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Heck reactions: a caveat on the use of palladium(II) PCP-type catalysts

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Abstract

A PCP-type catalyst was prepared and examined within the context of intramolecular Heck reactions. A substrate possessing a 1,4-diene system effectively poisoned the PCP catalyst leading to no reaction. This behavior contrasts with the typical palladium(0) catalyst system.

Keywords: Heck reaction; PCP-type catalyst.

The Heck reaction has emerged as a powerful method for carbon–carbon bond construction in organic synthesis.[1] In the intramolecular mode this reaction provides a useful approach towards the synthesis of carbocycles and heterocycles. The development of asymmetric variants of this process adds further value to the Heck reaction in the context of enantioselective synthesis; particularly in the introduction of chiral quaternary carbons.[2] An additional benefit of the Heck reaction is the overall atom economy of the process which requires only catalytic amounts of palladium(0) to effect often good turnover numbers and frequency.[3] The currently utilized palladium(0) systems do occasionally suffer from thermal and oxygen instability. Milstein has described highly active palladium(II) PCP-type[4] catalysts which display excellent thermal and oxygen stability as well as reactivity.[5] An intriguing feature of this catalyst system is that it has been proposed to operate through a Pd(II)/Pd(IV) cycle during the Heck reaction rather than the more common Pd(0)/Pd(II) cycle. We became interested in developing PCP-type catalysts that are chiral, or suitable for immobilization on a polymer support for use in Heck reactions for the assembly of carbocycles and heterocycles. We describe here the preparation of a new PCP catalyst and its application in intramolecular Heck reactions leading to carbocyclic ring systems (Scheme 1).

The synthesis of PCP complex **4** starts with deprotonation of borane–phosphine complex **1** and subsequent bromide displacement of an α,α′-dibromoxylene to give borane–phosphine complex **2**.[6,7] Borane decomplexation is followed by a palladium insertion using Milstein's conditions. Catalysts **4a** and **4b** displayed comparable behavior in the Heck reactions described in this letter. Catalysts **4a** and **4b**

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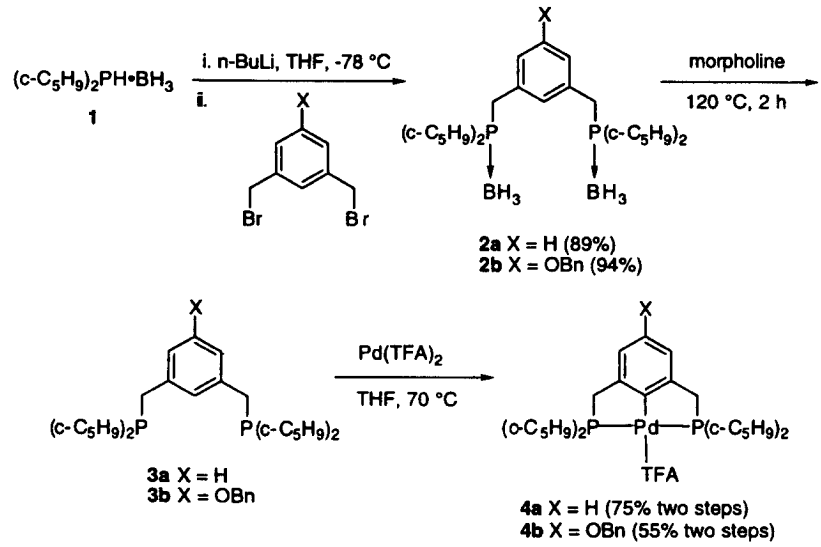
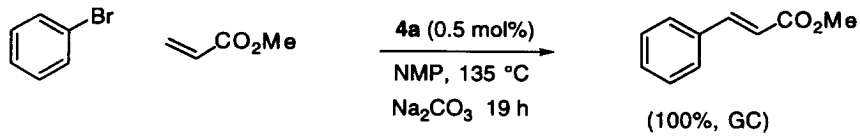


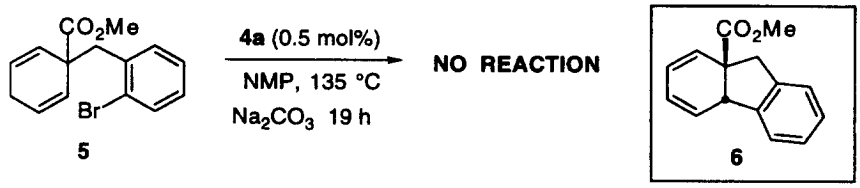
Scheme 1.

efficiently promoted the coupling of bromobenzene and methyl acrylate to afford methyl cinnamate in near quantitative yield (GC yield) (Eq. 1).

