was mixed with the amino acid solution (2 mL) at 25 °C, measurement of time was started (t = 0).

(15) The optical rotation was measured with a Perkin-Elmer Model 241 MC polarimeter. In regard to the optical rotation, the following abbreviations are used: mixture, mix.; catalyst, cat.; amino acid, amn. The subscript t indicates the time when the reaction was stopped.

(16) A solution of the racemic catalyst **2a** with the same concentration as that of the solution of **2b** was also prepared and mixed with L- or D-amino acid solution. The difference in the observed $\alpha_0^{mix.}$ values between the mixture containing **2b** and that containing **2a** was regarded as $\alpha_0^{cat.}$.

(17) For example, see M. Ando and S. Emoto, *Bull. Chem. Soc. Jpn.*, **42**, 2628 (1969).

(18) The calculation is based on the following equation: $K_{obsd} \times t = 2.30 \times (\log \alpha_0^{amn} - \log \alpha_t^{amn})$.

(19) When the racemization yield calculated as $100(\alpha_0^{amn} - \alpha_t^{amn})/\alpha_0^{amn}$ reached 70% (t = 40 h), the racemization rate of L-glutamic acid with **2b** decreased to the almost equal value to that of D-glutamic acid.

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## Regiocontrolled Aromatic Palladation

Sir:

The intramolecular coupling of phenols occupies a central position in the biosynthesis of a large number of structurally diverse natural products.[1] For example, *O*-methylnorbelladine (**1a**) is converted in vivo to oxomaritidine (**2**), and *O,N*-dimethylnorbelladine (**1b**) serves as precursor to narwedine (**3**).[2] Much progress toward the laboratory emulation of these conversions has been made in recent years,[3] but, as yet, no rational methodology exists to allow selective ortho coupling of substrates such as **1**.


1a, R = H
b, R = CH₃

2

3
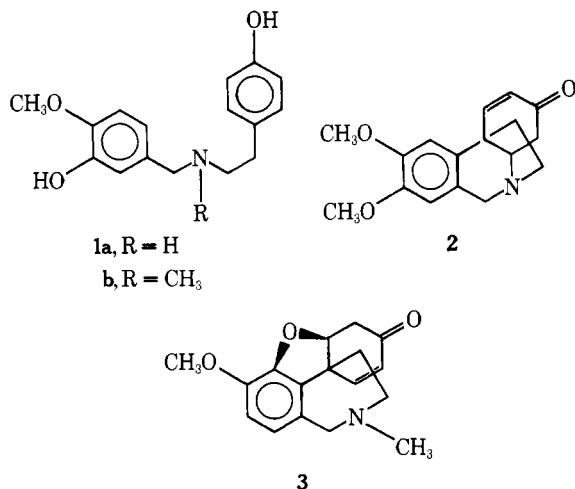
Our approach to this problem involves the development of procedures to allow the regiospecific activation of 3,4 dioxy-

genated benzylic amines (e.g., **4**) at either C-2 or C-6, followed by intramolecular replacement of activating functionality by an appropriate carbon moiety. We report herein the experimental realization of the first of these goals.

4a-g

5
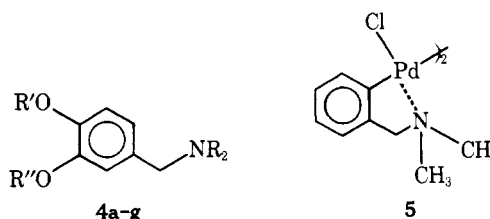
We initially dismissed the potential use of lithium[4] or copper as such activating groups, owing to their high reactivity toward a variety of functionality.[5] Instead, our attention was attracted to the facile electrophilic palladation of dimethylbenzylamine, giving rise to the stable ortho palladated complex **5** in high yield.[6,7]

Palladation of benzylic amines **4a-g** by lithium tetrachloropalladate (1 mol equiv) in methanol containing excess triethylamine or diisopropylethylamine gave complexes **6a-g** in high yield, as summarized in Table I. These complexes are

