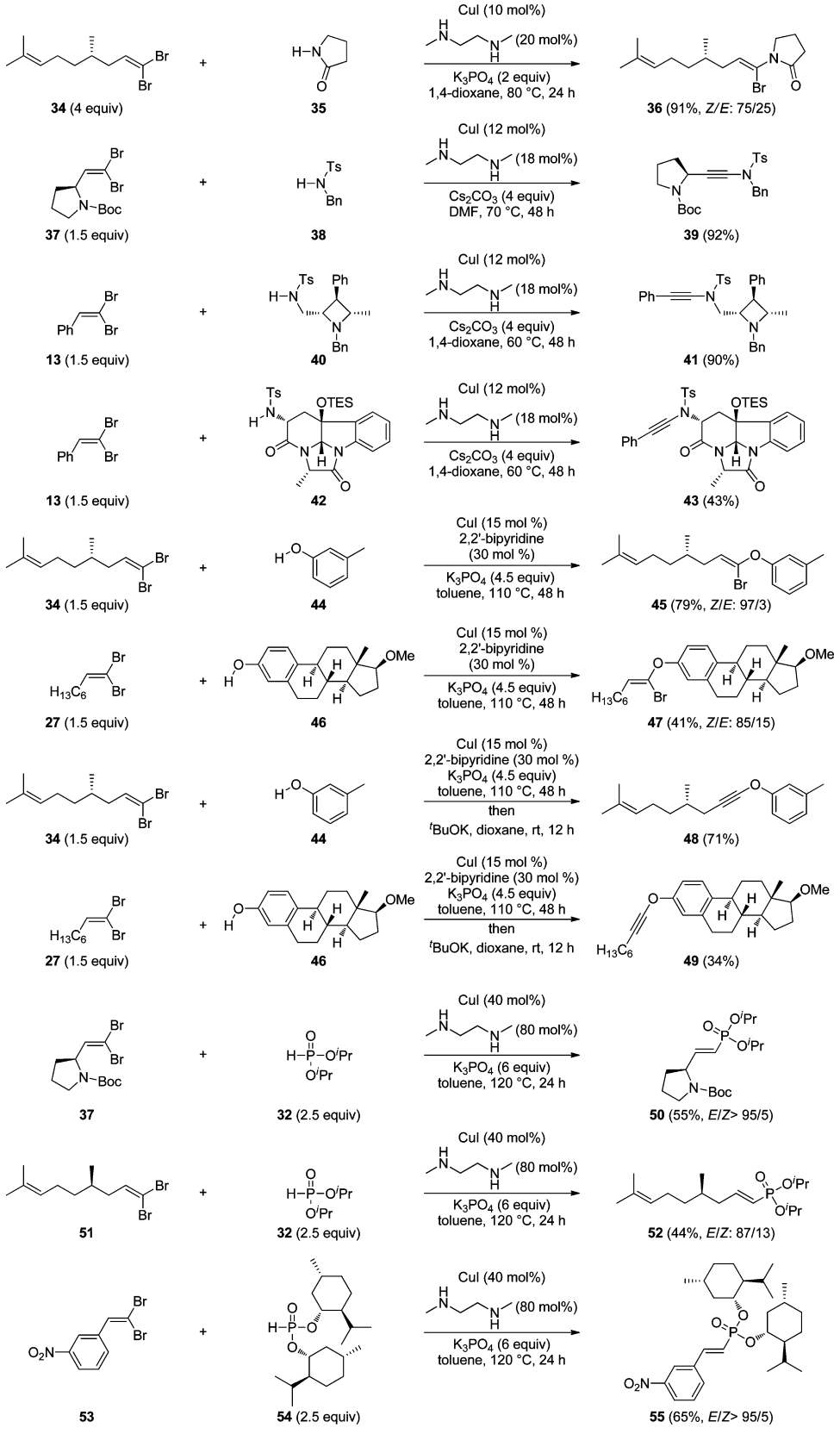
Chart 11. Gram-Scale Cross-Coupling with 1,1-Dibromo-1-alkenes



