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Mini account

Development of Pd–Cu catalyzed cross-coupling of terminal acetylenes with sp^2-carbon halides

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Abstract

The Pd-catalyzed cross coupling reactions between sp^2-C halides and terminal acetylenes have been independently reported by Heck, Cassar and us in 1975. The former two methods have been developed as an extension of the Heck reaction to an acetylenic CH-bond. Ours has been discovered on the base of combination of Pd-catalyzed cross-coupling of sp^2-C halides with terminal acetylenes and Cu-catalyzed alkynylation of metal complexes developed by us in the course of systematic studies on transition metal acetylide chemistry. The coupling reactions have been used extensively as a reliable method for the synthesis of eneyne-based acetylenic materials. Some recent advances of the coupling are also described. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Cross-coupling; Heck reaction; Stephens–Castro reaction; Pd–Cu catalyst; Terminal acetylene; sp^2-C halide

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1. Introduction

Two types of metal-catalyzed cross-coupling reactions of sp^2-C to sp-C atoms are available for the synthesis of conjugated acetylenes: coupling of unsaturated organic halides with terminal acetylenes (Sonogashira–Hagihara coupling) and coupling of the halides with the alkynylmetal reagents such as Still coupling for $M = Sn$, Suzuki coupling for $M = B$, Negishi coupling for $M = AlR_2$, and ZnX, and Kumada–Tamao–Corriu coupling for $M = MgX$ (Scheme 1). These are complementarily used in the synthesis of conjugated acetylenes.

The Pd–Cu catalyzed cross-coupling reaction of terminal acetylenes with sp^2-C halides provides a useful method for synthesizing conjugated acetylenic compounds, an important class of molecules that have found application in diverse areas ranging from natural products and pharmaceuticals to molecular organic materials in nanomaterials. This mini-account reports briefly historical circumstances for development of the Pd–Cu catalyzed cross-coupling reactions and recent progress in this area.

2. Historical note

The Pd-catalyzed cross-coupling reactions between sp^2-C halides **1** and terminal acetylenes **2** have been independently reported by three groups in 1975 [1–3] as shown in Scheme 2. The former two methods [1,2] have been reported as an extension of Heck reaction to terminal acetylenes. On the other hand, the latter has been developed on the basis of combining a copper catalyzed alkynylation of Pd complexes (cycle B and B′) and a Pd-catalyzed cross-coupling of sp^2-C halides with terminal acetylenes (cycle A) as shown in Scheme 3 [3,4], which can be considered as an application of Pd-catalysts to Stephens–Castro reaction (Scheme 4) [5].

The Cu-catalyzed alkynylation of metal halides [6] has been developed in the course of our systematic studies on transition metal acetylide chemistry [7]. Thus, by this new method, the first soluble high molecular weight Pt-butadiyne-polymer **11** has been synthesized successfully by using a CuI-catalyst in the polycondensation between trans-dichloroplatinum complex **9** and *trans*-bis-butadiynylplatinum complex **10** as shown in Scheme 5 [8].

The second successful example of an application of the Cu-catalyzed alkynylation of metal halides is the

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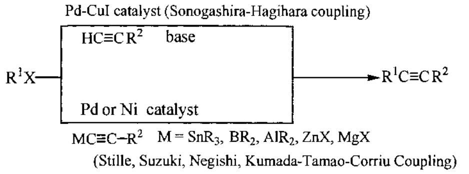
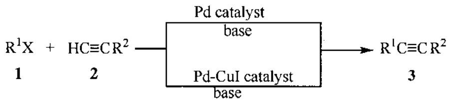
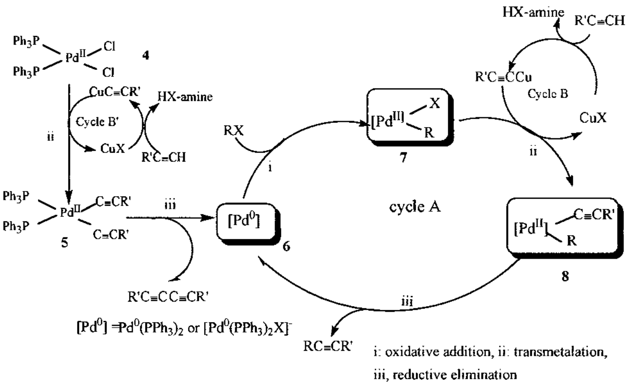
development of the Pd–Cu catalyzed cross-coupling reactions of sp^2-C halides with terminal acetylenes under mild conditions (Scheme 6). The early standard protocol is a reliable method for the synthesis of conjugated acetylenes by the Pd–Cu catalyzed coupling of vinyl halides, aryl iodides, bromides or triflates with terminal acetylenes. However, it requires careful choice of substrates and skillful tailoring of reaction conditions to synthesize structurally complex molecules. A handicap is the restriction of coupling substrates under mild conditions to alkenyl halides, and aryl iodides. Nevertheless, this method is suffering not only from the need for large amounts of a catalyst (3–5 mol% Pd and 3–10 mol% CuI) but also from the need of higher temperatures, causing side reaction of terminal acetylenes. The side reactions were often observed in the reaction with less reactive aryl bromides [3,9].



