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Transition Metal Promoted Synthesis of N,N-Dimethyl Tertiary Amides from 1,3-Dienes

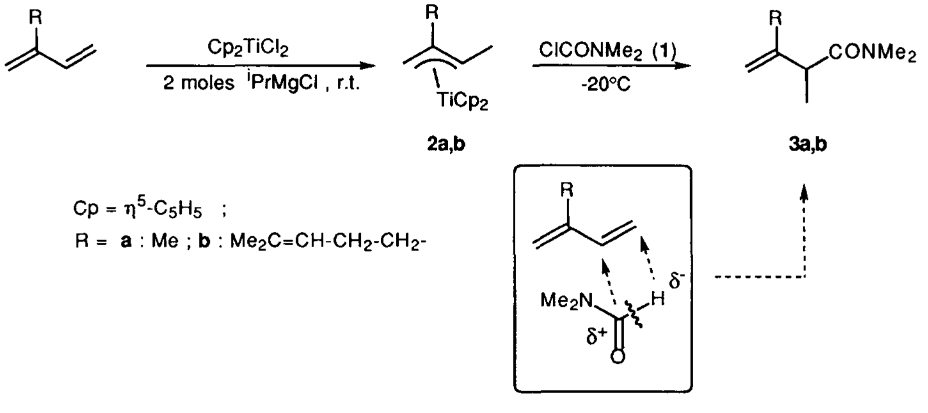
Jan Szymoniak*, Didier Felix and Claude Moïse*

Laboratoire de Synthèse et d'Electrosynthèse Organométalliques associé au CNRS, Faculté des Sciences, 6 bd Gabriel,
21000 Dijon, France

Abstract: A new procedure for a direct conversion of 1,3-dienes into N,N-dimethyl insaturated tertiary amides is reported. η^3-Allyltitanium(III) complexes generated *in situ* from various dienes reacted regiospecifically with dimethylcarbamoyl chloride to afford products in good to moderate yields. Acyclic, cyclic, incorporated into the polyene systems, and even sterically demanding dienes can be employed.

The conversion of 1,3-dienes into η^3-allyltitanocene complexes is a well known reaction.[1] Such complexes having nucleophilic properties add to aldehydes in a regio- and stereocontrolled fashion to afford anti homoallylic alcohols.[2] The use of only a few other electrophiles have been mentioned, such as benzalanine, acetone, phenyl isocyanate, acetonitrile[3a] or carbon dioxide.[3b]

We have developed some new functionalized allyltitanium reagents, and focused our attention on their application in organic synthesis.[4] In keeping with this aim, the search for new electrophiles appears as a complementary task. In this matter, we have recently noticed that methyl chloroformate can react with allyltitanocene complexes.[5] The reaction provides a one-pot conversion of 1,3-dienes into β,γ-unsaturated esters. With this finding, we expected the analogous incorporation of the amide function.



2a,b

3a,b

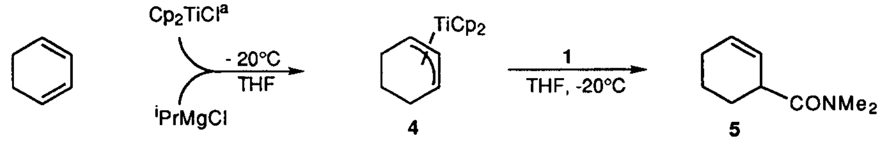
Cp = η^5-C_5H_5 ;
R = **a** : Me ; **b** : $Me_2C{=}CH{-}CH_2{-}CH_2{-}$

Scheme 1

Cheap and available in bulk (Aldrich) dimethylcarbamoyl chloride was chosen as a potential electrophilic reagent. First, we examine the reaction using a simple acyclic diene. The allyltitanocene complex **2a** (Scheme 1) was prepared by a conventional method. The reaction of Cp_2TiCl_2 (1eq) with two moles of ^{i}PrMgCl and isoprene (1eq) was carried out under argon at room temperature. Thereafter, the THF solution of **2a** was cooled to -20°C and equimolar quantity of **1** was added slowly via syringe. After stirring for 1h at -20°C the reaction mixture was quenched with a saturated solution of $NaHCO_3$. Extraction with ether followed by flash chromatography purification afforded amide **3a** (75%) as the sole product. The more substituted γ-carbon of the allyl moiety linked then to the N,N-dimethylcarboxamide function. Such regiocontrol is consistent with the regioselectivity exhibited by η^3-allyltitanium complexes in their reactions with aldehydes.[2]

