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Palladium Nanoparticle-Catalyzed Stereoretentive Cross-Coupling of Alkenyl Sulfides with Grignard Reagents

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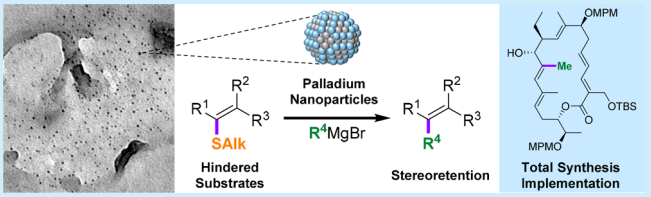
Supporting Information

ABSTRACT: Reaction conditions allowing a stereoretentive cross-coupling of alkenyl sulfides with Grignard reagents using ligand-free Pd catalysis are discussed here. The presence of an adequately positioned OH function is a key feature that allows a Mg-promoted Lewis acid activation of the mercaptide leaving group. This easy to implement procedure actually relies on an in situ generation of stable Pd nanoparticles by simply mixing $Pd_2(dba)_3$, the Grignard reagent, and the vinyl sulfide cross-coupling partner in THF. The efficiency of this procedure has been demonstrated in a natural product total synthesis context.

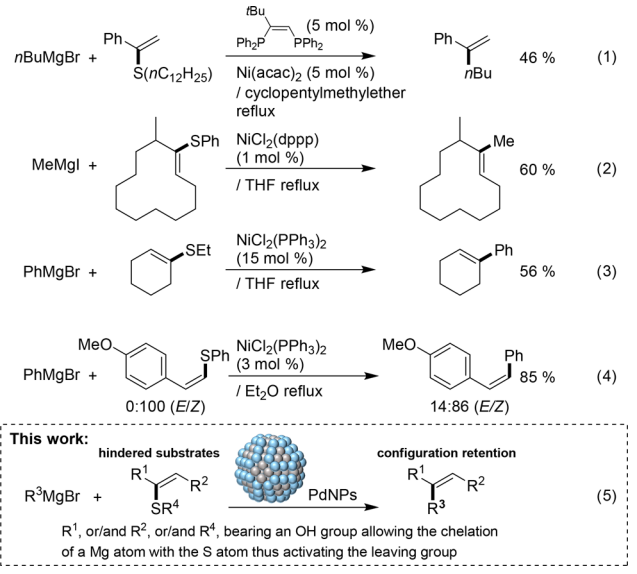


Stereodefined polysubstituted alkenes synthesis remains even today a challenge despite the ever growing number of transition-metal-catalyzed cross-coupling methods.[1] The abundance of the alkene functions in natural products[2] stimulates the demand for new selective accesses to this structural motive and offers many potential implementations. Seminal works by Kumada and Takei[3] that dealt with the cross-coupling of organosulfides with Grignard reagents have demonstrated the value of this approach to access polysubstituted alkenes.[4] Since then, many similar conditions have been described, but almost all remained in the Ni portfolio,[5] except two examples involving Fe[6] or Pd.[7]

Although vinyl sulfides are readily accessed stereoselectively and are stable compounds, their use in transition-metal-catalyzed cross-coupling reactions remains scarce compared with their vinyl halide analogues[8] and are even more rarely used in the total synthesis of natural products. This is attributable to the drawbacks inherent to the Ni-catalyzed cross-coupling of vinyl sulfides, which are a sensitivity to the steric hindrance around the mercaptide leaving group and a lack of stereoretention with some substrates of *cis* configuration. Thus, in many cases, it has been reported that nonterminal vinyl sulfides are poor substrates. Even with a simple substrate such as (1-phenylvinyl)alkylsulfane (Scheme 1, eq 1), yields remain at around 50% despite the use of specially designed Ni ligands,[5a] and obviously, intracatenary vinyl sulfides are equally mediocre cross-coupling partners (Scheme 1, eqs 2 and 3).[9] Conversely, terminal vinyl sulfides typically react in very high yields (Scheme 1, eq 4);[3b,10] however, with terminal *Z* substrates the stereoretention can be eroded.[13e] Single-electron-transfer mechanism a priori involved in Ni catalysis is likely responsible for this.