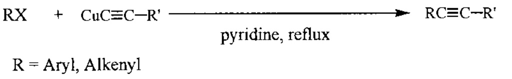
Scheme 1. Metal-catalyzed cross-coupling reactions of sp^2-C to sp-C atoms for syntheses of conjugated acetylenes.



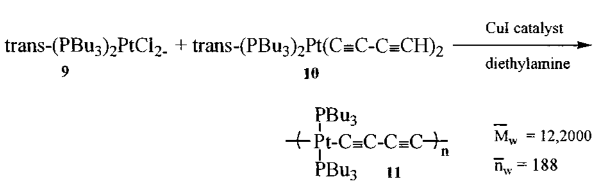
Scheme 2. Pd-catalyzed cross-coupling reactions of sp^2-C halides with terminal acetylenes.



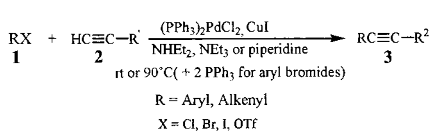
Scheme 3. Outline of the reaction scheme for Pd–Cu catalyzed cross-coupling of sp^2-C halides with terminal acetylenes.



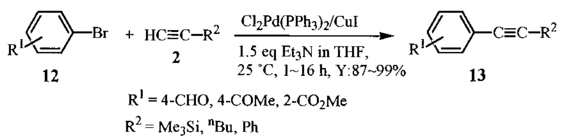
Scheme 4. Stephens–Castro reaction.



Scheme 5. Synthesis of Pt-polyyne polymer by Cu-catalyzed alkynylation of *trans*-Pt-dichlorides with *trans*-Pt-bisbutadiynyl complexes.



Scheme 6. Standard conditions for the Pd–Cu catalyzed cross-coupling of sp^2-C halides with terminal acetylenes.



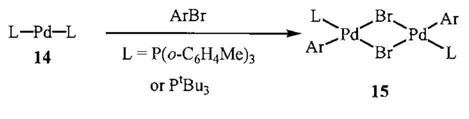
Scheme 7. Formation of dinuclear species by oxidative addition of aryl bromides.

As shown Scheme 3, this protocol is based on the discovery of CuI-catalyzed transmetalation in amine [6] and is constructed by a combination of three catalytic cycles A, B and B′. Although the reaction certainly follows the normal oxidative addition–reductive elimination process common to the Pd-catalyzed C–C bond-forming reactions, the exact mechanism for the reaction is not known. In particular, the structure of the catalytically active species and the role of the CuI catalyst remain obscure. The process may be considered to involve Pd^0 species $[Pd^0]$ **6**, neutral $Pd^0(PPh_3)_2$ [3] or anionic $[Pd^0(PPh_3)_2X]^-$ [4], which is generated from the Pd(II) pre-catalyst **4** and gives the Pd(II) intermediate **7** by the oxidative addition of the sp^2-C halide. Subsequent reaction with a terminal acetylene, possibly via a transient copper acetylide species (Cycle B), leads to the alkynylpalladium(II) derivatives **8** which proceeds to give the required coupled products and to regenerate the active Pd species **6**. There is no evidence for the acceleration of reductive elimination step by Cu(I) (step (iii), from **8** to **6**), although some destabilization of *cis*-alkenylacetylide **8** via a coordination of Cu(I) to the acetylide ligand is expected.