6a-e

6f-g
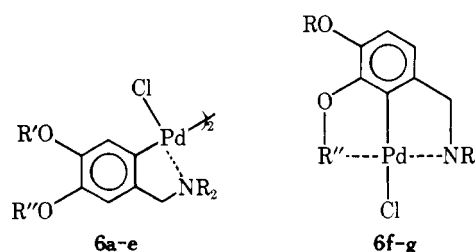
creamy yellow crystalline solids, remarkably stable to air and moisture, withstanding shelf storage without noticeable decomposition for indefinite periods of time. That palladation is tolerant of a range of functionality is indicated by the facile formation of complex **6b**, containing a free phenolic hydroxyl group. We have detected no side products from the reaction: complete material balance was realized through unreacted benzylic amine; yields based on recovered starting benzylic amine are virtually quantitative in all cases.
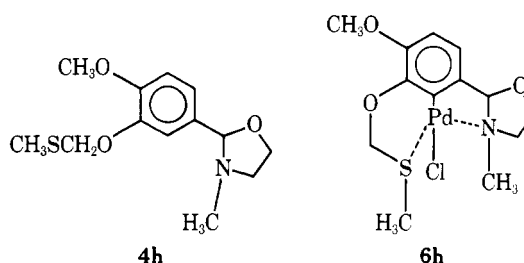

4h

6h

Table I. Regiospecificity of Ortho Palladation

Benzylic amine[8]				Palladium complex[8]				
No.	R	R'	R''	No.	6 isomer, %[a]	2 isomer, %[a]	% yield[b]	Mp,[c] °C
4a	C₂H₅	-CH₂-		**6a**	100	0	98	183–185[d]
4b	C₂H₅	CH₃	H	**6b**	100	0	95	158–160[d]
4c	C₂H₅	CH₃	COCH₃	**6c**	100	0	52	177–178[d]
4d	C₂H₅	CH₃	CH₂OCH₃	**6d**	100	0	85	155–156[d]
4e[9]	C₂H₅	CH₃	CH₂C₆H₅	**6e**	100	0	58	165–167[d]
4f[9]	C₂H₅	CH₃	CH₂SC₆H₅	**6f**	0	100	42	197–199.5[d]
4g[10]	C₂H₅	CH₃	CH₂SCH₃	**6g**	0	100	95	150–152
4h[11]				**6h**			93	235–237[d]

[a] Determined by NMR analysis; limit of detection of minor isomer: ~4%. [b] Yields of isolated, crystalline, chromatographically and spectrally homogeneous material. Reported yields are *not* based on recovered starting benzylic amine. [c] Uncorrected. [d] Decomposition.

**Table II.** ^{1}H NMR Spectra^a of Palladium Complexes

6a–g

	Chemical shifts^{b-d}					
Complex	H$_2$	H$_5$	H$_6$	H$_7$,H$_{7a}$	R'	R''
6a	6.72 [6.59]	6.43 [5.85]		3.86 [4.01]	5.80 [5.60]	5.80 [5.60]
6b	6.67 [6.60]	6.47 [5.83]		3.90 [4.00]	3.83 [2.88]	
6c	6.75 [6.70]	6.37 [6.03]		3.90 [4.00]	3.77 [2.87]	2.27 [2.22]
6d	6.68 [6.82]	6.68 [5.92]		3.90 [4.07]	3.80 [2.87]	5.10 [5.08] (OCH$_2$O)
						3.48 [3.47] (OCH$_3$)
6e	6.75 [6.60]	6.47 [5.93]		3.83 [4.03]	3.83 [2.88]	5.03 [5.60]
6f		6.65 (d, 8)	6.84 (d, 8)	4.49 (d, 14)	3.83	2.67, SCH$_3$
				3.49 (d, 14)		5.06 (d, 11) (OCH$_2$S)
						4.16 (d, 11) (OCH$_2$S)
6g		6.65 (d, 8)	6.85 (d, 8)	4.48 (d, 14)	3.78	7.89–8.04 (m) 2 (SC$_6$H$_5$)
				3.62 (d, 14)		7.50–7.82 (m) 3 (SC$_6$H$_5$)
						5.21 (d, 11) (OCH$_2$S)
						4.35 (d, 11) (OCH$_2$S)

^{a} Recorded at 90 MHz on a Perkin-Elmer R-32 spectrometer, in CDCl$_3$ solution. ^{b} Chemical shifts in parts per million (δ) downfield from TMS as internal standard (multiplicity, coupling constants in J, Hz). ^{c} Resonances are singlets unless otherwise noted. ^{d} Resonances in brackets were observed upon addition of triphenylphosphine (≥ 1 equiv); the absence of a bracketed value indicates no change in chemical shift in the presence of added triphenylphosphine.