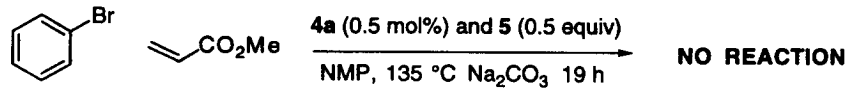


(1)

Much to our surprise, under the same reaction conditions, PCP catalyst **4a** failed to provide any product from an intramolecular Heck reaction using 1,4-diene **5**[8] as a substrate (Eq. 2) (no change by GC analysis). For comparison purposes **5** was cyclized under standard Heck reaction conditions using palladium(0) catalysis [$Pd(OAc)_2$, 5 mol%; PPh_3, 15 mol%; Et_3N, 115°C, 24 h] to give **6** in 79% isolated yield. A key control experiment was to repeat the Heck reaction between bromobenzene and methyl acrylate catalyzed by PCP-type catalyst **4a** (0.5 mol%) in the presence of 1,4-diene **5** (0.5 equiv.) (Eq. 3).

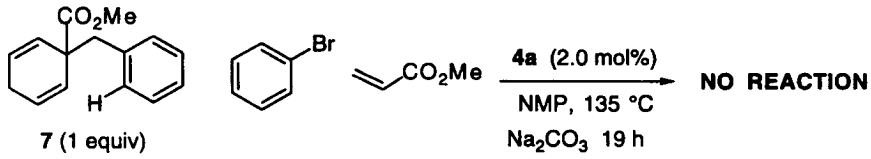


(2)



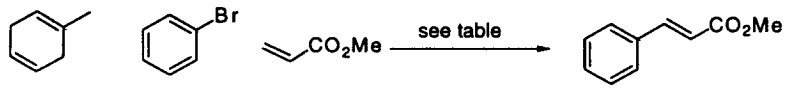
(3)

In contrast to the reaction outlined in Eq. 1, no reaction was observed on addition of **5**. This led us to the conclusion that 1,4-diene **5** is poisoning the PCP-type catalyst **4a**. In a second experiment designed to pin-down the functionality responsible for deactivating **4a**, we attempted the Heck reaction of bromobenzene and methyl acrylate, this time in the presence of halide-free diene **7** (1 equiv.) (Eq. 4).



(4)

Again no reaction was observed (no change by GC analysis) leading to the conclusion that **4a** binds strongly to the 1,4-diene functionality of **5** and **7** leading to catalyst deactivation. In order to probe the generality of 1,4-cyclohexadienes to inhibit the catalytic activity of **4a**, the half-life of a Heck reaction between bromobenzene and methyl acrylate was measured in the absence and presence of 2 equiv. of 1-methyl-1,4-cyclohexadiene (Eq. 5).



(5)

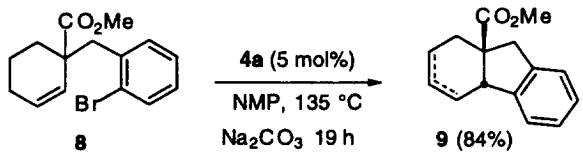
Table 1

Reaction Conditions	half-life ($t_{1/2}$)[a]
4a (0.5 mol%), Na_2CO_3, NMP, 135 °C, no diene	4.5 h
4a (0.5 mol%), Na_2CO_3, NMP, 135 °C, diene (2 equiv)	150 h
$Pd(OAc)_2$ (2 mol%), Ph_3P (6 mol%), Na_2CO_3, NMP, 135 °C, no diene	4.5 h[b]
$Pd(OAc)_2$ (2 mol%), Ph_3P (6 mol%), Na_2CO_3, NMP, 135 °C, diene (2 equiv)	3.5 h

[a]Reactions were monitored by gas chromatography using an internal standard. [b]Reaction did not proceed to completion presumably due to catalyst decomposition as evidenced by the formation of palladium black.