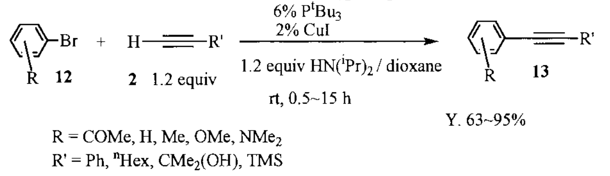
Aryl bromides **12** carrying an *ortho* or *para* electron-withdrawing group will more readily undergo oxidative addition to give coupled acetylenes **13** in Et_3N–THF at room temperature. The reaction does proceed without the copper co-catalyst but only under more forcing conditions and not with less active substrates such as aryl bromides and chlorides (Scheme 7) [10].

As a palladium source, $(PPh_3)_2PdCl_2$ in amines is used commonly, where a catalytically active, coordinatively unsaturated complex **6** is produced by reductive elimination of Pd-acetylide complex **5** generated from $(PPh_3)_2PdCl_2$ (**4**) and a terminal acetylene (Scheme 3). In many cases, $Pd(OAc)_2$ or $(CH_3CN)_2PdCl_2$, and two equivalents of a tertiary phosphine, L, and a terminal acetylene are used to reduce the Pd(II) complexes in situ to the catalytically active complexes **6**. The consumption of the terminal acetylene to generate the active species is unsuitable for the polymer synthesis by the cross-coupling methodology. $Pd^0(PPh_3)_4$, which generates active catalytic species, $Pd^0(PPh_3)_2$, after the endergonic loss of excess triphenylphosphine is also useful. However, $Pd^0(PPh_3)_2$ is often present only at a trace level, with the consequence of low catalytic activity for the active organic halides under milder reaction conditions. Contradictorily, the addition of extra two molar amounts of PPh_3 is required for the coupling of less reactive aryl bromides at a higher temperature to prevent the decomposition of active species, liberating colloidal metal. $Pd_2^0(dba)_3$ in the presence of phosphine ligands, L, is also a useful Pd^0 source, where dba should be easily removed to afford the active species, PdL_2, in nearly stoichiometric amounts. In contrast with $Pd^0(PPh_3)_4$, $Pd_2^0(dba)_3$ is insensitive to oxygen. Accordingly, any special care for its storage and manipulation is not needed.

Now, one can predict the mechanism for the cross-coupling to produce conjugated eneyne compounds catalyzed by palladium complexes containing both monodentate and chelating ligands. The catalytic cycles differ in the coordination number of the palladium complexes involved and factors that control the coupling reactions with organic halides. It has been shown that the catalytic cycle for the cross-coupling reaction of alkynes with sp^2-C halides catalyzed by palladium complexes with $P(o\text{-}C_6H_4Me)_3$ ligands exclusively contains mono-phosphine intermediates, Pd^0L. The active catalyst, Pd^0L_2, is added oxidatively by aryl halides to give dimeric aryl halide complexes **15** (Scheme 8) [11], In contrast, the chemistry catalyzed by palladium complexes with dppf or BINAP ligands involves bisphosphine complexes as a result of ligand chelation and the fact that reductive elimination can occur without ligand dissociation. One can suppose an ionic type complex as a reactive intermediate in this case.



Scheme 8. Pd-catalyzed cross-coupling of activated aryl bromides in mild conditions.



Scheme 9. An efficient catalyst for room temperature cross-coupling of aryl bromides.

3. Recent advances and future problems

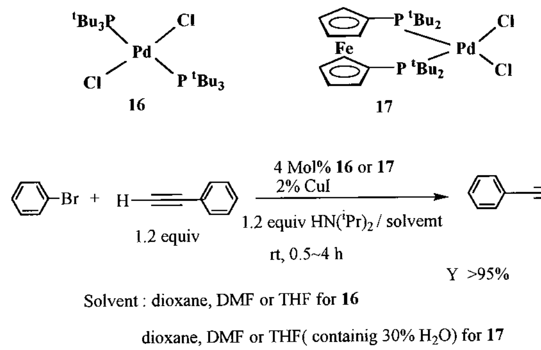
Until comparatively lately, there had remained three problems awaiting improvement of Pd-catalyzed cross-coupling of sp^2-C halides with terminal acetylenes. These are (i) suppression of the side reactions for terminal acetylenes at higher temperature, (ii) development of a catalyst for the coupling with aryl chlorides and (iii) improvement of TON (turn over numbers) for a catalyst.

