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Preliminary communication

CARBOPALLADATION-DEPALLADATION OF HOMOALLYLIC AMINES AND SULFIDES

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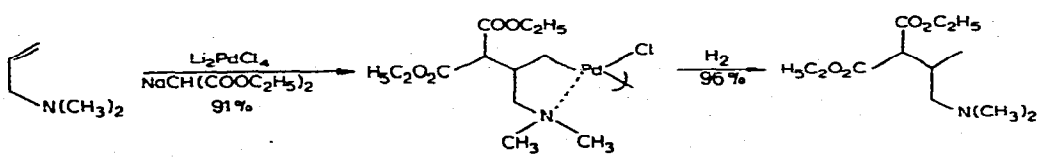
Summary

Methanol and stabilized enolates have been found to add to C-4 of homoallylic amines and sulfides in the presence of lithium tetrachloropalladate to give stable chelated palladium complexes in high yield. These complexes may either be isolated or reduced directly with sodium borohydride, providing a simple new route to ω-functionalized amines and sulfides.

We have recently demonstrated a new carbon—carbon bond forming reaction in which carbon nucleophiles may be regiospecifically attached to the β-carbon of allylic amines and sulfides in excellent yield [1]***. Thus, treatment of di-



(I) (II) (III)

methylallylamine (I) with sodiodiethylmalonate and lithium tetrachloropalladate (LTP) [3] in tetrahydrofuran (THF) for 6 h at room temperature gives palladocycle II in high yield. Complex II may be conveniently reduced to γ-aminodiester III simply by bubbling hydrogen gas through a THF solution of II. The overall

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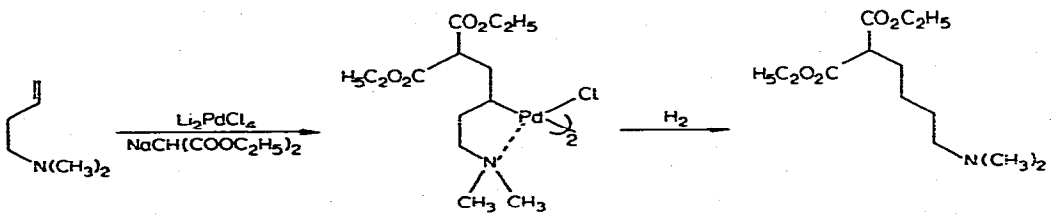
***Cyclometallation reactions have recently been reviewed [2].

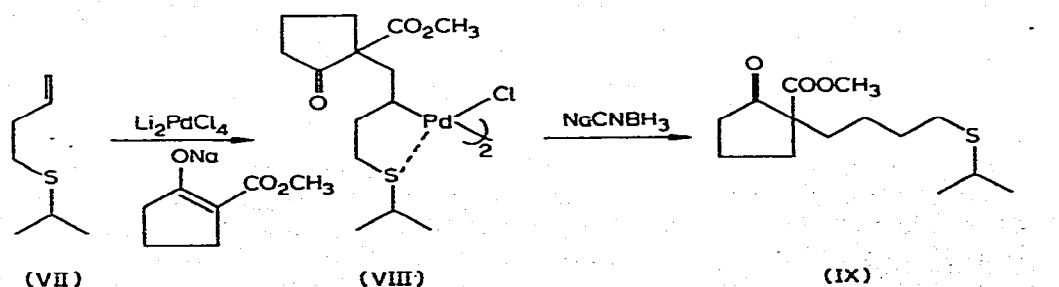
conversion of I to III may be carried out without isolation of complex II in 94% yield.

We have now extended carbopalladation to include homoallylic amines and sulfides. This methodology now provides access to regioisomerically pure products resulting from attachment of nucleophilic agents at C-4 of the olefinic amine or sulfide. Thus, treatment of 4-dimethylamino-1-butene (IV) with sodiodiethylmalonate and LTP in THF at room temperature for 1 h led to the production of palladocycle V, isolated as a yellow oil, NMR ($CDCl_3$) δ (ppm): 4.17 (q, 2, J 7 Hz), 4.15 (q, 2, J 7 Hz), 3.60 (t, 1, J 8 Hz), 2.72 (s, 3), 2.70 (s, 3), 1.6—2.7 (m, 7), 1.26 (t, 3, J 7 Hz), and 1.24 (t, 3, J 7 Hz); IR ($CHCl_3$): 5.73, 5.79, and 8.3 μ; in 86% yield. Hydrogenation of V in THF for 5 min leads to amino diester VI*, uncontaminated by regioisomers, in > 90% yield. The overall two-step conversion of IV to VI may be accomplished without isolation of complex V in 91% yield.