Insights into the Reaction Mechanism. First, noncatalyzed processes involving formation of bromoalkynes and addition of heteronucleophiles yielding heterosubstituted alkenes possessing a bromide in the 2-position[39] and their subsequent and low-yielding transformation to the corresponding heterosubstituted alkynes or ketene acetals under harsh conditions and/or with poor substrate scope[39a,40] have been rigorously discarded in all our cases by performing careful control experiments in the absence of the copper salt and ligand. Besides these noncatalytic processes, various reaction pathways involving at least one copper-catalyzed step can account for the formation of products resulting from formal site-selective, alkynylative, or double cross-coupling reactions in the case of N- and O-nucleophiles. Indeed, while the formation of products resulting from a mono-cross-coupling from **6** can only arise by activation of one bromide atom from the starting dibromides **1**, the

dx.doi.org/10.1021/om3005614 | *Organometallics* XXXX, XXX, XXX−XXX

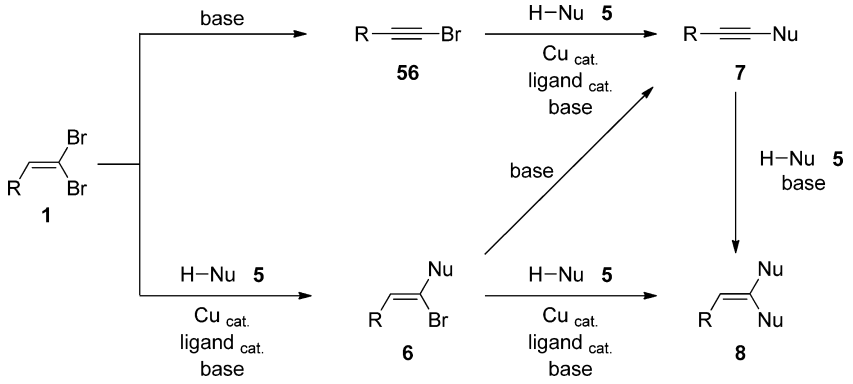
Scheme 6. Copper-Catalyzed Cross-Coupling Reactions with 1,1-Dibromo-1-alkenes on Complex Substrates



selective cross-coupling involving the sterically less hindered *trans* C−Br accounting for the preferential formation of the *Z*-isomer, the formation of heterosubstituted alkynes **7** can involve either an elimination step from bromoalkenes **6** or a cross-coupling from intermediate bromoalkynes **56** and the formation of bis-heterosubstituted alkenes **8** can arise from hydroamination/hydroalkoxylation of the corresponding alkynes **7** or a second copper-catalyzed cross-coupling from **6** (Scheme 7).

dx.doi.org/10.1021/om3005614 | *Organometallics* XXXX, XXX, XXX−XXX

Scheme 7. Possible Pathways Involved in the Copper-Catalyzed Cross-Coupling of 1,1-Dibromo-1-alkenes with Heteronucleophiles



The intermediacy of bromoalkynes **56** in the formation of ynamides is highly unlikely since control experiments have demonstrated that the latter are formed in really poor yields when bromoalkynes **56** are reacted with N-nucleophiles under our optimized conditions shown in Charts 2 and 3. Moreover, lowering the reaction temperature for the cross-coupling performed with alkyl-substituted dibromides **1** allowed for the isolation of significant amounts of 1-bromoenamides **6**, which were shown to be readily converted to the corresponding ynamides when treated with cesium carbonate at 70 °C in DMF. A unified mechanism involving site-selective cross-coupling followed by elimination therefore accounts for the formation of heterosubstituted alkynes **7** upon cross-coupling between dibromides **1** and heteronucleophiles **5**.