In the last decade, there have been tremendous developments in Pd-catalyzed coupling systems for Heck type reactions. Above three problems have been partially solved by new methodologies. Consequently, there was great interest in the development of coupling substrates that are both more economical and preparatively more easily accessible, and reactive even at lower reaction temperature.

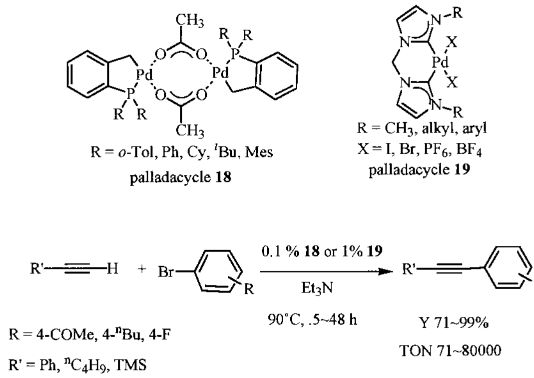
Recently, a room temperature Pd-catalyzed reaction for less reactive aryl bromides was developed: aryl bromide **12** coupled with an equimolar amount of terminal acetylenes **2** at room temperature in quantitative yield. The reaction proceeds in $^i\mathrm{Pr}_2\mathrm{NH}$–dioxane in the presence of $(PhCN)_2PdCl_2$(3%) CuI(2%), and $^t\mathrm{Bu}_3\mathrm{P}$(6%) within 0.5–15 h (Scheme 9) [12]. While other phosphine such as PPh_3, $P(o\text{-tolyl})_3$, dppf or PCy_3 is not effective, $^t\mathrm{Bu}_3\mathrm{P}$ is uniquely effective. This effect can be explained by the acceleration of the oxidative addition step (iii) in Scheme 3 through coordination of such a bulky electron-rich phosphine to the palladium center.

From the standpoint of the storage, the manipulation and the activity of the catalyst, air stable complex, *trans*-$(^t\mathrm{Bu}_3\mathrm{P})_2\mathrm{PtCl}_2$ (**16**), is recommendable more than $(PhCN)_2PdCl_2$–$2{}^t\mathrm{Bu}_3\mathrm{P}$ because of air-instability of free $^t\mathrm{Bu}_3\mathrm{P}$ ligands. Furthermore, the Pd-complex **17** coordinated by an electron rich chelate diphosphine ligand is also effective to the room temperature cross-coupling of phenyl bromide in a wet organic solvent (Scheme 10) [13].

Another successful approach towards a long lived catalyst involves the use of thermally stable palladacycles **18** and **19** as catalyst precursors. For the coupling of activated, electron-poor aryl bromides like 4-bromoacetophenone with phenylacetylene palladacycle catalyst **16** gives high TON of up to 8000 (mol product per mol Pd) in the absence of CuI at 90 °C. Only the reaction in Et_3N as the solvent and base gives satisfactory results. The addition of a co-solvent or co-base



Scheme 10. Palladium complex catalysts for room temperature cross-coupling.



Scheme 11. Utilization of Herrmann complexes for cross-coupling.

slows down the reaction dramatically. This effect is explained by a sensitive association–dissociation equilibrium at active intermediates and the almost quantitative precipitation of Et_3NHBr formed during the reaction (Scheme 11) [14]. The palladacycle catalysts constitute only a thermally stable reservoir for the active species. Being easy to activate aryl iodides and triflates, the in situ systems are good enough to obtain high yields of coupling products. For the coupling of bulky substrates or chlorides, both requiring high reaction temperatures, palladacycle systems should be the catalyst of choice.

4. Conclusions

This mini-account has highlighted the hystorical circumstances in development of Pd–Cu-catalysts based on the Pd-acetylide chemistry. Although the Pd–Cu-catalyzed cross-coupling of terminal acetylenes with sp^2-C halides is a broadly useful method for conjugated acetylenes, the search for the more reactive and long-living catalysts effective especially for aryl chlorides, remains yet to be a challenge for future research.

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