In the course of our synthesis of the aglycone of tiacumicin B,[11] a naturally occurring antibiotic drug of prime importance,

Scheme 1. Selected Examples of Ni-Catalyzed Cross-Coupling of Vinyl Sulfides



Ni catalysis failed at introducing a methyl by substituting the mercaptide group of an intracatenary (*Z*)-vinyl sulfide using MeMgBr. Our innovative strategy of synthesis was thus endangered in its whole by this failure, so to circumvent this dead end we carried out a study with vinyl sulfide **2a** (Scheme 2), a model substrate mimicking our intermediate of total synthesis. For a more atom-economical total synthesis,[12] as well as for strategic convenience, we wanted to keep free of

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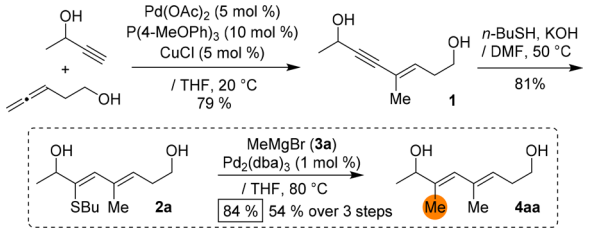
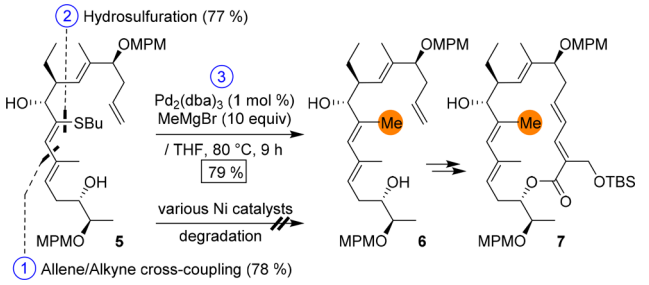
Scheme 2. Devising Conditions on Model Substrate 2a



protective groups the alcohol functions of model substrate **2a**, and this had surprisingly productive consequences. Vinyl sulfide **2a** was prepared by regio- and *trans*-selective hydrosulfuration[13] of enyne **1**, itself readily synthesized using a Pd/Cu dual-catalyzed allene/alkyne cross-coupling.[14] As anticipated, despite a large excess of MeMgBr **3a** and a loading in Ni of 10 mol %, whatever the ligand used the intracatenary hindered vinyl sulfide **2a** failed to give **4aa** in a synthetically useful yield. Inspired by a previous report,[7] we decided then to shift to Pd catalysis. Thus, the $Pd[P(t\text{-}Bu)_3]_2$ complex[15] gave a cleaner result than $NiCl_2(dppe)$, but the yield in **4aa** remained at around 35%. However, we found that using $Pd_2(dba)_3$ without phosphane ligand improved the yield up to 84% with a total stereoretention and with a loading of only 1 mol % (Scheme 2). Hence, this cross-coupling reaction gathering the prerequisites of stereoretentivity and efficacy, we included it in our synthetic strategy of the aglycone of tiacumicin B (**7**) (Scheme 3). Thus,

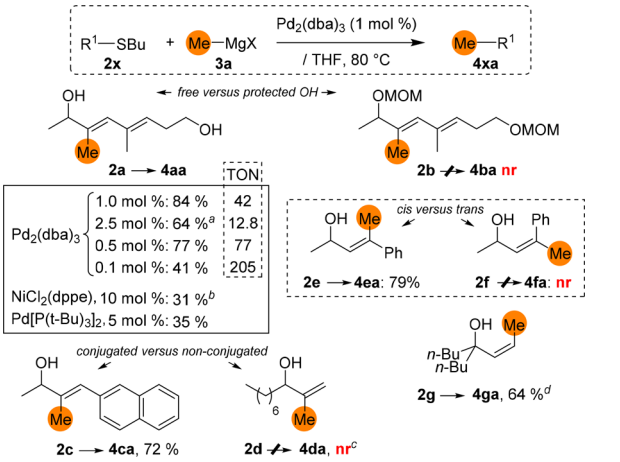
Scheme 3. New Strategy To Build Polysubstituted Dienes



we succeeded in transforming the polyfunctionalized and enantioenriched vinyl sulfide **5** into fragment **6** with a yield of 79% with no isomerization, and this enabled us to ultimately reach our target.[11] Note that although Ni catalyzed the transformation of **2a** into **4aa** with a 31% yield, it led only to the degradation of the precious vinyl sulfide **5**. Note also that this [allene−alkyne cross-coupling/selective hydrosulfuration/PdNPs-catalyzed cross-coupling with MeMgBr] sequence is a new and promising strategy of access to polysubstituted dienes, and it can be seen as an alternative to more traditional Suzuki, Negishi, or Stille-based strategies. Applied to tiacumicin B, this three-step sequence took place with an overall yield of 48% delivering a complex and enantioenriched chiral fragment, and no additional protective-group installation was needed.