Concerning the formation of ketene acetals **8**, hints concerning the reaction mechanism were found in their isolation upon copper-catalyzed reactions between heteronucleophiles **5** and heterosubstituted bromoalkenes **6**, under the reaction conditions shown in Charts 5 and 8, and in the presence of bromoalkenes **6** before completion of the reaction yielding ketene acetals **8**. To unambiguously demonstrate the mechanism involved in their formation, deuterated ($\mathbf{13}_D$ and $\mathbf{57}_D$) and nondeuterated (**13** and **57**) dibromoalkenes were respectively reacted with deuterated and nondeuterated pyrrolidinone and phenols under our coupling conditions optimized for the site-selective cross-coupling (Scheme 8). Results from these experiments unambiguously demonstrate that the vinylic hydrogen atom of the starting dibromides is fully retained during the reaction, clearly indicating that β-elimination followed by hydroamination or hydroalkoxylation is not a competitive pathway and that ketene acetals **8** are formed by two consecutive copper-mediated cross-coupling reactions.

Finally, and because of the high polarization of the triple bonds of ynamides and ynol ethers, which renders these compounds highly sensitive to nucleophilic addition, even with weak nucleophiles, the formation of bromoenamides and bromoenol ethers might result from hydrobromination of these highly electrophilic alkynes, which is however rather unlikely under basic conditions. To make sure this was however not the case, especially when mixtures of isomers were obtained where one of them could be formed through a different, non-copper-catalyzed mechanism, additional experiments with deuterated and non-deuterated vinyl dibromides **27** and $\mathbf{27}_D$ were performed with deuterated and nondeuterated pyrrolidinone and phenols, respectively. Here again, the vinylic hydrogen atom of the starting dibromides is fully retained during the reaction, therefore allowing us to discard a competitive hydrobromination reaction in the formation of **6**.

A different mechanism is involved in the formation of vinylphosphonates upon cross-coupling between dibromides **1** and dialkylphosphites **29**, where the latter serve as both coupling partners and reducing agents. Starting from these reagents, a Hirao reduction involving phosphite conjugate addition/protonation/halophilic elimination would yield an intermediate vinyl bromide whose cross-coupling would then account for the formation of **30**.[41] Alternatively, a site-selective cross-coupling might occur first and would generate an α-bromovinylphosphonate, an intermediate in which the electron-withdrawing group would facilitate the conjugate addition involved in the Hirao-like reduction. Based on the greater reactivity of vinyl dibromides than that of bromoalkenes toward copper-mediated cross-coupling reactions and on the easier reduction of α-bromovinylphosphonates than vinyl dibromides with dialkylphosphites, the first hypothesis, which would first involve a Hirao reduction that typically proceeds under harsher conditions and with more polar solvents, seems highly unlikely. Indeed, a simple control experiment consisting of the reaction between excess diisopropylphosphite and (2,2-dibromovinyl)benzene in toluene at 120 °C with or without potassium phosphate showed that the Hirao reduction does not proceed under the conditions used for the copper-catalyzed cross-coupling, indicating that the cross-coupling is most certainly the first step of the process that would proceed through the intermediacy of α-bromovinylphosphonates resulting from a site-selective cross-coupling and whose reduction with a second equivalent of phosphite would yield the corresponding vinylphosphonates.

