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TPM: a new protecting group for alkynes

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Abstract

A new alkyne protecting group, trispyrazolylborateplatinum(methyl) (TPM), that can tolerate various reaction conditions and is particularly useful for electron-deficient acetylenes allows for synthetic manipulations of polyfunctional acetylenes. This protecting group withstands a variety of reaction conditions, including basic and acidic media, and the environment required for catalytic hydrogenation and for chromate oxidation reaction. The alkyne product is conveniently released from the protecting complex by the use of carbon monoxide under neutral conditions and ambient temperatures.

Keywords: alkynes; amides; platinum; platinum compounds; protecting groups.

Alkynes are generally very reactive in various addition reactions, such as hydrogenation, acid-catalyzed hydration, hydroboration, and other hydrometallation reactions. Hence, protection of a carbon–carbon triple bond in a polyfunctional organic molecule is essential for selective synthetic transformations. Coordination of the alkyne group to dicobalt hexacarbonyl has been the most successful approach towards the deactivation of the triple bond.[1] This method, first presented by Nicholas and Pettit,[2] employs $Co_2(CO)_8$, which reacts with mono- and dialkyl acetylenes to form stable (alkyne)dicobalt(hexacarbonyl) complexes.[3] Liberation of the alkyne from this complex is achieved by oxidative degradation with Fe(III) salts. Although this protecting group can endure under various reaction conditions it is ineffective under conditions of catalytic hydrogenation using various catalysts, such as Pd/C or PtO_2.[4] Furthermore, the stability of $Co_2(CO)_6$(alkyne) is limited under either peroxide-base combination[2a] or under simple basic conditions.[5] The limitations of the cobalt complexation protection approach are even greater with the more reactive, electron-deficient acetylenes.

Aiming for a general protecting group of acetylenes we focused our attention on the TpPtMe(alkyne) complexes (Tp=tris-pyrazolylborate), which are known to be chemically stable under various conditions.

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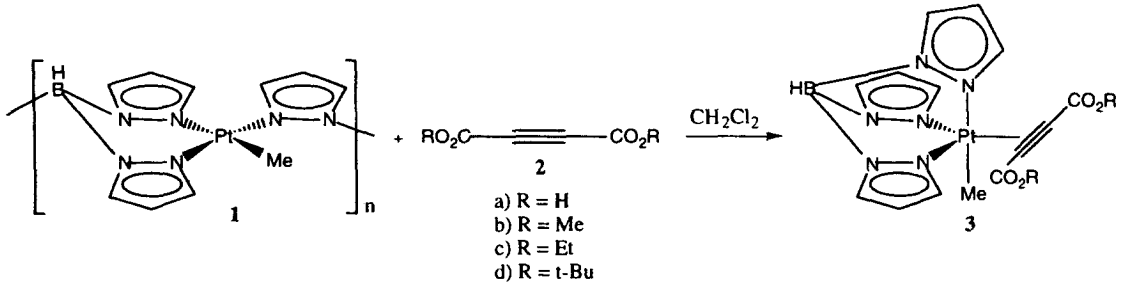
These complexes are easily prepared by reacting any given acetylene with the polymeric material $[TpPtMe]_n$, **1** (Scheme 1),[6] which is readily available in two steps from $(COD)PtMe_2$.[7]



Scheme 1.

