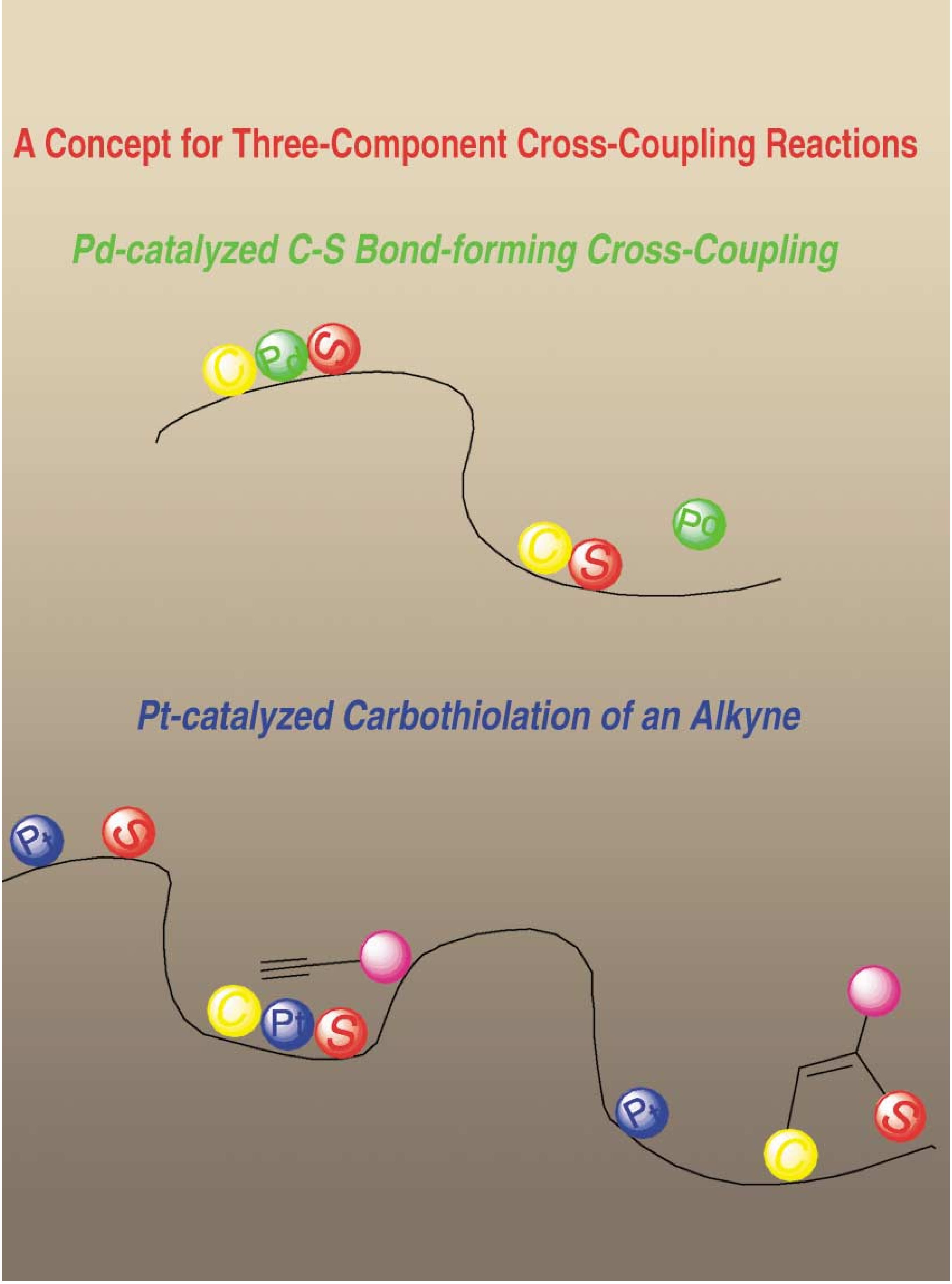

A Concept for Three-Component Cross-Coupling Reactions
Pd-catalyzed C-S Bond-forming Cross-Coupling
C
Pd
S
C
S
Pd
Pt-catalyzed Carbothiolation of an Alkyne
Pt
S
C
Pt
S
Pt
S
C

Transition-Metal-Catalyzed Carbon–Heteroatom Three-Component Cross-Coupling Reactions: A New Concept for Carbothiolation of Alkynes

