been described; these include carbonylation,[15] alkylation and arylation,[16] and ketovinylation.[17] Doubly chelated complexes **6f–h** appear to be much less reactive than the foregoing examples. Complex **6g** does not react with carbon monoxide (1 atm) in refluxing xylene for 3 days; the complex is similarly inert to treatment with methyl vinyl ketone in refluxing toluene. Treatment of **6g** with alkyllithium reagents does give rise to regiospecifically alkylated products along with varying amounts of reduction to amino sulfide **4g.** Preliminary studies indicate that other organometallic reagents may be superior to organolithiums for the purpose of regiospecific alkylation or arylation.

The results of these studies and our attempts to exploit complexes similar to **6g** as intermediates in the synthesis of phenolic alkaloids will be reported in due course.

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(8) All new compounds gave satisfactory combustion analyses.
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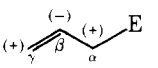
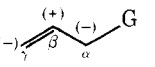
Carbopalladation–Depalladation of Allylic Amines and Sulfides

Sir:

The utility of allylic units in the construction of a variety of organic molecules has been amply demonstrated; the development of new allylic reagents possessing altered reactivity is an area of recent interest. The nucleophilic and electrophilic site reactivity of an allylic moiety may be governed by a terminally attached activating functionality (denoted by E or G); electrophilic and nucleophilic sites have been designated by (+) and (−) symbols, respectively.[1] Practical utilization of



1, E = O, NH, OR, NH_2, halogen

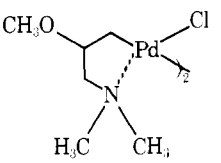


2, G = SR, SOR, SO_2R, NO_2, CN, BR_2, $\overset{+}{P}R_3$, metal

many of these potential reaction modes has been realized: nucleophilic substitution of substrates such as **1** at either α or γ positions is common, reaction of **1** with electrophiles at the β carbon has been achieved via metallation,[2] α and γ alkylation of **2** has recently been accomplished through metallated allylic sulfoxides,[1,3a] sulfides,[3b-l] and boranes.[3m] Similar α and γ alkylation of **1** has been achieved by a polarity inversion involving lithiation of allylic ethers[4a-d] and amines.[4e-g] We are unaware, however, of any previously known real examples of carbon–carbon bond forming reactions using the potentially electrophilic β carbon of species such as **2.**

We report herein the development of a highly efficient method for the regiospecific attachment of carbon nucleophiles to the β-carbon of allylic sulfides and amines, thus providing experimental fulfillment of the anticipated reactivity of **2,** and simultaneously generating a synthetically useful method for polarity inversion of **1** (E = NR_2) at the β position.

Several examples of nucleophilic addition to olefin complexes of transition metals have been reported.[5] Our attention was attracted to the reaction of dimethylallylamine (**3**) and allyl methyl sulfide (**4**) with lithium tetrachloropalladate (LTP) in methanol to produce palladium complexes[6] **5**[7] and



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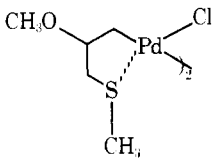

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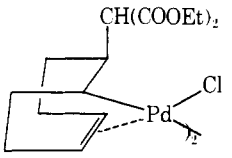

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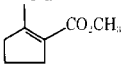
6,[8] respectively. Tsuji[9] and others[10] have observed the addition of sodiodiethylmalonate to 1,5-cyclooctadiene palladium chloride complex (**7**) to generate adduct **8.**

We have found that carbon nucleophiles may be added to allylic sulfides and amines in the presence of lithium tetrachloropalladate in high yield with complete regiospecificity. Thus, addition of 1.0 mol equiv of sodiodiethylmalonate to a tetrahydrofuran (THF) solution containing equimolar amounts of dimethylallylamine and LTP gave rise, after stirring for 6–8 h at room temperature, to palladocycle **9a:**[11] mp 184–187 °C dec; NMR ($CDCl_3$) δ 1.20 (t, 6, J = 7 Hz), 1.5–2.1 (m, 3), 2.53 (m, 2), 2.65 (s, 3), 2.77 (s, 3), 3.15 (d, 1, J = 8 Hz), and 4.12 (q, 4, J = 7 Hz); IR ($CHCl_3$) 5.73, 5.79, and 8.3 μ; 91% yield.[12]