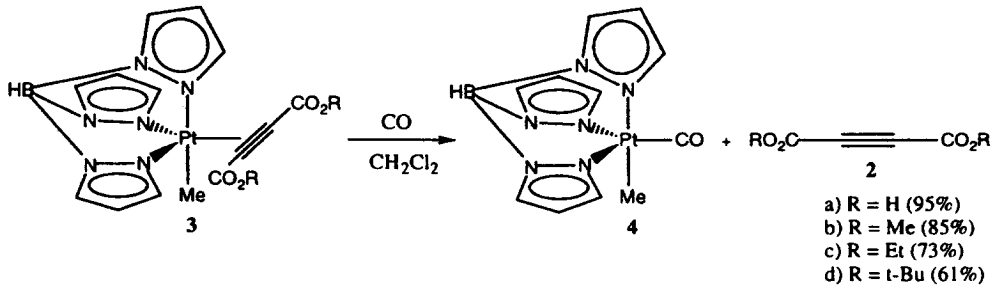
Polymer **1** is a white-gray solid, which is practically insoluble in most organic solvents. It reacts readily with various neutral ligands, such as alkynes, alkenes and carbon monoxide, to form TpPtMe(ligand), which is soluble in organic solvents. Thus, the alkyne protection procedure involves merely stirring a dichloromethane solution of the given alkyne **2** with **1** (1 equiv.) at room temperature for 1–2 h (Scheme 1). The progress of the reaction can be visually observed as the heterogeneous mixture clears gradually and turns into a homogeneous solution. For example, complexes **3a–d** were prepared and isolated in 70–95% yields by passing the reaction mixture through a short florisil column (5 cm) using either CH_2Cl_2 or hexane–ethyl acetate followed by removal of the solvent under reduced pressure.[8]

Complex **3** is known to adopt a trigonal bipyramide geometry in which the Tp ligand is coordinated in a rigid tridentate fashion. The high stability of **3** renders the TPM a good protecting group of alkynes, but also makes the deprotection step a non-trivial challenge. The fact that **3** is coordinatively saturated requires that the ligand exchange reaction with this complex will occur via a dissociative mechanism.[9] Obviously, dissociation of the alkyne ligand from the platinum center forming a tetracoordinate intermediate seems to be the most desirable pathway. Our attempts to release **2** via ligand exchange reactions with π-acceptor ligands, such as tetracyanoethylene, hexafluoropropene and diethyl acetylene dicarboxylate, were unsuccessful. Apparently, the equilibrium between complex **3** and the free alkyne **2** in solution is too slow to allow the ligand exchange reaction.

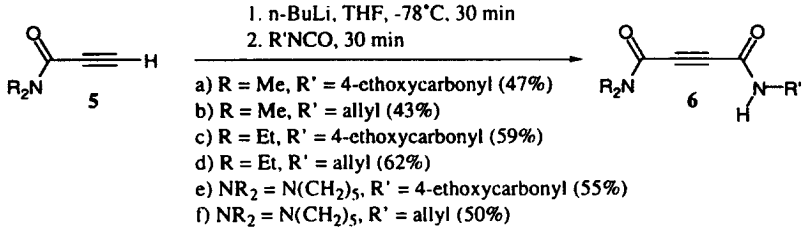
An alternative mechanism could involve dissociation of one of the pyrazolyl rings from the metal center. In fact, certain TpPt(II)Me complexes are known to exhibit fluxional behavior of the Tp ligand.[10] If the Tp in **3** equilibrates between the tri and bidentate modes, a strong acceptor ligand, such as carbon monoxide could be added to the coordination sphere, labilize the other acceptor ligand **2** and facilitate its release. Indeed, when a dichloromethane solution of complex **3** was stirred under 1 atm of carbon monoxide at room temperature, slow release of **2** could be detected either by TLC or by ^1H NMR. Unfortunately, under these conditions the conversion rates were disappointingly low ($\leq$10%) even after several hours. Nevertheless, when the reaction was carried out under high pressure of CO (60 atm) compounds **2a–d** were obtained in good yields together with TpPtMeCO, **4** (Scheme 2).[10]

We demonstrated the synthetic opportunities available with this protecting technique using a series of non-symmetrical bis-amides of acetylene dicarboxylic acid.[11] We found that these yet unknown bis-amides could be conveniently prepared in one step from the 2-propynamides, **5**,[12] and the appropriate isocyanate (Scheme 3).[13] The reaction of compounds **6a–f**[14] with **1** in CH_2Cl_2 produced their corresponding TPM complexes.