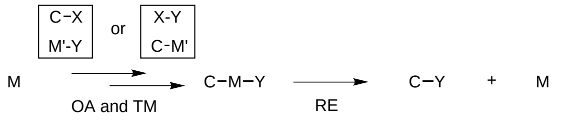
Hitoshi Kuniyasu* and Hideo Kurosawa[a]

Abstract: The deep-seated understanding of flexible ligand behavior of thiolate on transition-metals has paved the way to achieve metal-catalyzed carbothiolations of terminal alkynes. The strategy of the reaction is quite simple: 1) generation of the complex with C–Pt–S fragments formed after the Pd-catalyzed C–S bond-forming cross-coupling reaction, 2) insertion of an alkyne into Pt–S bond to form the complex with a C–Pt–C fragment, and 3) C–C bond-forming reductive elimination.

Keywords: alkynes · carbothiolation · cross-coupling · platinum · vinylsulfide

Introduction

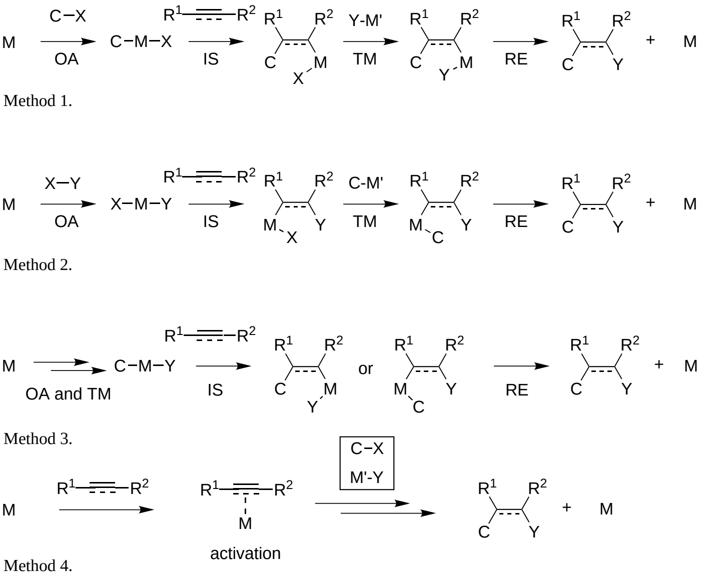
Since the advent of nickel-catalyzed reactions of Grignard reagents with aryl or alkenyl halides, a wide variety of metal-catalyzed C–C bond-forming cross-coupling reactions have been developed.[1] Furthermore, recent research interest has extended to the effective carbon and heteroatom bond-forming cross-coupling reactions (CHC), such as C–N[2] and C–O[3] (represented by C–Y) bond formation. Among the transition metals studied so far Pd complexes have been proved to be the best catalysts in most cases. The reaction routes can be generally explained by the oxidative addition (OA) of C–X (C: carbon functionality, X: halogen or pseudohalogen) to a zero-valent transition metal (M) to afford a complex with a C–M–X fragment; this is followed by transmetallation (TM) with M′–Y (Y: heteroatom functionality) to generate a complex with a C–M–Y fragment, and subsequent C–Y bond-forming reductive elimination (RE). In principle, the oxidative addition of X–Y to M^0 to furnish complexes with X–M–Y fragments followed by transmetallation with C–M′ is also possible for the formation of a C–M–Y intermediate (Scheme 1).



C: carbon functional group X: halogen or pseudohalogen
Y: heteroatom functional group

Scheme 1. Possible routes for transition-metal-catalyzed C–Y bond-forming cross-coupling reactions (CHC).

When thinking about conversion of transition-metal-catalyzed CHC into the three-component cross-coupling reaction (TCC), which is defined here as the coupling of a carbon functionality (C), C–C unsaturated molecule, and heteroatom functionality (Y), four reaction routes can be conceivable depending on the timing of the reaction of the unsaturated molecule (Scheme 2).[4, 5] The insertion (IS) into a C–C



Scheme 2. Possible reaction routes for three-component coupling reactions (TCC).