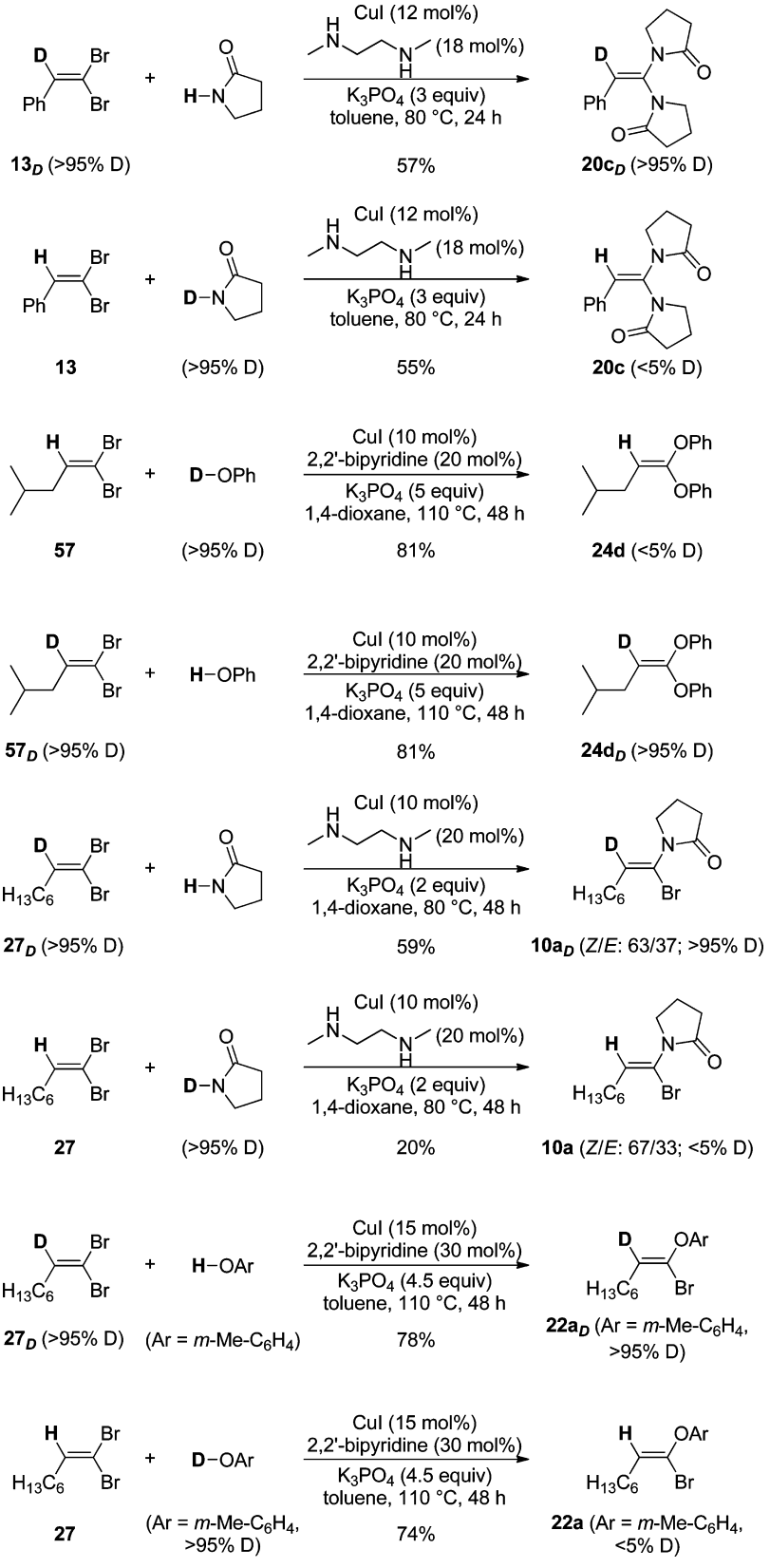
CONCLUSION

As stated in the Introduction, copper catalysis has undergone nothing short of a renaissance over the past decade and has enabled the design of efficient and general reactions for the formation of carbon–heteroatom bonds, which are now commonly used for the preparation of simple building blocks and complex molecules as well. These developments provided the chemical community with highly efficient tools that have found numerous academic and industrial applications and clearly had a deep impact on organic synthesis.

Further developments in copper catalysis will mostly follow two main directions, the first one being the design of new catalytic systems with improved efficiencies that will allow overcoming the existing limitations, such as the catalyst loading, the need for thermal activation, or the limited efficiency of cross-

dx.doi.org/10.1021/om3005614 | *Organometallics* XXXX, XXX, XXX–XXX

Scheme 8. Mono- and Double-Cross-Coupling with Deuterated Substrates



coupling involving aryl chlorides, and the second one being the development of new reactions and the use of novel coupling partners for copper catalysis. In this area, we have demonstrated that vinyl dibromides can be successfully coupled with a wide range of heteronucleophiles and therefore provide efficient and straightforward entries to numerous building blocks such as 1-bromoenamides, ynamides, ketene *N*,*N*-acetals, 1-bromoenol ethers, ynol ethers, ketene *O*,*O*-acetals, and vinylphosphonates.

dx.doi.org/10.1021/om3005614 | *Organometallics* XXXX, XXX, XXX−XXX

We envision great acceptance of these new processes, which, combined with the high versatility of 1,1-dibromoalkenes and their availability, should break new ground in copper catalysis.