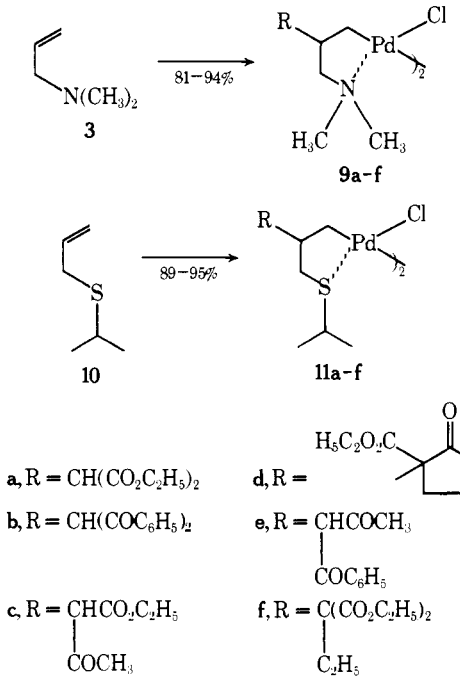
Isopropyl allyl sulfide (**10**) reacted with sodiodiethylmalonate and LTP somewhat more sluggishly, requiring ~24 h at room temperature, or 1 h at reflux, in THF for conversion to **11a:**[11] NMR ($CDCl_3$) δ 1.25 (t, 6, J = 7 Hz), 1.48 (d, 3, J = 7 Hz), 1.56 (d, 3, J = 7 Hz), 1.7–2.7 (m, 5), 2.90 (m, 1), 3.30 (d, 1, J = 7 Hz), and 4.16 (q, 4, J = 7 Hz); IR ($CHCl_3$) 5.73 and 5.79 μ; 95% yield.[12]

As shown in Table I, these reactions have been found to give

Table I. Carbopalladation of Allylic Amines and Sulfides[a]

Nucleophile	Olefin	Palladium complex[11]	% yield[12]	Mp,[b] °C
$NaCH(COOC_2H_5)_2$	3	9a	91	184–187[d]
	10	11a	95	
$NaCH(COC_6H_5)_2$	3	9b	89	154–155
	10	11b	93	195–196[d]
$NaCH(COCH_3)CO_2C_2H_5$	3	9c	93	210–211[d]
	10	11c	93	135–137
	3	9d	91	208–209[d]
	10	11d	94	>300[d]
$NaCHCOCH_3COC_6H_5$	3	9e	93	194–195[c,d] 203–204[d]
	10	11e	92	209–210
$NaC(CO_2C_2H_5)_2C_2H_5$	3	9f	81	108–111
	10	11f	89	

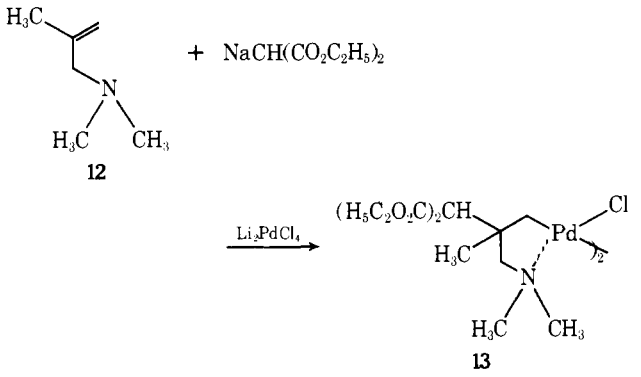
[a] Carried out in THF at 25 °C for 6.24 hr. [b] Complexes 11a and 11f were isolated as yellow oils which we have been unable to obtain in crystalline form. [c] Diastereomers separable by preparative layer chromatography. [d] Decomposition.