This success in a natural product synthesis is a testimony to the usefulness and the relevance of this synthetic pathway, and it encouraged us to further explore the scope and the limitations of this cross-coupling method. First, we centered the study on MeMgBr (Scheme 4). As already mentioned, **4aa** was obtained in 84% yield from **2a** with 1 mol % of $Pd_2(dba)_3$, but a loading of 2.5 mol % led to the formation of byproducts and a lower yield (64%), while a loading of 0.5 mol % yielded

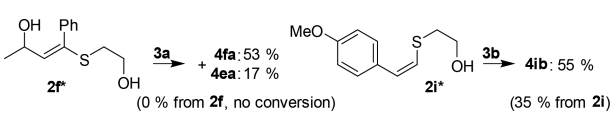
Scheme 4. Exploration of the Scope with MeMgBr



[a]Completed within 2 h, byproducts are formed. [b]$NiCl_2(dppe)$ (10 mol %), MeMgBr (10 equiv)/THF, 120 °C, 4 h. [c]The leaving group is −SEt instead of −SBu. [d]The leaving group is $-SC_8H_{17}$ instead of −SBu.

4aa in 77%. Remarkably, with 0.1 mol % of $Pd_2(dba)_3$ the cross-coupling still took place (**4aa**: 41%), even though 28% of **2a** was recovered after 55 h of reaction. The reaction was also performed with a series of analogues of **2a** the mercaptide leaving groups of which being $-SC_8H_{17}$, $-SC_{12}H_{25}$, or $-SC_{18}H_{37}$, but with no impact. Much more interesting was the behavior of **2b**, the MOM-protected version of **2a**, which remained inert, thus revealing the importance of having a vicinal free OH group. As expected, naphthyl derivative **2c** gave **4ca** in 72% yield, while nonconjugated vinyl sulfide **2d** remained unreactive. Although in *Z* vinyl sulfide **2e** the distance between the OH and the SBu groups has been lengthened by one notch compared to **2a**, trisubstituted alkene **4ea**[16] could still be obtained stereoretentively in only 2 h of reaction. Similarly, the coupling of *Z* vinyl sulfide **2g** gave product **4ga**, while in contrast, **2f**, the *E* isomer of **2e**, remained inert. These observations suggested that the reactivity of sulfides **2a**, **2c**, **2e**, and **2g** could result from the chelation of a magnesium atom between the alcoholate and the proximal sulfur atom, while such chelation is impossible with unreactive **2b** (MOM-protected) and **2f** (*trans* configuration). Therefore, this chelation seems to activate the C−S bond, probably favoring the Pd^0 oxidative insertion. Indeed, theoretical calculations we carried out on models predicted that the Mg/S interaction actually lowers the C−S bond dissociation energy by ca. 31 $kcal.mol^{-1}$.[17] These led us to imagine that the inertness of **2f** could possibly be circumvented by replacing the −SBu by a "self-chelating" mercaptide leaving group such as $-S(CH_2)_2OH$. This hypothesis was confirmed as **2f*** was transformed into **4fa**[16] (Scheme 5), although stereoretention was slightly eroded. However, there is no such loss of stereoretention with **2i***, which in addition provided **4ib** with a yield now improved to 55%. Csp^2 Grignards were also

Scheme 5. Using $-S(CH_2)_2OH$ a Self-Chelating Mercaptide Leaving Group, Instead of −SBu



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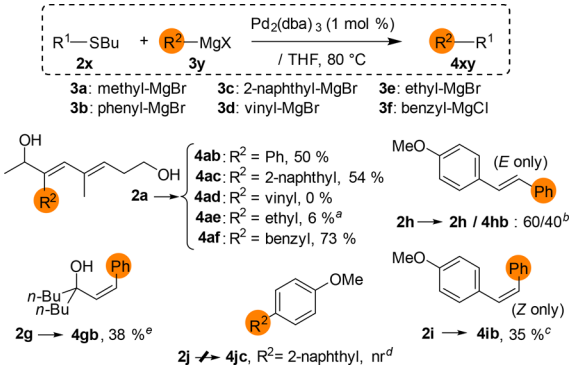
evaluated (Scheme 6): thus, *Z* vinyl sulfides **2i** reacted with phenylmagnesium bromide **3b** to give known **4ib**[18] in only 35%