■ ASSOCIATED CONTENT

Supporting Information

Complete experimental procedures, characterization, and copies of ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: gevano@ulb.ac.be.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the CNRS, the University of Versailles, the University of Brussels, and the ANR (projects ProteInh ANR-07-JCJC-0025-01, DYNAMITE ANR-2010-BLAN-704, and VINFLUSUP ANR-11-JS07-003-01) for financial support. K.J. and A.C. respectively acknowledge the Ministère de la Recherche and the National Cancer Institute for graduate fellowships. G.K. and K.T. acknowledge the University of Versailles for postdoctoral fellowships.

■ REFERENCES

(1) For reviews, see: (a) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954. (b) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054.

(2) For a perspective article, see: Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2010**, *1*, 13.

(3) For an account, see: Ma, D.; Cai, Q. *Acc. Chem. Res.* **2008**, *41*, 1450.

(4) (a) Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2382. (b) Ullmann, F.; Sponagel, P. *Ber. Dtsch. Chem. Ges.* **1905**, *38*, 2211.

(5) Goldberg, I. *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 1691.

(6) Ramirez, F.; Desal, N. B.; McKelvie, N. *J. Am. Chem. Soc.* **1962**, *84*, 1745.

(7) (a) Fang, Y.-Q.; Lifchits, O.; Lautens, M. *Synlett* **2008**, 413. (b) Bryan, C.; Aurregi, V.; Lautens, M. *Org. Synth.* **2009**, *86*, 36.

(8) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *36*, 3769.

(9) For reviews, see: (a) Legrand, F.; Jouvin, K.; Evano, G. *Isr. J. Chem.* **2010**, *50*, 588. (b) Chelucci, G. *Chem. Rev.* **2012**, *112*, 1344.

(10) For a review on site-selective cross-coupling of polyhalogenated compounds, see: Wang, J.-R.; Manabe, K. *Synlett* **2009**, 1405.

(11) (a) Zapata, A. J.; Rúiz, J. *J. Organomet. Chem.* **1994**, *479*, C6. (b) Shen, W.; Wang, L. *J. Org. Chem.* **1999**, *64*, 8873. (c) Shen, W.; Thomas, S. A. *Org. Lett.* **2000**, *2*, 2857.

(12) Lera, M.; Hayes, C. J. *Org. Lett.* **2000**, *2*, 3873.

(13) Thiegles, S.; Meddah, E.; Bisseret, P.; Eustache, J. *Tetrahedron Lett.* **2004**, *45*, 907.

(14) (a) Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2005**, *7*, 3549. (b) Fang, Y.-Q.; Lautens, M. *J. Org. Chem.* **2008**, *73*, 538. (c) Nagamochi, M.; Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2007**, *9*, 2955. (d) Fayol, A.; Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2006**, *8*, 4203. (e) Bryan, C. S.; Lautens, M. *Org. Lett.* **2008**, *10*, 4633. (f) Fang, Y.-Q.; Yuen, J.; Lautens, M. *J. Org. Chem.* **2007**, *72*, 5152. (g) Newman, S. G.; Aureggi, V.; Bryan, C. S.; Lautens, M. *Chem. Commun.* **2009**, 5236. (h) Yuen, J.; Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2006**, *8*, 653. (i) Bryan, C. S.; Braunger, J. A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 7064. (j) Newman, S. G.; Lautens, M. *J. Am. Chem. Soc.* **2010**, *132*, 11416.