We used several model reactions to illustrate the usefulness of our protecting technique. For example, alkyne **6a** was found to be unstable under the basic conditions required for the hydrolysis of its ester group. We protected compound **6a** by reacting it with **1** to produce complex **7** (Scheme 4). This

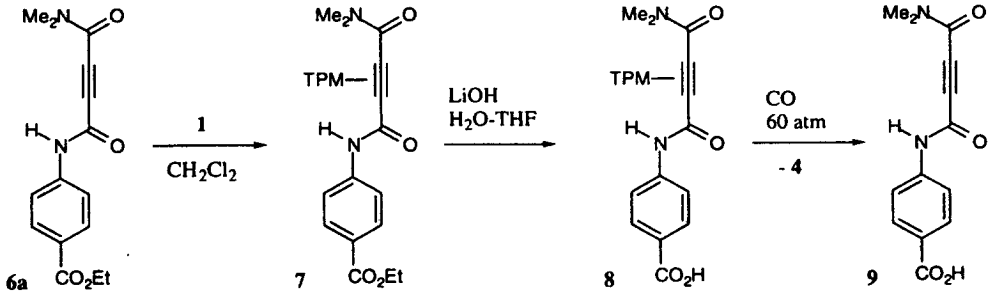


Scheme 2.



Scheme 3.

transformation could be reversed by pressurizing the CH_2Cl_2 solution of **7** with CO to regenerate **6a** in 76% yield. Complex **7** was dissolved in a 3:2 mixture of THF and aqueous LiOH (0.5M) and was stirred at room temperature for 3 days. The resultant carboxylic acid **8**,[15] which was obtained in 90% yield, was treated with CO to produce the free alkyne **9** in 70% yield.

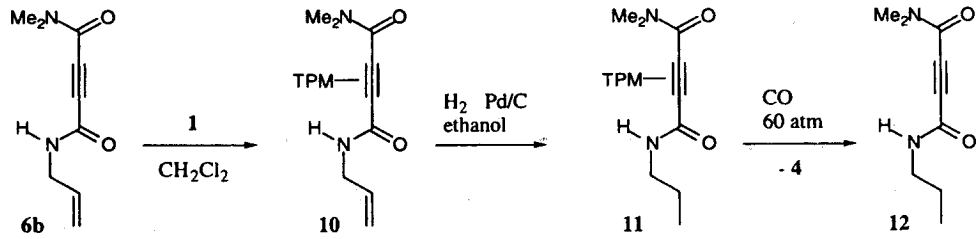


Scheme 4.

To examine the applicability of our protecting group to conditions of catalytic hydrogenation we used the ene-yne substrate **6b** (Scheme 5). This compound was protected with **1** to produce complex **10**,[16] which was then subjected to catalytic hydrogenation with 10% of palladium on carbon in ethanol and hydrogen (1 atm) for 1 h. The resultant propylamide **11** was obtained in 80% yield.[17] Finally, deprotection with CO afforded alkyne **12** in 60% yield.[18]

The acid stability of complex **7** was examined by dissolving it in a 3:1 mixture of acetone-d_6 and acetic acid-d_4. The mixture was kept in an NMR tube at room temperature for 24 h. No decomposition could be detected by ^{1}H NMR spectroscopy. In stronger acidic media, however, slow decomposition of **7** was observed. For example, in a 2:1 mixture of acetone-d_6 and aqueous HCl (0.2 M) complex **7** decomposed at a rate of approximately 20% per hour.

To examine the compatibility of **7** under oxidation conditions we mixed it in dry CH_2Cl_2 with benzyl alcohol in a 1:10 molar ratio and added PCC (1.5 equiv. with respect to benzyl alcohol). The mixture was



Scheme 5.

stirred at room temperature for 30 min. While complete conversion of the alcohol to benzaldehyde was evident by TLC no decomposition of **7** could be detected. Nevertheless, slow decomposition of **7** was observed upon prolonged stirring with excess PCC.

