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β'-Lithiation of α,β-Unsaturated Secondary Amides

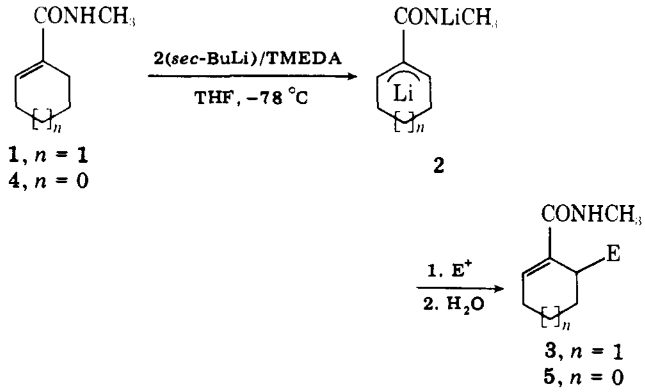
Sir:

Although "ortho" metalations of aromatic systems have been known for some time, directed metalations of nonaromatic systems have been much less studied.[1] The potential value of regiospecifically metalated functionally substituted molecules is high and investigations in this area could provide both new and useful results.

Consideration of the functional groups which might be generally effective for directed metalations of nonaromatics suggests that dilithiation of secondary amides would be of interest for at least three reasons: initial proton removal from nitrogen would deactivate the carbonyl group toward both nucleophilic addition and enolate anion formation; the secondary amide is one of the strongest directors of "ortho" metalation; and the amide group can be readily converted into other functions.[1-4]

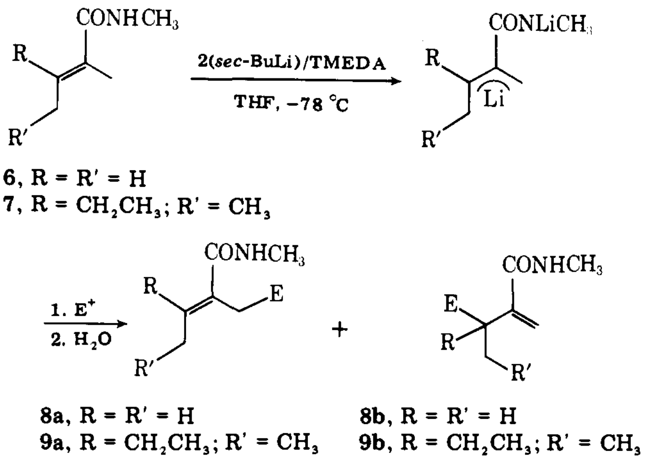
We now report that in the dilithiation of α,β-unsaturated secondary amides the second metalation occurs at the β' position. This result is unprecedented for an α,β-unsaturated carbonyl system which has potentially acidic γ and β protons.

Treatment of *N*-methyl-1-cyclohexenecarboxamide (**1**) with 2.1 equiv of *sec*-butyllithium–tetramethylethylenediamine in tetrahydrofuran at −78 °C followed by addition of methanol-*O-d*, *n*-hexyl bromide, tri-*n*-butyltin chloride, carbon dioxide, acetone, or benzophenone gives the *N*-methyl-6-substituted 1-cyclohexenecarboxamides **3** in useful yields as shown in Table I. Similar results are obtained for the conversion of *N*-methyl-1-cyclopentenecarboxamide (**4**) into the β'-substituted products **5**, also shown in Table I. The dilithiated species **2** is the proposed intermediate in these reactions.



1, *n* = 1
4, *n* = 0
2
3, *n* = 1
5, *n* = 0

Acyclic cases behave similarly. Thus, (*E*)-*N*-methyl-2-methyl-2-butenamide (**6**) and *N*-methyl-3-ethyl-2-methyl-2-pentenamide (**7**) on treatment with 2.1 equiv of *sec*-butyllithium–tetramethylethylenediamine in tetrahydrofuran at −78 °C for 15–45 min, followed by reaction with an added electrophile, provide the products **8** and **9** in the yields indicated in Table I. The formation of isomers **8a–8b** and **9a–9b**, which were separated and characterized in each case, does show the lack of regiospecificity often found with allylic organometallics. The reaction of **7** is particularly interesting as it demonstrates regiospecific metalation even in the presence of a γ proton which is cis to the amide group.