Scheme 6. Exploration of the Scope with Other Grignard Reagents



[a](3*E*,5*E*)-4-Methylocta-3,5-diene-1,7-diol **8** was isolated in 32% yield. [b]Not separable from starting material **2h**; ratio evaluated by ^{1}H NMR; no other products are formed. [c]49% of the starting material **2i** was recovered. [d]The leaving group is SMe instead of SBu. [e]The leaving group is $-SC_8H_{17}$ instead of $-$SBu.

yield but with full stereoretention.[19] In contrast, the same transformation catalyzed by Ni yielded a 14:86 *E*/*Z* mixture (Scheme 1, eq 4).[10] (*E*)-Vinyl sulfide **2h** also reacted stereoretentively with PhMgBr **3b**.[19] Vinyl sulfide **2a** reacted with PhMgBr **3b** or with 2-naphthylmagnesium bromide **3c** to give **4ab** (50%) and **4ac** (54%), respectively. However, vinylmagnesium bromide **3d** led to degradation, and aromatic sulfides **2j** remained inert under our reaction conditions. Other types of Csp^3 Grignard reagents were tested on vinyl sulfide **2a** (Scheme 6). Thus, EtMgBr **3e** led to the desired diene **4ae** in only 6% yield, desulfurated diene **8** being the main product. The isolation of the latter suggests that *β*-hydride elimination on a [Pd]−Et species gave reactive hydridopalladium. This hypothesis was verified by using a Csp^3 nucleophile bearing no *β*-eliminable H such as benzylmagnesium chloride **3f**, which led to the efficient formation of **4af** (73%) with no trace of **8**.

These reaction conditions being ligand-free, we came to suspect that palladium nanoparticles (PdNPs) could form and therefore be the catalyst in this reaction. To gain some insights into this hypothesis, we submitted a sample of our reaction medium (**2a** → **4aa**) to transmission electron microscopy (TEM), which revealed the presence of a multitude of particles strongly diffracting the electrons (Figure 1). The diameter

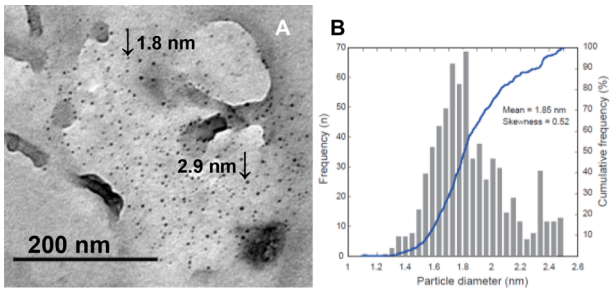
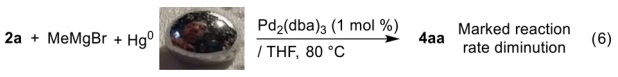


Figure 1. TEM image of a sample of our reaction medium. (A) TEM image of a sample of monodispersed PdNPs formed during the reaction **2a** + **3a** → **4aa** (1 mol % of $Pd_2(dba)_3$). (B) PdNP diameter distribution.