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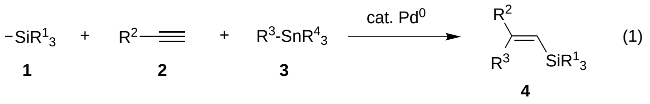
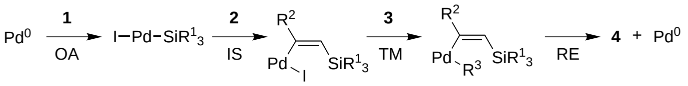
unsaturated molecule can take place right after the oxidative addition of C–X (Method 1) or X–Y (Method 2) bond to M and the following transmetallation and reductive elimination may close the catalytic cycles to afford the desired TCC products. The insertion may be achieved into either C–M or M–Y bond of the C–M–Y intermediate and the following $^{\mathrm{vinyl}}$C–Y or $^{\mathrm{vinyl}}$C–C bond-forming reductive elimination can also yield the TCC products (Method 3). The C–C unsaturated molecule may react with M first and subsequent reaction with C–X and M′–Y can produce the desired TCC products (Method 4).[6] Actually, some significant examples in accordance with these strategies as well as reactions classified as applications of these have been already reported.

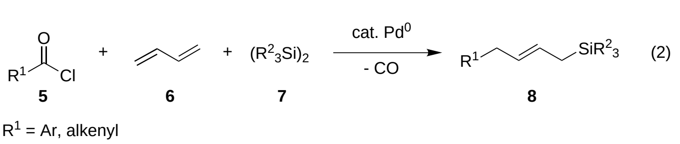
In 1991, Chatani and Murai et al. have the alkyne carbosilylation reaction, that is, the simultaneous introduction of carbon and silicon functionalities by using $\mathrm{I{-}SiR^1_3}$ (**1**), alkyne (**2**), and $\mathrm{R^3{-}SnR^4_3}$ (**3**)[7a] (or $\mathrm{R^3_2Zn}$[7b]), which can be considered as a Method 2-type reaction [Eq. (1)]. The proposed reaction path is illustrated in Scheme 3; this involves the oxidative addition of **1** to Pd^0, insertion of **2** into the Pd–SiR^1 bond, transmetallation with **3**, and subsequent C–C bond-forming reductive elimination to give **4** and Pd^0.



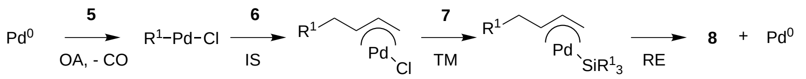


Scheme 3. Proposed mechanism of carbosilylation categorized as Method 2.

In 1993, Obora and Tsuji et al. have also disclosed the Pd-catalyzed carbosilylation of 1,3-diene using R^{1}C(O)-Cl (**5**) (R^1 = Ar or vinyl), 1,3-diene (**6**), and $\mathrm{(R^2_3Si)_2}$ (**7**) to produce **8**; this reaction falls into the category of Method 1 [Eq. (2)].[8]

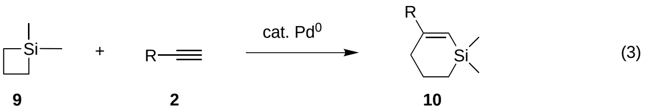


The proposed reaction mechanism shown in Scheme 4 starts with the oxidative addition of **5** to Pd^0 followed by decarbonylation, insertion of **6** into R^1–Pd bond, transmetallation with **7**, and finally C–Si bond-forming reductive elimination to give **8** and Pd^0. Employing phosphine-free palladium complexes is crucial to achieve the reaction.

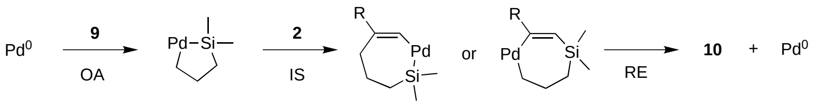


Scheme 4. Proposed mechanism of carbosilylation categorized as Method 1.

The oxidative addition of C–Si and C–Sn bonds to M to generate complexes with C–M–Si and C–M–Sn fragments have also been exploited for TCC; this can be explained as the application of Method 3 in Scheme 2. In 1977, Sakurai et al. demonstrated the carbosilylation of alkyne **2** using strained silane **9** to afford **10** [Eq. (3)].[9]

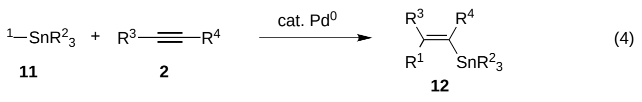


The reaction proceeds through the oxidative addition of C–Si bond of **9** to Pd^0 giving the complex with C–Pd–Si fragment, insertion of **2** into either C–Pd or Pd–Si bond, and finally reductive elimination to afford **10** and Pd^0 (Scheme 5).