6, R = R' = H
7, R = CH$_2$CH$_3$; R' = CH$_3$
8a, R = R' = H
9a, R = CH$_2$CH$_3$; R' = CH$_3$
8b, R = R' = H
9b, R = CH$_2$CH$_3$; R' = CH$_3$

These results suggest a new direct approach to the synthesis of a variety of α,β-unsaturated carbonyl derivatives. For example, the lactones **10** and **11** are produced in 52 and 33%

Table I. Lithiation and Electrophilic Substitution of **1**, **4**, 6, and 7

amide	equiv of *s*-BuLi/TMEDA	electrophile	product	yield,[a] %
1	2.1/2.1	CH_3OD	**3**, E = D	81 (79 d_1)
1	2.1/2.1	$CH_3(CH_2)_5Br$	**3**, E = $(CH_2)_5CH_3$	58
1	2.1/2.1	$(n\text{-}C_4H_9)_3SnCl$	**3**, E = $Sn(n\text{-}C_4H_9)_3$	49
1	2.7/2.3	CO_2	**3**, E = CO_2H	42
1	2.1/2.1	$(CH_3)_2CO$	**3**, E = $COH(CH_3)_2$	62
1	4.5/4.2	$(C_6H_5)_2CO$	**3**, E = $COH(C_6H_5)_2$	59
4	3.3/6.3	CH_3OD	**5**, E = D	44 (98 d_1)
4	2.1/2.1	$CH_3(CH_2)_5Br$	**5**, E = $(CH_2)_5CH_3$	30[b]
4	3.3/8.0	$(C_6H_5)_2CO$	**5**, E = $COH(C_6H_5)_2$	53
6	2.1/2.1	CH_3OD	**8a**, **8b**, E = D	77 (96 d_1)[c]
6	2.1/2.1	$CH_3(CH_2)_5Br$	**8a**, **8b**, E = $(CH_2)_5CH_3$	78[d]
7[e]	2.1/2.1	CH_3OD	**9a**, **9b**, E = D	84 (67 d_1)[f]
7[e]	2.1/2.1	$(CH_3)_2CO$	**9a**, **9b**, E = $COH(CH_3)_2$	55[g,h]
7[e]	2.1/2.1	$CH_3(CH_2)_5Br$	**9a**, **9b**, E = $(CH_2)_5CH_3$	56[b,i,j]

[a] Analytically pure material. [b] The spectral properties for **5** and **9a** (E = *n*-hexyl) are satisfactory but analytical samples have not been obtained. [c] 89:11 **8a:8b**. [d] 43:57 **8a:8b**. [e] The amide **7** contains 10% *N*-methyl-3-ethyl-2-methyl-3-pentenamide. [f] 93:7 **9a:9b**. [g] 95:5 **9a:9b**. [h] Contains ~25% **11**. [i] In addition, 10% *N*-hexyl-*N*-methyl-amides corresponding to **9a** and **9b** are obtained. [j] 23:77 **9a:9b**.

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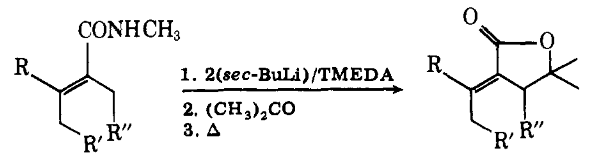
overall yield from **1** and **7**, respectively, a result which also provides chemical confirmation of the position of substitution.



1, R = H; R′, R″ = CH_2CH_2 **10**, R = H; R′, R″ = CH_2CH_2
7, R = CH_2CH_3; R′ = CH_3; R″ = H **11**, R = CH_2CH_3; R′ = CH_3; R″ = H

Specific activation of the β' position for metalation by the amide is indicated by the fact that cyclohexene is not metalated under similar conditions and that similar dimetalations of allyl and cyclopropyl carbinols generally require much more forcing conditions.[5]

Dimetalations of α,β-unsaturated secondary amides which lack a β' hydrogen have been reported to occur with proton loss from the γ carbon, a result which is consistent with the behavior of other α,β-unsaturated carbonyl derivatives.[6,7] Metalation of an α,β-unsaturated carbonyl system at the β' position seems to be precedented only by formation of a transient intermediate for a case in which γ protons are not present. Kauffmann et al. have found that *N,N*-diisopropyl-2-methylpropenamide undergoes allylic metalation prior to either self-addition or in situ addition to azobenzene on treatment with lithium diisopropylamide at −60 °C.[8,9] We have found that *N,N*-dimethylcyclohexenecarboxamide on treatment with *sec*-butyllithium–tetramethylethylenediamine under conditions for the metalation of **1** gives a mixture of products which appear to result from the expected additions and γ metalations. We also observe that *N*-methyl-2,3-dimethyl-2-butenamide appears to undergo substitution at more than one methyl group on treatment with *sec*-butyllithium–tetramethylethylenediamine at −78 °C in tetrahydrofuran and subsequent treatment with benzophenone.