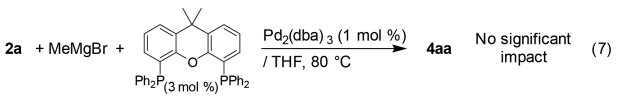
distribution of these NPs ranges mainly from 1.5 to 2.0 nm with a mean of 1.85 nm for the main population (skewness = 0.52), which is rather classical for catalytically active PdNPs.[29b,30] The PdNPs formed under these conditions being stable, this raised the question of the nature of the stabilizer because unless stabilized by quaternary ammonium salt,[29b,20] polymers[27,21] or heteroatom-containing ligands,[22] PdNPs are thermodynamically unstable with respect to agglomeration and tend to form clusters with lower or even no catalytic activity.[23] Platinum-group metals have a strong affinity for soft sulfur-based donors, which makes S-containing molecules highly efficient NPs stabilizers.[22] Thus, PdNPs can be efficiently stabilized by sulfur-doped graphene[24] or by thiol-treated silica that allows Heck and Suzuki reactions to take place.[25] Simple lipophilic *n*-alkanethiols have been used to prepare "alkanethiol-protected" PdNPs; however, their catalytic properties were not studied.[26] Therefore, in our case, the BuS moiety being a reaction product, it is reasonable to think that it also plays this key role of PdNP stabilizer. The exact nature of the Pd-active species in PdNP-catalyzed cross-couplings has given rise to intense debates,[27] but now it is unequivocally established that PdNPs can be highly active catalytic entities.[28] Research in this field is gaining in intensity. Thus, the role of PdNPs in the Heck reaction (Jeffery conditions)[29] or in ligand-free Suzuki−Miyaura cross-couplings have been thoroughly studied, and in 2017, Feringa and co-workers[30] demonstrated that their ultrafast cross-coupling of aryllithium with halogenated Csp^2 electrophiles is in fact catalyzed by PdNPs. Therefore, it has appeared particularly important to verify if our cross-coupling belongs or not to the family of the PdNP-catalyzed transformations because if yes it would mean that the Kumada−Corriu reaction also belongs to the PdNP portfolio. Test experiments were carried out to prove it:

Experiment A (eq 6): Mercury (Hg^0) is a selective poison for surface chemical processes,[31] and addition of Hg^0 to PdNPs led



to encapsulated by a monolayer of Hg atoms.[28] Some Hg^0 drops were thus added in the reaction medium at t = 1 h (TLC indicating 40% of conversion of **2a** into **4aa**), and at t = 68 h we saw that the reaction was blocked, ca. 20% of starting material remaining nonconverted, while this reaction normally reaches completion in 10−15 h. This marked reaction rate diminution suggests that the catalytic activity could be exclusively due to PdNPs and not to soluble Pd species.

Experiment B (eq 7): Rigid large-bite-angle bisphosphines[32] are known to strongly slow down the speed of the reductive



elimination step, impacting negatively the catalytic cycle in homogeneous Pd-catalyzed reactions and putting two large-bite-angle bisphosphines on a Pd atom just impair all reaction. Thus, at t = 1 h, we added 1.5 molecules of Xantphos[33] per atom of Pd so there was considerably more Xantphos than possibly remaining dissolved Pd. At t = 1 h, TLC indicated 40% of conversion of **2a** into **4aa**, and at t = 18 h the reaction reached completion. This nondiminished transformation rate

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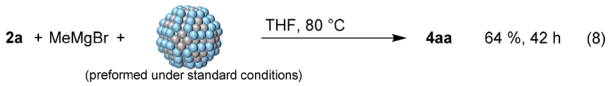
suggests that dissolved Pd is not the catalytically active species of this reaction.

Experiment C (eq 8): PdNPs were prepared as described in the literature from $Pd(NO_3)_2$ and $Bu_4N(OAc)$[20] and used as



catalyst instead of $Pd_2(dba)_3$ under our standard conditions with the same overall amount of Pd, which allowed us to transform **2a** into **4aa** in 64% yield after 42 h of reaction. This demonstrates that this reaction can be catalyzed by traditionally formed PdNPs; however, we may notice that our reaction conditions, which feature an in situ formation of the PdNPs, are more efficient (80% in 10−15 h). The results of experiments A, B, and C, together with the fact that PdNPs are visible by TEM, constitute a corpus of evidence showing that this cross-coupling likely takes place at the surface of PdNPs.

We have devised reaction conditions allowing the PdNP-catalyzed stereoretentive cross-coupling of vinyl sulfides with Grignard reagents. High stereoretention, even with Z substrates, and good yields with hindered vinyl sulfide are observed, while this is usually not the case with Ni catalysis. These active and stable palladium nanoparticles are obtained in situ through an operationally simple and robust procedure. This reaction involves an interesting activation of the mercaptide leaving group by chelation and therefore tolerates protective group free OH. More efficient at transferring a methyl group from MeMgBr, this reaction gives a new valuable access to structural motive abundantly present in natural products and pharmaceutical drugs, and our own total synthesis of the aglycon of tiacumicin B is the first testimony of the usefulness and the relevance of this upgraded synthetic pathway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00208.

Experimental procedures and analytical data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(17) See the Supporting Information, Figure 2.

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