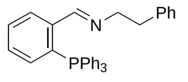


Scheme 5. Possible mechanism of carbosilylation categorized as an application of Method 3.

In 1998, Shirakawa and Hiyama et al. reported very practical Pd-catalyzed carbostannylation of alkyne **2** using alkynylstannane **11** to produce the vinylstannane **12**, which can serve as the reagent of Migita–Stille cross-coupling reaction [Eq. (4)].[10]



They demonstrated that the oxidative addition of C–Sn bond of **11** to Pd^0, coordinated by iminophosphine **13**, triggered the reaction[10b] and proposed that subsequent insertion of **2** into the R^1–Pd bond followed by reductive elimination provided **12** and Pd^0 (Scheme 6).



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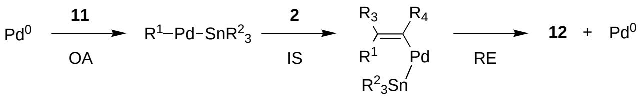
By using the Ni^0 complex allyl- and acylstannylations were also realized.[10c]



Scheme 6. Proposed mechanism of carbostannylation categorized as an application of Method 3.

The present carbostannylation is quite versatile and the reactions are also successfully achieved by using allene,[11] 1,3-diene,[12] benzyne,[13] and enone.[14] In 1996, Miura et al. reported the Rh-catalyzed carbochlorination of alkyne **2** [Eq. (5)].[15] The proposed reaction mechanism involves the oxidative addition of **5** to Rh$^{\mathrm{I}}$ followed by decarbonylation, insertion of **2** into Rh–Cl bond, and reductive elimination to furnish **14** and Rh$^{\mathrm{I}}$ (Scheme 7).

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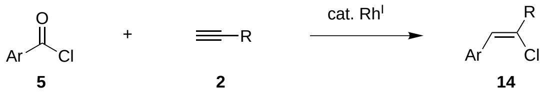

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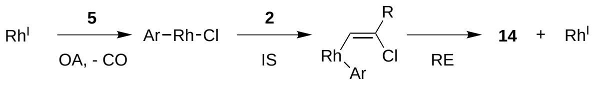
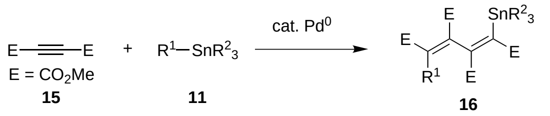


Scheme 7. Proposed mechanism of carbochlorination.

The TCC reaction, classified as a modified Method 4, was also reported in 1999 [Eq. (6)].[16] The palladium-catalyzed reaction of electron-deficient alkynes, such as dimethyl acetylenedicarboxylate (DMAD; **15**), with electron-rich stannane **11** successfully provided the dimerization–carbostannylation product **16**. It was demonstrated that Pd^0 reacted with **15** to form the palladacycle,[6] which then reacted with **11** to furnish **16** and Pd^0 (Scheme 8). The use of a diimine ligand such as **17** was critical to achieve the transformation.



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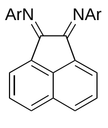

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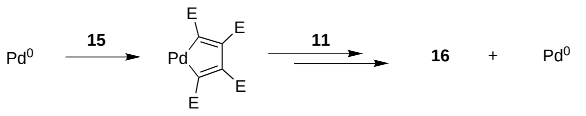
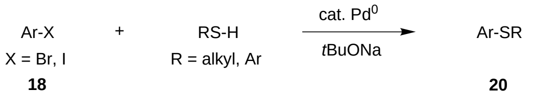


Scheme 8. Proposed mechanism of carbostannylation categorized as Method 4.

So far, we have looked over the progress of TCC reactions in the case of $Y = SiR_3$, SnR_3, and Cl. Independently, we have found the carbothiolation of alkyne can be categorized as a Method 3 reaction in Scheme 2 based on the information about the contrasting ligand behavior of thiolate on Pd- and Pt-complexes.[17]