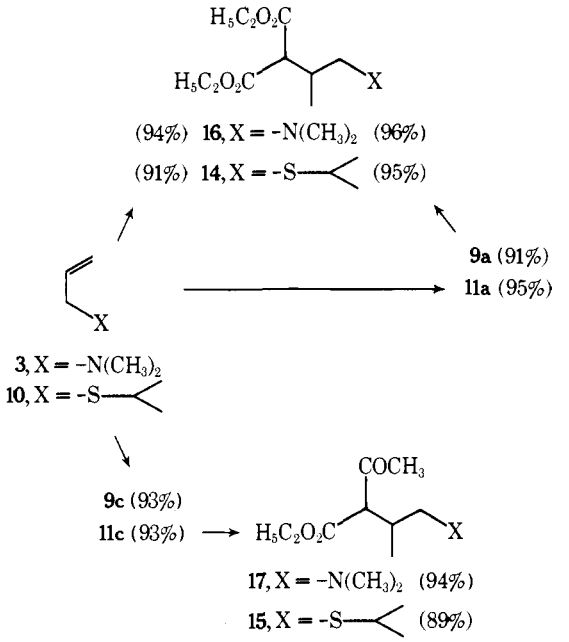
yields of complexes consistently between 80 and 95% with a series of representative β-dicarbonyl enolates. However, we have been unable to obtain satisfactory results using nucleophilic agents which lie outside a narrow pK_a range.[13] For example, use of the lithium enolate of cyclohexanone (generated from LDA in THF) gave rise to no perceptible amount of palladocycle; other cyclic or acyclic unstabilized enolates behaved similarly. Copper and Grignard reagents react, even at −78 °C, to give metallic palladium and an intractable mixture of products.

The bidentate nature of ligands **3** and **10** is apparently necessary for the reaction to proceed. Allyl alcohol, allyl phenyl ether, ethyl acrylate, and 1-octene all failed to give any trace of addition product with sodiodiethylmalonate and LTP in THF.

The addition has been shown to be relatively insensitive to steric crowding in the nucleophilic partner: sodiodiethylethylmalonate and sodio-2-carbomethoxycyclopentanone gave palladocycles in excellent yield (Table I). Steric effects in the allylic substrate appear to be somewhat more important, but still tolerable: use of 2-methyl-3-dimethylamino-1-propene (**12**) with sodiodiethylmalonate and LTP in THF containing 20% hexamethylphosphorictriamide (HMPA) gave rise to palladocycle **13**,[11] mp 135–136 °C, in 60% yield.[14] In view of the traditional difficulty of nucleophilic displacement at tertiary centers, we conceive the formation of **13** to be an important and potentially very useful observation.



Complexes **9** and **11** may be conveniently reduced to the corresponding γ-amino or γ-alkylthio esters or ketones. Thus, palladocycle **11a** was instantaneously reduced by sodium borohydride[15] at −78 °C in a 1:4 methanol–tetrahydrofuran mixture to produce the sulfide **14**[11] in 95% yield.[12] These conditions led to competing carbonyl reduction with complex **11c**; this difficulty was overcome by the use of sodium cyanoborohydride in 1:4 methanol–THF at −78 °C to give **15**[11] in 89% yield.[12] Sodium borohydride reduction of **9a** affords **16**[11] in 90% yield;[12] this conversion could also be conveniently carried out simply by bubbling hydrogen through a THF solution of **9a** for 2 min, giving **16** in 96% yield.[12] Similarly, amino ketone **17**[11] was produced in 94% yield[12] by hydrogenation of **9c**. Thus, complexes **9a–f** could be reduced efficiently by either hydrogen or sodium borohydride; complexes **11a–f** were reduced by sodium borohydride, but were found to be refractory to hydrogenation in THF for 1 h.