In summary, we have found that directed lithiation and electrophilic substitution can be achieved selectively at the β' position of α,β-unsaturated secondary amides in the presence of γ and β protons. This result is useful for achieving carbon–carbon bond formation at a site in α,β-unsaturated carbonyl systems which has not been previously recognized as readily available for substitution. Moreover, the demonstration of a convenient, selective, and novel, directed metalation in a nonaromatic system by a group which is available for subsequent transformations could lead to development of a number of new synthons. Investigation of the apparent role of the amide as a strong complexing agent in directed metalations, extensions of other functionalities, and possibilities for more remote metalations are under further study.

Acknowledgment. We are grateful to the National Institutes of Health-Institute of General Medicine for support of this work.

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(9) NOTE ADDED IN PROOF. H. W. Gschwend independently has observed β' metalation of methyl acrylamides: private communication, March 26, 1980.

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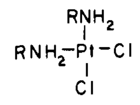
Antitumor Agents. Synthesis of Novel *cis*-Palladium Complexes and Their Action on Supercoiled DNA

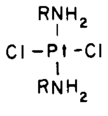
Sir:

In 1969 Rosenberg et al. reported that *cis*-dichlorodiammineplatinum(II) (**1**) was the potential antitumor metal chelate;[1] currently **1** has worldwide application in the treatment of cancer.[1,2] However, owing to its severe nephrotoxicity, various analogues have been synthesized by ligand modification[3] to circumvent this limitation. In contrast to these cytotoxic platinum complexes, the palladium analogues were reported to be marginally active[4] and more recently demonstrated to be active against Landschutz ascites (in vitro and in vivo) and Sarcoma 180 systems in anticancer screening.[5] The antitumor properties of several related *cis*-(amine)$_2$PtX_2 complexes and the dramatic inactivity of the corresponding trans isomer have been shown throughout initial screening and clinical trials. To extend the ligand framework in these antitumor agents, we recently reported *trans*-**3**,[6] which possesses structural similarity to **2** but has two trans σ-carbon–palladium bonds. *We herein report the synthesis of the stable cis-organometallic reagent* **4**, *which contains two cis σ-palladium–carbon bonds making up a novel* [5.5.5] *fused-ring system*[7] *and has the ability to nick supercoiled DNA at low concentrations.*



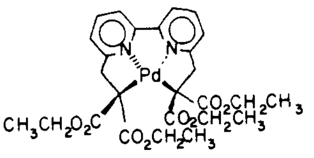
$\mathrm{RNH_2{-}\overset{\displaystyle RNH_2}{\underset{\displaystyle Cl}{Pt}}{-}Cl}$

1 (R=H) [DDP]



$\mathrm{Cl{-}\overset{\displaystyle RNH_2}{\underset{\displaystyle RNH_2}{Pt}}{-}Cl}$

2



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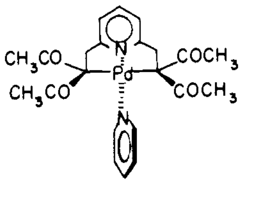

3

Treatment of 6,6′-dibromo-2,2′-bipyridyl with excess *n*-butyllithium in THF at −100 °C gave the dilithio intermediate, which upon treatment with *N,N*-dimethylformamide gave 6,6′-diformyl-2,2′-bipyridyl:[11] mp 236–237 °C. Reduction with sodium borohydride in absolute methanol gave the diol, which upon treatment with redistilled thionyl chloride afforded (45% overall) **5**: mp 157–158 °C. When a mixture of **5**, diethyl malonate, and anhydrous potassium carbonate in DMF was stirred at 25 °C for 12 h, the desired bis adduct **6**[12] [mp 55–56

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