The C–S Bond-Forming Cross-Coupling Reactions

In 1978, Kosugi and Migita et al. reported the Pd-catalyzed reaction of Ar–X (**18**, X = Br, I) with Na–SR (**19**, R = alkyl, Ar), generated from RS–H and *t*BuONa, to afford Ar–SR (**20**) [Eq. (7)].[18] A possible reaction path is illustrated in Scheme 9, which includes oxidative addition of **18** to Pd^0, transmetallation with **19**, and subsequent C–S bond-forming reductive elimination to yield **20** and Pd^0. Initiated by this report, a significant number of Pd- or Ni-catalyzed reactions which end in with C–S bond formation through reductive elimination have been published. Recently, these works were surveyed in reviews[19] and the mechanism of C–S bond-forming reductive elimination from Pd^{II} was examined in detail.[20] Among the Pd-catalyzed reactions, two typical examples were shown in Equations (8) and (9). In 1987, Osakada and Yamamoto et al. reported the Pd-catalyzed decarbonylation of R^{1}C(O)–SR^2 (**21**) to afford R^1–SR^2 (**20'**), which was produced by oxidative addition of **21** to Pd^0, decarbonylation, and C–S bond-forming reductive elimination.[21] The Pd-catalyzed addition of ArS–SAr **22** to alkyne **2** yielded **23** [Eq. (9)].[22] The proposed reaction mechanism shown in Scheme 10 starts with the oxidative addition of **22** to Pd^0, followed by *cis*-insertion of **2** into the Pd–S bond, with Pd bound at the terminal carbon to furnish the vinylpalladium **24**,[23] and reductive elimination of **23** with regeneration of Pd^0.



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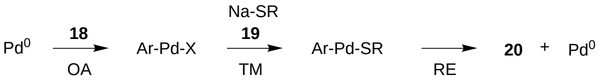
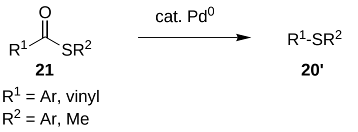


Scheme 9. Proposed mechanism of C–S bond-forming CHC.



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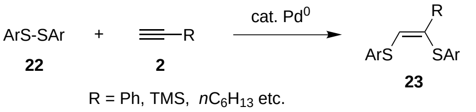

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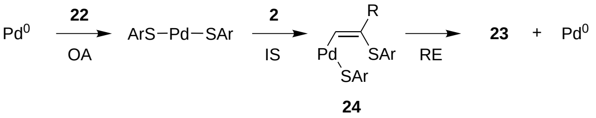
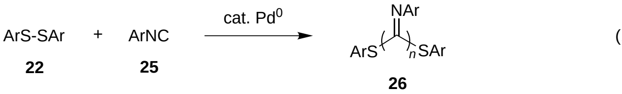


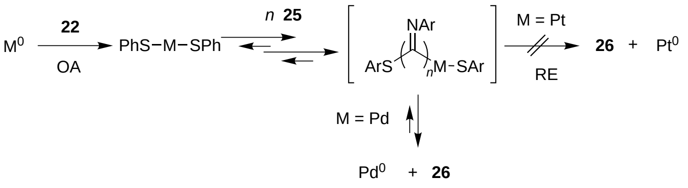
Scheme 10. Proposed mechanism of addition of disulfide.

Conversion into Three-Component Cross-Coupling Reactions

In 1997, we reported the Pd-catalyzed addition of ArS–SAr **22** to isocyanide **25** to give ArS(C=NAr)$_n$(SAr) **26** [Eq. (10)].[23] When a similar reaction was carried out using Pt^0 instead of Pd^0, some unidentified polymeric products were produced. The results of mechanistic study indicated that after the oxidative addition of **22** to M (Pd^0, Pt^0), insertion of **25** into the S–M bonds was reversible in both metal complexes (Scheme 11).

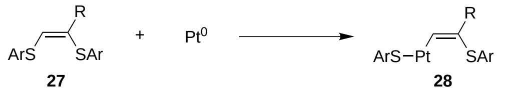


(10)



Scheme 11. Contrasting reactivities of thiolate on Pd and Pt as ligand.

However, while C–S bond-forming reductive elimination could proceed from the resultant Pd^{II} complex, that from the corresponding Pt^{II} complex did not take place for thermodynamic reasons. In 2000, we also disclosed the stoichiometric oxidative addition of vinylsulfide **27** to Pt^0 to furnish the vinylplatinum **28** [Eq. (11)].[25] It must be noted that: 1) R in **27** can be Ar and TMS with [Pt(PPh$_3$)$_2$(C$_2$H$_4$)] as Pt^0, and 2) the reaction shown in Equation (9) can take place by using phenylacetylene and (trimethylsilyl)acetylene as alkynes with [Pd(PPh$_3$)$_4$] as a catalyst precursor. Accordingly, the ligands in complexes **24** can be identical to those in **28**. These results clearly demonstrate that the direction of reductive elimination and its reverse oxidative addition can be controlled by simply changing the metals but keeping the same ligand combination; C–S bond formation occurred easily on C–Pd–S fragment, but this process tended to be suppressed with the Pt^{II} complex due to thermodynamic reasons (Scheme 12). That is, if the Pt catalyst was substituted for the Pd catalyst in the C–S bond-forming CHC, the complex possessing C–Pt–S fragment, if generated, can be exploited as an intermediate that is resistant to C–S bond-forming reductive elimination.