(15) (a) Vieira, T. O.; Meaney, L. A.; Shi, Y.-L.; Alper, H. *Org. Lett.* **2008**, *10*, 4899. (b) Arthuis, M.; Pontikis, R.; Florent, J.-C. *Org. Lett.* **2009**, *11*, 4608. (c) Wang, Z.-J.; Yang, J.-G.; Yang, F.; Bao, W. *Org. Lett.* **2010**, *12*, 3034. (d) Xia, Z.; Wang, K.; Zheng, J.; Ma, Z.; Jiang, Z.; Wang, X.; Lv, X. *Org. Biomol. Chem.* **2012**, *10*, 1602.

(16) (a) Toumi, M.; Couty, F.; Evano, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 572. (b) Toumi, M.; Couty, F.; Evano, G. *J. Org. Chem.* **2007**, *72*, 9003. (c) Toumi, M.; Couty, F.; Evano, G. *Synlett* **2008**, 29. (d) Coste, A.; Toumi, M.; Wright, K.; Razafimahaléo, V.; Couty, F.; Marrot, J.; Evano, G. *Org. Lett.* **2008**, *10*, 3841. (e) Toumi, M.; Couty, F.; Marrot, J.; Evano, G. *Org. Lett.* **2008**, *10*, 5027. (f) Evano, G.; Toumi, M.; Coste, A. *Chem. Commun.* **2009**, 4166. (g) Jouvin, K.; Couty, F.; Evano, G. *Org. Lett.* **2010**, *12*, 3272. (h) Laouiti, A.; Rammah, M. M.; Rammah, M. B.; Marrot, J.; Couty, F.; Evano, G. *Org. Lett.* **2012**, *14*, 6.

(17) (a) Coste, A.; Karthikeyan, G.; Couty, F.; Evano, G. *Angew. Chem., Int. Ed.* **2009**, *48*, 4381. (b) Coste, A.; Couty, F.; Evano, G. *Org. Lett.* **2009**, *11*, 4454. (c) Coste, A.; Couty, F.; Evano, G. *Org. Synth.* **2010**, *87*, 231. (d) Jouvin, K.; Evano, G. *Chim. Oggi* **2011**, *29*, 31.

(18) Jouvin, K.; Bayle, A.; Legrand, F.; Evano, G. *Org. Lett.* **2012**, *14*, 1652.

(19) Evano, G.; Tadiparthi, K.; Couty, F. *Chem. Commun.* **2011**, *47*, 179.

(20) Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P.; Coverdale, H.; Frederick, M. O.; Shen, L.; Zificsak, C. A. *Org. Lett.* **2003**, *5*, 1547.

(21) For reviews, see: (a) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2840. (b) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064.

(22) (a) Frederick, M. O.; Mulder, J. A.; Tracey, M. R.; Hsung, R. P.; Huang, J.; Kurtz, K. C. M.; Shen, L.; Douglas, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 2368. (b) Dunetz, J. R.; Danheiser, R. L. *Org. Lett.* **2003**, *5*, 4011. (c) Zhang, Y.; Hsung, R. P.; Tracey, M. R.; Kurtz, K. C. M.; Vera, E. L. *Org. Lett.* **2004**, *6*, 1151.

(23) Hamada, T.; Ye, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 833.

(24) Jia, W.; Jiao, N. *Org. Lett.* **2010**, *12*, 2000.

(25) Jouvin, K.; Heimburger, J.; Evano, G. *Chem. Sci.* **2012**, *3*, 756.

(26) (a) Laroche, C.; Li, J.; Freyer, M. W.; Kerwin, S. M. *J. Org. Chem.* **2008**, *73*, 6462. (b) Burley, G. A.; Davies, D. L.; Griffith, G. A.; Lee, M.; Singh, K. *J. Org. Chem.* **2010**, *75*, 980. (c) Das, B.; Reddy, G. C.; Balasubramanyam, P.; Salvanna, N. *Synthesis* **2011**, 816.

(27) Wang, M.-G.; Wu, J.; Shang, Z.-C. *Synlett* **2012**, *23*, 589.

(28) Das, B.; Salvanna, N.; Reddy, G. C.; Balasubramanyam, P. *Tetrahedron Lett.* **2011**, *52*, 6497.