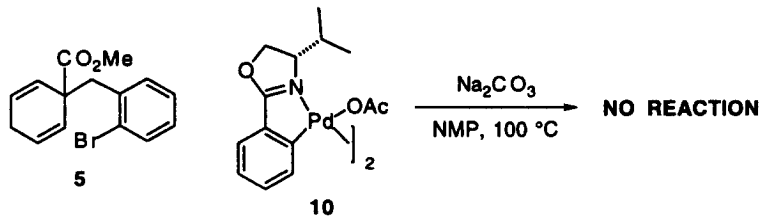
The half-life of the diene-free reaction was measured to be 4.5 h. As indicated in Table 1 the addition of 2 equiv. of diene significantly inhibited the Heck reaction ($t_{1/2} \approx 150$ h). In contrast, the same Heck reaction using palladium(0) as catalyst was not inhibited by the addition of 1-methyl-1,4-cyclohexadiene.

In order to further support our conclusion that **5** fails to undergo a Heck reaction promoted by **4** due to strong binding to the 1,4-cyclohexadiene ring we attempted cyclization of cyclohexene **8** catalyzed by **4a**.[9] In this case, both PCP-type catalyst **4a** and the standard palladium(0) protocol worked with equal efficacy to give **9** as a nearly 1:1 mixture of double bond isomers (Eq. 6).



(6)

Preliminary work suggests that other palladium(II) catalysts known to be active in Heck reactions are also inactive with a 1,4-diene substrate like **5**.[11] Specifically, the bis(aryloxazoline)palladium(II) complex **10**[12] in reaction with **5** at 100°C (Na_2CO_3 as base) in NMP gave no significant reaction.



(7)

In conclusion, these results show differences in substrate specificity between PCP-type palladium(II) Heck catalysts and more common palladium(0) Heck catalysts. The inhibition effect of 1,4-dienes on PCP-type catalysts is probably related to the propensity of higher oxidation states of palladium to strongly coordinate 1,4-diene ligands.[10] Variation at the PCP ligand or counterion may be a way to circumvent inhibition but we have not studied this effect. In any case, although PCP catalysts of the form **4** have the potential for introducing chiral centers at the benzylic carbon leading to new chiral catalysts for application in Heck reactions, caution needs to be exercised in selecting substrates to probe the enantioselectivity of such systems.

Acknowledgements

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References

1. Demeijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1995**, *33*, 2379–2411.
2. (a) Shibasaki, M.; Boden, C. D. J.; Kojima, A. *Tetrahedron* **1997**, *53*, 7371–7395. (b) Ashimori, A.; Bachand, B.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6477–6487. (c) Ashimori, A.; Bachand, B.; Calter, M. A.; Govek, S. P.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6488–6499.
3. Trost, B. M. *Science* **1991**, *254*, 1471–1477.
4. PCP-type catalysts are complexes incorporating the phosphorous–carbon–phosphorous tridentate ligand system such as those derived from the cyclometalation of 2,6-bis(dialkylphosphinomethyl)benzene.
5. Ohff, M.; Ohff, A.; van der Boom, M. E.; Milstein, D. *J. Am. Chem. Soc.* **1997**, *119*, 11687–11688.
6. (a) Longmire, J. M.; Zhang, X. M.; Shang, M. Y. *Organometallics* **1998**, *17*, 4374–4379. (b) Rimml, H.; Venanzi, L. M. *J. Organomet. Chem.* **1983**, *259*, C6–C7.
7. Compound **4a**: ^{1}H NMR ($CDCl_3$) δ 1.57–1.74 (m, 24H), 1.86–1.89 (m, 4H), 2.02–2.05 (m, 4H), 2.37–2.47 (m, 4H), 3.17 (t, *J*=4.4 Hz, 4H), 6.95 (m, 3H); ^{31}P NMR ($CDCl_3$) δ 53.5; ^{13}F ($CDCl_3$) δ 117.6.
8. Beckwith, A. L. J.; Oshea, D. M.; Roberts, D. H. *J. Chem. Soc., Chem. Commun.* **1983**, 1445–1446.
9. Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130–4133.
10. (a) Tomita, K.; Caires, A. C.; DeLucca, N.; Vincente, A.; Mauro, A. E. *Acta Crystallogr., Sect. C: Cryst Struct. Commun.* **1994**, *C50*, 1872–1873. (b) Lewis, J.; Hill, M. N. S.; Johnson, B. F. G. *J. Chem. Soc. A* **1971**, 2341–2347.
11. Ohff, M.; Ohff, A.; Milstein, D. *J. Chem. Soc., Chem. Commun.* **1999**, 357–358.
12. Izumi, T.; Watabe, H.; Kasahara, A. *Bull. Chem. Soc. Jpn.* **1981**, *5*, 1711–1714.