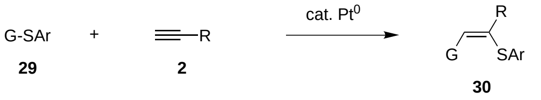
(11)

R = Ar, TMS, or CH$_2$OMe

$$\begin{array}{lcll} C\text{-}Pd\text{-}S & \rightleftharpoons & C\text{-}S & + \ \mathrm{Pd}^0 \\ C\text{-}Pt\text{-}S & \rightleftharpoons & C\text{-}S & + \ \mathrm{Pt}^0 \end{array}$$

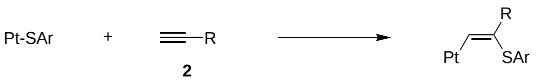
Scheme 12. General trends of RE and OA of C–S bond.

On the other hand, triggered by the reaction shown in [Eq. (9)], some Pt-catalyzed additions of G–SAr (**29**) to terminal alkyne **2**, such as the additions of H–SAr[26] and Cl$_3$Si–SAr[27] have been documented [Eq. (12)]; this suggests that the Pt–SAr fragment can be converted into Pt–^{vinyl}C fragment by the *cis* insertion of **2**, with Pt bound at the terminal carbon [Eq. (13)].[27] Furthermore, it was also reported that the ^{sp2}C–^{sp2}C bond-forming reductive elimination from the PPh$_3$-ligated Pt complex proceeded at about 60 °C [Eq. (14)].[28]



(12)

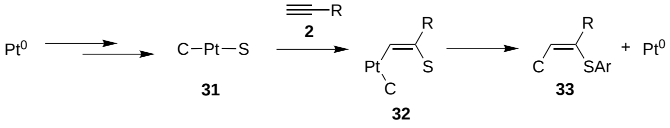
G = H, Cl$_3$Si



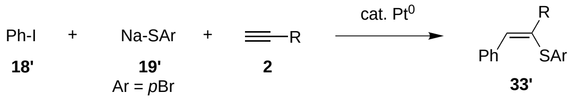
(13)

$$\mathrm{C{-}Pt{-}C} \longrightarrow \mathrm{C\text{-}C} + \mathrm{Pt}^0 \qquad (14)$$

The information described above led us to believe that the TCC reaction based on the strategy shown in Scheme 13 could be realized. That is, if the reaction, which starts with oxidative addition to Pd^0 and closes its catalytic cycle by C–S bond-forming reductive elimination from Pd^{II} is performed with a Pt^0 catalyst instead in the presence of alkyne **2**, the complex **31** with a C–Pt–S fragment can be converted into the vinylplatinum complex **32**, which may undergo the reductive elimination to produce TCC product **33** and Pt^0. Actually, when the reagents used in reactions of Equations (7) and (8) were treated with the Pt^0 catalyst in the presence of **2**, the desired TCC products **33′** were obtained with the anticipated regio- and stereochemistry [Eqs. (15) and (16)]. Moreover, when the principle was applied to the reaction shown in Equation (9), the dimerization–addition product **34** was obtained selectively [Eq. (17)]. The formation of **34** can also be rationalized by oxidative addition of PhS–SPh (**22′**) to Pt^0, insertion of two molecule of **2′** into both S–Pt bonds of **35** to afford divinylplatinum **36**, and eventual C–C bond-forming reductive elimination (Scheme 14).



Scheme 13. Schematic strategy for carbothiolation of alkyne.