(29) Ketene *N,N*-acetals related to **20** have been prepared by acylation of acetamidines. See: (a) Miescher, K.; Marxer, A.; Urech, E. *Helv. Chim. Acta* **1951**, *34*, 16. (b) Ono, M.; Tanaka, H.; Hayakawa, K.; Tamura, S. *Chem. Pharm. Bull.* **1983**, *31*, 3534.

(30) Fukudome, Y.; Naito, H.; Hata, T.; Urabe, H. *J. Am. Chem. Soc.* **2008**, *130*, 1820.

(31) Coste, A.; Couty, F.; Evano, G. *Synthesis* **2010**, 1500.

(32) Yu, W.; Jin, Z. *J. Am. Chem. Soc.* **2000**, *122*, 9840.

(33) Jones, G. O.; Liu, P.; Houk, K. N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 6205.

(34) Yu, H.-Z.; Jiang, Y.-Y.; Fu, Y.; Liu, L. *J. Am. Chem. Soc.* **2010**, *132*, 18078.

(35) For a general reference, see: Witulski, B.; Alayrac, C. In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; de Meijere, A., Ed.; Thieme: Stuttgart, 2005; Vol. *24*, pp 933−956.

(36) (a) Stang, P. J.; Surber, B. W. *J. Am. Chem. Soc.* **1985**, *107*, 1452. (b) Stang, P. J.; Surber, B. W.; Chen, Z.-C.; Roberts, K. A.; Anderson, A. G. *J. Am. Chem. Soc.* **1987**, *109*, 228. (c) Tuncay, A.; Anaclerio, B. M.; Zolodz, M. *Tetrahedron Lett.* **1999**, *40*, 599. (d) Stang, P. J.; Boehshar, M.; Lin, J. *J. Am. Chem. Soc.* **1986**, *108*, 7832. (e) Stang, P. J.; Kitamura, T.; Boehshar, M.; Wingert, H. *J. Am. Chem. Soc.* **1989**, *111*, 2225.

(37) For reviews, see: (a) Dembitsky, V. M.; Al Quntar, A. A. A.; Haj-Yehia, A.; Srebnik, M. *Mini-Rev. Org. Chem.* **2005**, *5*, 91. (b) Gaumont, A. C.; Gulea, M. In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Molander, G. A., Ed.; Thieme: Stuttgart, 2006; Vol. *33*, pp 665−694.

(38) For a Wadsworth−Horner−Emmons approach, see: (a) Teulade, M.-P.; Savignac, P.; Aboujaoude, E. E.; Liétge, S.; Collignon, N. *J. Organomet. Chem.* **1986**, *304*, 283. (b) Inoue, H.; Tsubouchi, H.; Nagaoka, Y.; Tomioka, K. *Tetrahedron* **2002**, *58*, 83. For a review on transition-metal-catalyzed preparation of vinylphosphonates, see: Maffei, M. *Curr. Org. Synth.* **2004**, *1*, 355.

(39) (a) Xu, H.; Gu, S.; Chen, W.; Li, D.; Dou, J. *J. Org. Chem.* **2011**, *76*, 2448. (b) Yamagishi, M.; Okazaki, J.; Nishigai, K.; Hata, T.; Urabe, H. *Org. Lett.* **2012**, *14*, 34.
(40) (a) Jin, H.; Yang, Y.; Kuang, C.; Yang, Q. *Synlett* **2011**, 2886. (b) Ni, Z.; Wang, S.; Mao, H.; Pan, Y. *Tetrahedron Lett.* **2012**, *53*, 3907.
(41) (a) Hirao, T.; Masunaga, T.; Ohshiro, Y.; Agawa, T. *J. Org. Chem.* **1981**, *46*, 3745. (b) Abbas, S.; Hayes, C. J.; Worden, S. *Tetrahedron Lett.* **2000**, *41*, 3215. (c) Kuang, C.; Senboku, H.; Tokuda, M. *Tetrahedron* **2002**, *58*, 1491.