The observed regiospecificity of metalation is apparently controlled by the complexing ability of the group attached to C-3.[12] Methylthiomethyl (MTM) ethers[10] **4g** and **4h** appear to be exceptionally well suited to this task. In addition to the completely regiospecific metallation at C-2 in complexes **6g** and **6h**, the rate of metalation is significantly enhanced by the presence of an MTM ether at C-3. Whereas amine **4a** requires 5-10 min for complete palladation by lithium tetrachloropalladate in methanol at 0 °C, substrates **4g** and **4h** are instantaneously metallated at −78 °C. Exclusive metalation of amines **4a–e** at the 6 position may be attributed to the feeble coordination of oxygen ligands to palladium, along with steric effects.

Structures were assigned to **6a–h** primarily on the basis of their ^{1}H NMR spectra (Table II). Aromatic protons in **6a–e** appear as slightly broadened singlets, indicative of a para relationship. Addition of triphenylphosphine to deuteriochloroform solution of **6a–e** produced a dramatic upfield shift of the H$_5$ resonance and a similar large upfield shift of the adjacent methoxy resonances (C-4); other perturbations were relatively minor. These observations are consistent with the previous assertion[13] that triphenylphosphine prefers a trans relationship to the amino ligand in **7**. This arrangement in **6a–e**


7
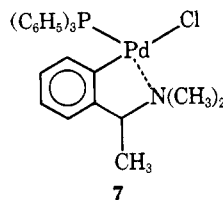
would place substituents at C-4 and C-5 within the shielding cone of an aromatic ring. Also consistent with our assignments is the observation of typical ortho (8 Hz) aromatic coupling constants in **6f** and **6g**. Addition of triphenylphosphine to **6f, 6g** and **6h** in deuteriochloroform produced no observable changes in chemical shift, and both complexes were recovered

unchanged from the mixture. Furthermore, molecular weight measurements[14] indicate dimeric structures for **6a–e**, whereas complexes **6f, 6g**, and **6h** are clearly monomeric (**6g** calcd mol wt, 410.25; found, 410.27).

In a typical experiment, a solution of 0.426 g of lithium tetrachloropalladate in 20 mL of methanol under nitrogen was cooled to 0 °C. To this red solution was added via syringe a precooled (0 °C) mixture of 0.23 mL of triethylamine, 0.434 g of benzylic amine **4g**, and 20 mL of methanol, immediately producing a faintly yellow solution and a creamy yellow precipitate. Filtration of the precipitate followed by washing with methanol and drying gave 0.630 g of complex **6g** (95%), free of impurities by TLC and NMR analysis. An additional small portion of **6g** could be obtained by evaporation of methanol from the filtrate and dissolution of the residue in chloroform. The chloroform solution was then extracted with water, dried, and evaporated to leave crystalline palladium complex. Analytically pure **6g** was obtained by recrystallization from chloroform/hexane.

The facility with which **4g** and **4h** gave rise to complexes **6g** and **6h** led us to explore the possibility of orthopalladation of the methylthiomethyl ether of phenol (**8**). Treatment of **8** with lithium tetrachloropalladate in methanol containing triethylamine gave rise only to complex **9**; no orthopalladated product could be detected.

8   **9**
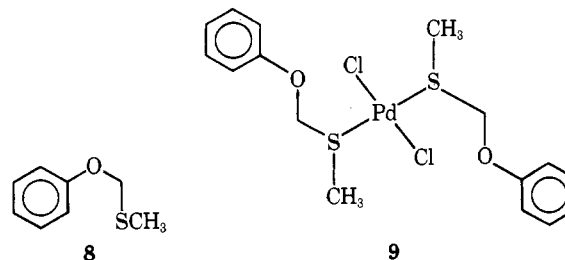
Several procedures for the regiospecific replacement of palladium by carbon moieties in complexes similar to **6a–e** have