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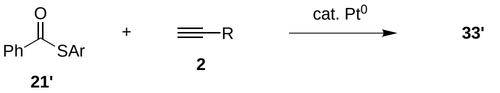

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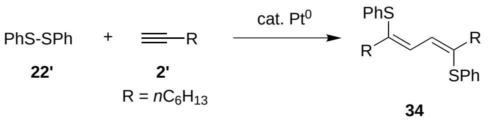
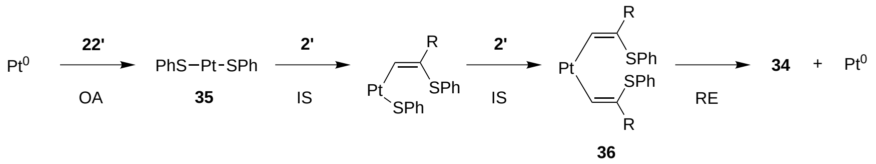


(17)

In summary, a new concept to realize the carbothiolation of alkynes has been clearly demonstrated. This study proved that



Scheme 14. Proposed mechanism of dimerization-addition of disulfide.

accurate information on the reactivities of carbon and heteroatom functionalities, bound to transition metals, toward oxidative addition, transmetallation, insertion, and reductive elimination were essential to design and develop TTC reactions.

Acknowledgement

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[1] *The Metal-Catalyzed Cross-coupling Reactions* (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, Weinheim, **1998**.

[2] a) J. P. Wolfe, S. Wagaw, J.Marcoux, S. L. Buchwald, *Acc. Chem. Res.* **1998**, *31*, 805; b) G. H. Yang, S. L. Buchwald, *J. Organomet. Chem.* **1999**, *576*, 125; c) J. F. Hartwig, *Angew. Chem.* **1998**, *110*, 2154; *Angew. Chem. Int. Ed.* **1998**, *37*, 2046; d) J. F. Hartwig, *Synlett* **1997**, 329.

[3] a) Q.Shelby, N. Kataoka, G. Mann, J. F. Hartwig, *J. Am. Chem. Soc.* **2000**, *122*, 10718; b) K. E. Torraca, X. Huang, C. A. Parrish, S. L. Buchwald, *J. Am. Chem. Soc.* **2001**, *123*, 10770, and references therein.

[4] The three- or four-component coupling reactions involving of carbon functionalities and C–C unsaturated molecules have been recently reviewed: a) S. Ikeda, *Acc. Chem. Res.* **2001**, 511; b) A. G. Fallis, P. Forgione, *Tetrahedron* **2001**, *57*, 5899.

[5] The carbometalation of C–C unsaturated molecules and subsequent trapping by a heteroatom-centered electrophile is also feasible for TCC: a) I. N. Houpis, J. Lee, *Tetrahedron* **2000**, *56*, 817; b) S. Nii, J. Terao, N. Kambe, *J. Org. Chem.* **2000**, *65*, 5291, and references therein.

[6] The C–unsaturated-molecule–C coupling reaction based on this strategy has been reported: a) R. Belzen, H. Hoffmann, C. J. Elsevier, *Angew. Chem.* **1997**, *109*, 1833; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1743; b) R. Belzem, R. A. Klein, H. Kooijman, N. Veldman, A. L. Spek, C. J. Elsevier, *Organometallics* **1998**, *17*, 1812.

[7] a) N. Chatani, N. Amishiro, S. Murai, *J. Am. Chem. Soc.* **1991**, *113*, 7778; b) N. Chatani, N. Amishiro, T. Mori, T. Yamashita, S. Murai, *J. Org. Chem.* **1995**, *60*, 1834.

[8] a) Y. Obora, Y. Tsuji, T. Kawamura, *J. Am. Chem. Soc.* **1993**, *115*, 10414; b) Y. Obora, Y. Tsuji, T. Kawamura, *J. Am. Chem. Soc.* **1995**, *117*, 9814; c) F. Yang, M. Wu, C. Cheng, *Tetrahedron Lett.* **1999**, *40*, 6055; d) M. Wu, F. Yang, C. Cheng, *J. Org. Chem.* **1999**, *64*, 2471.

[9] a) H. Sakurai, T. Imai, *Chem. Lett.* **1975**, 891; b) H. Saso, W. Ando, *Chem. Lett.* **1988**, 1567.

[10] a) E. Shirakawa, H. Yoshida, T. Kurahashi, Y. Nakao, T. Hiyama, *J. Am. Chem. Soc.* **1998**, *120*, 2975; b) E. Shirakawa, H. Yoshida, T. Hiyama, *Tetrahedron Lett.* **1997**, *38*, 5177; c) E. Shirakawa, K. Yamasaki, H. Yoshida, T. Hiyama, *J. Am. Chem. Soc.* **1999**, *121*, 10221; d) E. Shirakawa, H. Yoshida, Y. Nakao, T. Hiyama, *Org. Lett.* **2000**, *2*, 2209; e) H. Yoshida, E. Shirakawa, T. Kurahashi, Y. Nakao, T. Hiyama, *Organometallics* **2000**, *19*, 5671.