(IV) (V) (VI)

Similarly, isopropyl-3-butenyl sulfide (VII), upon treatment with the sodium salt of 2-carbomethoxycyclopentanone and LTP in THF at room temperature, gave palladocycle VIII in 96% yield. As previously described [1], sulfide com - plexes are resistant to hydrogenation, but may be efficiently reduced by hydride

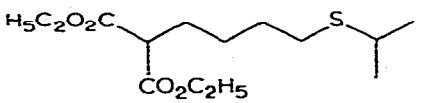


(VII) (VIII) (IX)

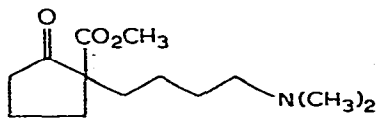
*Compounds VI, IX—XII and XIV were characterized by correct combustion analysis.

reagents. The reduction of palladocycle VIII was rapidly effected by sodium cyanoborohydride in methanol to afford IX in 93% overall yield from sulfide VII.

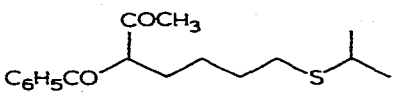
Other examples of the overall conversion of homoallylic amines and sulfides to ω-amino and ω-alkylthio esters and ketones are listed below. Yields refer to isolated products and are based on starting amine IV or sulfide VII.



(X) 92%

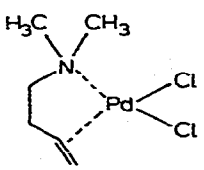


(XI) 88%



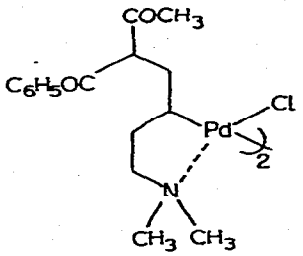
(XII) 94%

We envision these reactions to involve the intermediacy of an olefin—palladium complex similar to XIII [4, 5]. Nucleophilic attack by enolate directly on the co-ordinated olefin then gives rise to the isolated palladocycles. The preference of

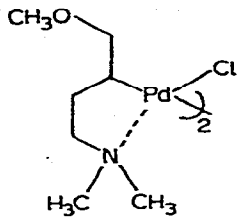


(XIII)

palladium for forming five-membered σ-complexes [2] is envisioned to govern the regiochemistry of nucleophilic attack. In fact, amine IV and LTP alone in THF produce a crystalline, yellow, slightly soluble complex, presumably XIII. As a result of its insolubility, this complex reacts more slowly with representative nucleophiles in THF than does the analogous sulfide complex. Reaction of the sodium salt of benzoylacetone with a mixture of IV and LTP in THF was found to be intolerably sluggish. However, introduction of 20% dimethyl sulfoxide (DMSO) into the mixture was sufficient for dissolution of the insoluble complex, and allowed the isolation of palladocycle XIV in 78% yield after stirring at room temperature for 12 h.



(XIV)



(XV)

Methoxypalladation [6] follows a similar course with homoallylic amines and sulfides. For example, treatment of IV with LTP in methanol containing excess potassium carbonate at room temperature for 20 min produced an 83% yield of palladocycle XV.

In a typical experiment, isopropyl-3-butenyl sulfide (VII) (130 mg, 1.0 mmol) was added to a solution of 262 mg (1.0 mmol) of lithium tetrachloropalladate in 15 ml of tetrahydrofuran (distilled from lithium aluminum hydride) under nitrogen at room temperature. To the resulting red-orange solution was added via syringe a solution of 164 mg (1.0 mmol) of the sodium salt of 2-carbomethoxycyclopentanone in 5 ml of tetrahydrofuran. Stirring was continued for 20 min at room temperature, during which time the color of the solution faded to bright yellow. The yellow solution was cooled to 0°C and a solution of 0.5 g of sodium cyanoborohydride in 10 ml of methanol was added, instantaneously producing a black precipitate. After separation of palladium (centrifugation or filtration)* the solution was diluted with chloroform, extracted with water, dried over sodium sulfate, and evaporated to leave 254 mg (93%) of ketosulfide VIII as a very pure colorless oil. An analytical sample was obtained via kugelrohr distillation at 1.0 mmHg with essentially no loss of material.

Thus, it is now possible to introduce either oxygen or carbon nucleophiles regiospecifically at either C-2 or C-4 of an olefinic amine or sulfide in high yield. We believe that these methods will be of great utility in organic synthesis. We are continuing to explore the stereospecificity of these reactions and the application of this methodology to natural product synthesis**.

References

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*Removal of palladium was facilitated in some cases by the addition of methanol (ca. 20 ml).

**Although these reactions are not catalytic in palladium, we do not believe that this limits their synthetic utility. Palladium is easily and quantitatively recovered in each case by centrifugation or filtration through celite, and may subsequently be recycled.