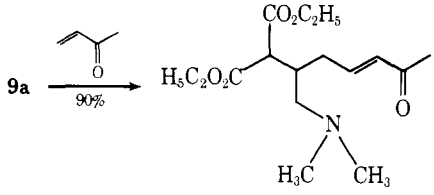


Isolation of the intermediate palladium complex is unnecessary for the high yield preparation of these γ-amino and γ-alkylthio esters and ketones: treatment of a mixture of **10** and LTP in THF with sodiodiethylmalonate at 25° for 24 h, followed by cooling to −78 °C and introduction of methanolic sodium borohydride, leads to the isolation of **14** in 91% yield.[12] A mixture of **3**, LTP, and sodiodiethylmalonate in THF was stirred at 25 °C for 6 h; hydrogen was then bubbled through

the resulting yellow solution for 2 min, providing **16** in 94% yield.[12]

A typical experimental procedure follows. To a solution of 0.33 g (1.26 mmol) of LTP in 20 mL of THF (distilled from lithium aluminum hydride) under nitrogen was added 170 μL (1.3 mmol) of dimethylallylamine. A yellow precipitate immediately formed and redissolved after about 1 min to produce a red solution. To this solution was added 0.23 g (1.26 mmol) of sodiodiethylmalonate in 4 mL of THF. The color of the solution immediately faded to yellow-orange. Stirring at room temperature was continued for 6 h, and the mixture was diluted with chloroform. The chloroform solution was washed with water, dried, and evaporated to leave 0.45 g of yellow crystalline complex **9a,** which was recrystallized from benzene/hexane to provide analytically pure material.

Although complexes **9a–f** and **11a–f** are insensitive to air and moisture and are amenable to shelf storage for months, they are also sufficiently reactive, under appropriate conditions, to allow replacement of palladium by carbon moieties. For example, treatment of **9a** with methyl vinyl ketone in refluxing benzene containing triethylamine[16] gives adduct **18**[11] in 90% yield.[12]



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We foresee considerable synthetic utility in carbopalladation and subsequent transformations. We are actively investigating the range of allylic substrates amenable to these reactions, the further applicability of palladocycles to formation of new carbon–carbon bonds, and the stereochemistry of the nucleophilic addition–reduction sequence. Applications of this chemistry to the synthesis of natural products are in progress. The results of these studies will be reported in due course.

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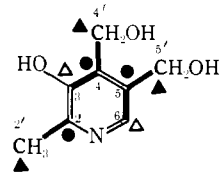
Biosynthesis of Vitamin B_6. The Incorporation of [1,3-$^{13}C_2$]Glycerol[1]

Sir:

Radioactivity from specifically ^{14}C-labeled glycerol is incorporated nonrandomly into pyridoxol (Scheme I). Chemical degradation showed one third of the activity of pyridoxol derived from [2-^{14}C]glycerol to be located at each of C-2, C-4, and C-5, accounting for all radioactivity in the sample.[2] These three carbon atoms were free of activity when [1-^{14}C]glycerol served as the precursor.[2,3] It was established that one fifth of the activity within pyridoxol derived from this substrate resides at each of C-2′, C-4′, and C-5′.[3] The only uncertainty which remains concerns the mode of distribution of the unaccounted two fifths of activity from [1-^{14}C]glycerol among the two carbon atoms of pyridoxol, C-3 and C-6. We have resolved this uncertainty by determining the quantitative distribution of ^{13}C in pyridoxol derived from [1,3-$^{13}C_2$]glycerol by ^{13}C NMR spectrometry.

A 2-L culture of *E. coli* B, strain WG2, was incubated in the presence of [1,3-$^{13}C_2$]glycerol containing 90% isotopic enrichment at each terminal carbon atom (Merck Sharp & Dohme, Montreal, Canada) (1 g). This tracer served as the sole carbon source. Culture conditions and the procedure for the isolation of pyridoxol hydrochloride were as previously described.[3] In the carrier dilution procedure of the isolation, 3.80 mg of unlabeled pyridoxol hydrochloride was added. All reisolated pyridoxol hydrochloride (2.0 mg) was transferred to a standard melting point tube (90 mm × 1 mm i.d.) and dissolved in D_2O (30 μL). The proton noise-decoupled (without NOE) carbon-13 spectrum[4] of this solution (~0.4 M) was determined on a JEOL PS-100 NMR spectrometer, operating in the pulse Fourier transform mode. The natural abundance

Scheme I



[a] Mode of incorporation of glycerol into pyridoxol. Sites of activity derived from [1-^{14}C]glycerol (▲, △) (relative specific activity ~20%) and from [2-^{14}C]glycerol (●) (relative specific activity ~33%) shown by degradation (▲, ●) or inferred (△).