In conclusion, the use of TPM as an alkyne protecting group allows for synthetic manipulations of polyfunctional acetylenes. This protecting group withstands a variety of reaction conditions, including basic and acidic media, and the environment required for catalytic hydrogenation and for chromate oxidation reaction. The alkyne product is conveniently released from the protecting complex by the use of carbon monoxide under neutral conditions and ambient temperatures. Although platinum is costly, the simple protection/deprotection procedures and the easy recovery of the metal make this technique an attractive tool in organic synthesis.

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8. Spectral data of compound **3c**: ^{1}H NMR ($CDCl_3$): 7.77 (d, J=2.09 Hz, 2H), 7.75 (d, J=2.09 Hz, 2H), 7.61 (d, J=2.09 Hz, 1H), 7.29 (d, J=2.09 Hz, 1H), 6.27 (t, J=2.09 Hz, 2H), 6.10 (t, J=2.09 Hz, 1H), 6.09 (t, J=2.24 Hz, 1H), 4.26 (q, J=6.85 Hz, 2H), 1.32 (t, J=6.85 Hz, 3H), 0.98 (s, J_{Pt-C}=66.80 Hz, 3H). ^{13}C NMR ($CDCl_3$): 155.9, 141.3, 137.5, 136.1, 135.9, 106.6, 105.7, 80.7, 62.4, 15.1, −15.0 ppm. MS (ESI$^+$): 616 (MNa^+).
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13. Synthesis of the bis-amide **6a**: *N*-Dimethyl-2-propynamide (300 mg, 3.1 mmol) was dissolved in dry THF (100 mL) under argon. The solution was cooled to −78°C, *n*-BuLi (2.1 mL, 1.6 M) was added slowly and the solution was stirred at the same temperature for 30 min. A solution of ethyl-4-isocyanatobenzoate (600 mg, 3.1 mmol) in dry THF (10 mL) was added, the mixture was stirred at −78°C for 30 min and then quenched with saturated aq. NH_4Cl. The mixture was worked up with ethyl acetate and brine, the organic layer dried over $MgSO_4$, solvents were removed under reduced pressure and the crude product was purified by column chromatography (silica gel, hexane:ethyl acetate, 9:1 to 6:4) to give **6a** in the form of yellowish crystals. Mp 104–106°C. ^{1}H NMR ($CDCl_3$): 9.81 (br, 1H), 7.98 (d, *J*=8.68 Hz, 2H), 7.67 (d, *J*=8.68 Hz, 2H), 4.33 (q, *J*=7.19 Hz, 2H), 3.24 (s, 3H), 3.02 (s, 3H), 1.36 (t, *J*=7.19 Hz, 3H). ^{13}C NMR ($CDCl_3$): 166.0, 152.9, 149.1, 141.5, 130.7, 126.6, 119.3, 83.4, 75.4, 60.9, 38.5, 34.5, 14.3 ppm. MS (ESI$^+$): 289 (MH^+).