[11] E. Shirakawa, Y. Nakao, T. Hiyama, *Chem. Commun.* **2001**, 263.

[12] E. Shirakawa, Y. Nakao, H. Yoshida, T. Hiyama, *J. Am. Chem. Soc.* **2000**, *122*, 9030.

[13] H. Yoshida, Y. Honda, E. Shirakawa, T. Hiyama, *Chem. Commun.* **2001**, 1880.

[14] E. Shirakawa, Y. Yamamoto, Y. Nakao, T. Tsuchimoto, T. Hiyama, *Chem. Commun.* **2001**, 1926.

[15] K. Kokubo, K. Matsumasa, M. Miura, M. Nomura, *J. Org. Chem.* **1996**, *61*, 6941.

[16] a) E. Shirakawa, H. Yoshida, Y. Nakao, T. Hiyama, *J. Am. Chem. Soc.* **1999**, *121*, 4290; b) H. Yoshida, E. Shirakawa, Y. Nakao, Y. Honda, T. Hiyama, *Bull. Chem. Soc. Jpn.* **2001**, *74*, 637.

[17] K. Sugoh, H. Kuniyasu, T. Sugae, A. Ohtaka, Y. Takai, A. Tanaka, C. Machino, N. Kambe, H. Kurosawa, *J. Am. Chem. Soc.* **2001**, *123*, 5108.

[18] a) M. Kosugi, T. Shimizu, T. Migita, *Chem. Lett.* **1978**, 13; b) T. Migita, T. Shimizu, Y. Asami, J. Shiobara, Y. Kato, M. Kosugi, *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1385.

[19] a) T. Kondo, T. Mitudo, *Chem. Rev.* **2000**, *100*, 3205; b) H. Kuniyasu, in *Catalytic Heterofunctionalization* (Eds.: A. Togni, H. Grützmacher), Wiley-VCH, Weinheim, **2001**, p. 217.

[20] G. Mann, D. Baranano, J. F. Hartwig, A. L. Rheingold, I. A. Guzei, *J. Am. Chem. Soc.* **1998**, *120*, 9205.

[21] K. Osakada, T. Yamamoto, A. Yamamoto, *Tetrahedron Lett.* **1987**, *28*, 6321.

[22] H. Kuniyasu, A. Ogawa, S. Miyazaki, I. Ryu, N. Kambe, N. Sonoda, *J. Am. Chem. Soc.* **1991**, *113*, 9796.

[23] We have recently reported that the *cis*-insertion of DMAD into a Pd–S bond of $[Pd(SAr)_2(dppe)]$ (dppe = 1,2-bis(diphenylphosphino)-ethane) produced the $[Pd\{(Z)\text{-}C(CO_2Me)=C(SAr)(CO_2Me)\}(dppe)]$; K. Sugoh, H. Kuniyasu, H. Kurosawa, *Chem. Lett.* **2002**, 106.

[24] H. Kuniyasu, K. Sugoh, S. Moon, H. Kurosawa, *J. Am. Chem. Soc.* **1997**, *119*, 4669.

[25] H. Kuniyasu, A. Ohtaka, T. Nakazono, M. Kinomoto, H. Kurosawa, *J. Am. Chem. Soc.* **2000**, *122*, 2375.

[26] a) H. Kuniyasu, A. Ogawa, K. Sato, I. Ryu, N. Kambe, N. Sonoda, *J. Am. Chem. Soc.* **1992**, *114*, 5902; b) A. Ogawa, T. Ikeda, K. Kimura, T. Hirao, *J. Am. Chem. Soc.* **1999**, *121*, 5108; c) Y. Gareau, A. Orellana, *Synlett* **1997**, 803.

[27] L. Han, M. Tanaka, *J. Am. Chem. Soc.* **1998**, *120*, 8249.

[28] a) P. S. Braterman, P. S. Cross, G. B. Young, *J. Chem. Soc. Dalton. Trans.* **1976**, 1306; b) P. J. Stang, M. H. Kowalski, *J. Am. Chem. Soc.* **1989**, *111*, 3356; c) R. K. Merwin, R. C. Schnabel, J. D. Koola, D. M. Roddic, *Organometallics* **1992**, *11*, 2972, and references therein.

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