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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(1) For a review of this topic, see A. R. Battersby, "Oxidative Coupling of Phenols", W. I. Taylor and A. R. Battersby, Ed., Marcel Dekker, New York, N.Y., 1967.
(2) D. H. R. Barton and T. Cohen, "Festschrift A. Stoll", Birkhauser, Basel, 1957, p 117; J. M. Paton, P. L. Pauson, and T. S. Stevens, *J. Chem. Soc. C*, 1309 (1969).
(3) See, for example, M. A. Schwartz and I. S. Mami, *J. Am. Chem. Soc.*, **97**, 1239 (1975).
(4) R. C. Ronald, *Tetrahedron Lett.*, 3973 (1975).
(5) C. F. Normant, *Synthesis*, 63 (1972).
(6) A. C. Cope and E. C. Friedrich, *J. Am. Chem. Soc.*, **90**, 909 (1968).
(7) Cyclometallation reactions have recently been reviewed: J. Dehand and M. Pfeffer, *Coord. Chem. Rev.*, **18**, 327 (1976).
(8) All new compounds gave satisfactory combustion analyses.
(9) Prepared in >90% yield from chloromethyl phenyl sulfide and 3-hydroxy-4-methoxy-N,N-diethylbenzylamine: R. A. Holton and R. V. Nelson, manuscript in preparation.
(10) Prepared in >90% yield from chloromethyl methyl sulfide and 3-hydroxy-4-methoxy-N,N-diethyl benzylamine: R. A. Holton and R. G. Davis, *Tetrahedron Lett.*, 533 (1977).
(11) Prepared in 95% yield from the MTM ether[10] of isovanillin and 2-(methylamino)ethanol, bp 210–212 °C (1 mm); see, for example, E. D. Bergmann, E. Zimkin, and S. Pinchas, *Recl. Trav. Chim. Pays-Bas*, **71**, 237 (1952).
(12) Our initial attempts to direct palladation to C-2 involved the use of phosphinite as directing functionality: diphenylphosphinite derivative **4i** (R = C₂H₅; R′ = CH₃; R″ = P(C₆H₅)₂) gave rise to a complex apparently analogous to **6f** and **6g**; however, this complex deteriorated rapidly upon attempted purification and remains relatively poorly characterized. This approach has been abandoned in deference to the more palatable use of sulfur ligands.
(13) S. Otsuka, A. Nakamura, T. Kano, and K. Tani, *J. Am. Chem. Soc.*, **93**, 4301 (1971).
(14) Performed by Dr. C. S. Yeh, Purdue Microanalytical Laboratory.
(15) J. M. Thompson and R. F. Heck, *J. Org. Chem.*, **40**, 2667 (1975).
(16) S. Murahashi, Y. Tanaba, M. Yamamura, and I. Moritani, *Tetrahedron Lett.*, 3749 (1974).
(17) R. A. Holton, *Tetrahedron Lett.*, 355 (1977).
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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, NH₂, halogen

2, G = SR, SOR, SO₂R, NO₂, CN, BR₂, P̅R₃, metal
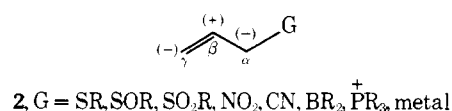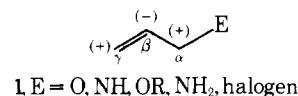
many of these potential reaction modes has been realized: nucleophilic substitution of substrates such as **1** at either α or γ positions is common, reaction of **1** with electrophiles at the β carbon has been achieved via metallation,[2] α and γ alkylation of **2** has recently been accomplished through 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 = NR₂) 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

5

6

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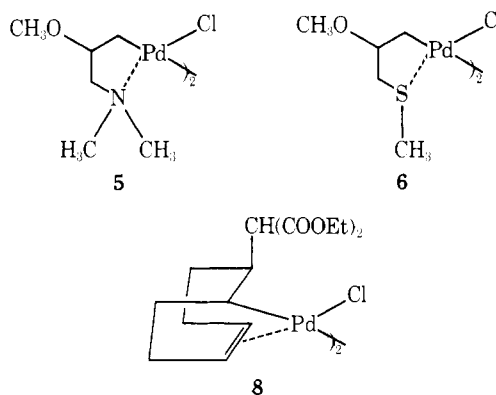
6,[8] respectively. Tsuji[9] and others[10] have observed the addition of sodiodiethylmalonate to 1,5-cyclooctadiene palladium chloride complex (**7**) to generate adduct **8**.

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 (CDCl₃) 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 (CHCl₃) 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 (CDCl₃) 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 (CHCl₃) 5.73 and 5.79 μ; 95% yield.[12]

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