14. Spectral data of compound **6e**: ^{1}H NMR ($CDCl_3$): 10.14 (br, 1H), 7.93 (d, *J*=8.43 Hz, 2H), 7.64 (d, *J*=8.43 Hz, 2H), 4.29 (q, *J*=7.11 Hz, 2H), 3.64 (t, *J*=5.22 Hz, 2H), 3.56 (t, *J*=5.22 Hz, 2H), 1.55 (m, 6H), 1.31 (t, *J*=7.11 Hz, 3H). ^{13}C NMR ($CDCl_3$): 165.9, 151.0, 149.2, 141.5, 130.5, 126.3, 119.2, 83.5, 75.3, 60.8, 48.3, 42.7, 26.2, 25.2, 24.0, 14.2. MS (ESI$^+$): 329 (MH^+). Mp=58–60°C.
15. Spectral data of compound **8**: ^{1}H NMR ($CDCl_3$): 11.48 (br, 1H), 8.05 (d, *J*=8.67 Hz, 2H), 7.97 (d, *J*=2.06 Hz, 1H), 7.85 (d, *J*=8.67 Hz, 2H), 7.77 (d, *J*=2.06 Hz, 1H), 7.72 (d, *J*=2.06 Hz, 1H), 7.68 (d, *J*=2.06 Hz, 1H), 7.64 (d, *J*=2.06 Hz, 1H), 7.20 (d, *J*=2.06 Hz, 1H), 6.30 (br, 2H), 6.11 (t, 2.06 Hz, 1H), 3.38 (s, 3H), 3.11 (s, 3H), 1.02 (s, J_{Pt-C}=66.38 Hz, 3H). ^{13}C NMR ($CDCl_3$): 171.1, 153.7, 150.4, 143.5, 141.4, 138.8, 136.6, 135.5, 135.4, 135.1, 131.5, 123.4, 118.7, 106.2, 105.9, 105.2, 93.7, 73.5, 38.6, 35.2, −15.3 ppm. MS (ESI$^+$): 706 (MNa^+).
16. Spectral data of compound **10**: ^{1}H NMR ($CDCl_3$): 8.52 (t, *J*=5.44 Hz, 1H), 7.91 (d, *J*=1.96 Hz, 1H), 7.73 (d, *J*=2.48 Hz, 1H), 7.69 (br, 2H), 7.61 (d, *J*=2.48 Hz, 1H), 7.19 (d, *J*=1.96 Hz, 1H), 6.26 (t, *J*=2.48 Hz, 1H), 6.25 (t, *J*=2.48 Hz, 1H), 6.08 (t, *J*=1.96 Hz, 1H), 5.90 (m, 1H), 5.24 (dd, *J*=17.24, 1.00 Hz, 1H), 5.14 (dd, *J*=10.32, 1.00 Hz, 1H), 4.00 (m, *J*=5.44 Hz, 2H), 3.33 (s, 3H), 3.02 (s, 3H), 0.96 (s, J_{Pt-C}=66.9 Hz, 3H). ^{13}C NMR ($CDCl_3$): 153.6, 152.4, 140.7, 138.6, 136.1, 135.0, 134.8, 134.6, 133.7, 115.8, 105.6, 105.3, 104.6, 90.7, 72.5, 41.8, 38.1, 34.6, −16.2 ppm. MS (ESI$^+$): 626 (MNa^+).
17. Spectral data of compound **11**: ^{1}H NMR ($CDCl_3$): 8.33 (t, *J*=5.30 Hz, 1H), 7.91 (d, *J*=2.24 Hz, 1H), 7.73 (d, *J*=2.24 Hz, 1H), 7.70 (br, 2H), 7.61 (d, *J*=2.24 Hz, 1H), 7.18 (d, *J*=2.24 Hz, 1H), 6.27 (t, *J*=2.24 Hz, 1H), 6.26 (t, *J*=2.24 Hz, 1H), 6.09 (t, *J*=2.24 Hz, 1H), 3.33 (m, 2H), 3.34 (s, 3H), 3.03 (s, 3H), 1.59 (m, *J*=7.36 Hz, 2H), 0.95 (s, J_{Pt-C}=64.86 Hz, 3H), 0.94 (t, *J*=7.36 Hz, 3H). ^{13}C NMR ($CDCl_3$): 154.9, 153.9, 141.9, 139.9, 137.4, 136.2, 136.0, 135.9, 106.9, 106.5, 105.8, 92.2, 73.3, 42.4, 39.4, 35.9, 23.7, 12.4, −15.0 ppm. MS (ESI$^+$): 628 (MNa^+).
18. Spectral data of compound **12**: ^{1}H NMR ($CDCl_3$): 6.12 (br, 1H), 3.27 (q, *J*=7.32 Hz, 2H), 3.21 (s, 3H), 2.98 (s, 3H), 1.55 (m, *J*=7.32 Hz, 2H), 0.93 (t, *J*=7.32 Hz, 3H). ^{13}C NMR ($CDCl_3$): 152.7, 151.4, 82.3, 74.7, 41.8, 38.3, 34.3, 22.4, 11.2 ppm. MS (ESI$^+$): 205 (MNa^+).