Next we examined more complicated diene substrates. Myrcene has been shown to give a stable allyltitanium complex **2b** (Scheme 1), unlike several other 1,3-dienes which contain a supplementary isolated double bond.[6] The reaction involving **2b** carried out as above afforded amide **3b** (70%),[7] analogous to **3a**. *In both cases the overall transformation is thereby rendered the synthetic equivalent of the anti-Markownikov-like addition of dimethylformamide to a double bond of 1,3-diene (Scheme 1).*

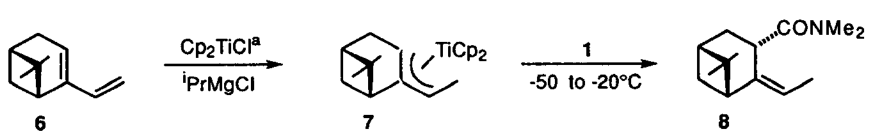
Having demonstrated the feasibility of the preparation of amides from simple acyclic dienes, our attention was focused on the use of cyclic substrates. First, we studied the reaction of 1,3-cyclohexadiene for which regiochemistry is not concerned. The reaction of the corresponding complex **4** with **1** occurred readily at -20°C to produce the expected amide **5** (72%) (Scheme 2).



(a) = preformed : Cp_2TiCl_2 + ^{i}PrMgCl , r.t.

Scheme 2

Further experiments dealt with more particular cyclic systems. Nopadiene (**6**) derived complex **7** has been shown to exhibit limited reactivity.[8] Nevertheless, **7** reacted with dimethylcarbamoyl chloride (**1**) in standard conditions to produce compound **8** (38%)[7] as a unique product, bearing the amide function on the C3-atom and possesing the Z-configuration of the double bond (NOE mesurements) (Scheme 3).

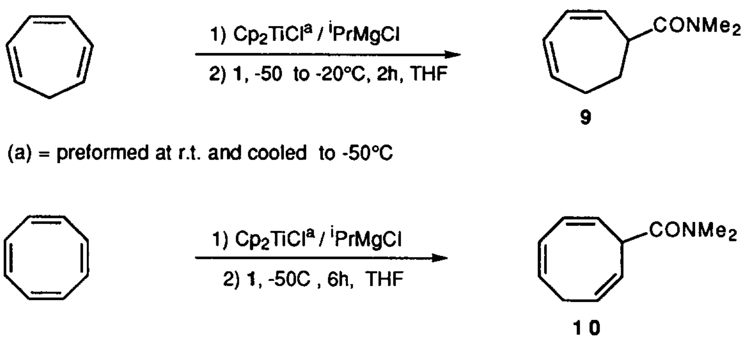


(a) = preformed at r.t. and cooled to -50°C

Scheme 3

The regiochemistry observed is consistent with the results obtained for similar reactions in which aldehydes were employed as electrophiles.[8] In our opinion, the preferred formation of the exocyclic over the endocyclic (attack on C10) C=C bond in the product can be rationalized by assuming a reactant-like cyclic transition state with the endocyclic precursor double bond.[9]

Methods for the functionalization of a seven-membered ring were developed in relation to the useful synthons or biologically active molecules.[10] However, those using organometallic methodology usually involve a nucleophile rather than an electrophile addition to the cationic iron,[11] molybdenum[12] or palladium[13] complexes. We have recently reported that cycloheptenyl-η^3-allyltitanium complexes, derived from cycloheptatriene, can add to aldehydes or carbon dioxide to produce respectively cycloheptadienyl carbinols or acids (esters).[4c] Here we demonstrate that the amide function can be introduced into the seven and also the eight-ring skeletons in this way. Cycloheptatriene-derived allyltitanium complex(es) was first prepared in a one-pot procedure including two successive reduction steps. The reaction with **1** was then carried out at -50°C to -20°C within 2 h, affording the conjugated cycloheptadienylcarboxamide **9** (62%)[7] exclusively (Scheme 4). It is noteworthy that in analogous reactions involving aldehydes or carbon dioxide, mixtures of two regioisomers have always been formed.[4c] Also the use of cyclooctatetraene as starting polyene led to a unique regioisomer **10** (44%).[7]



(a) = preformed at r.t. and cooled to -50°C

Scheme 4

In summary, the reaction described above constitutes a first entry to tertiary amides directly from dienes. It seems to possess a general applicability. Different acyclic, cyclic and even sterically demanding 1,3-dienes can be used. Other than dimethyl-, readily available N,N-dialkylcarbamoyl chlorides[14] could also be envisaged.

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7. All new compounds were fully characterized by spectroscopic methods. Relevant examples:
   3b: IR (neat) 1640 cm^{-1}; ^1H NMR (C_6D_6) δ 5.18-5.08 (m, 1H), 4.89-4.82 (m, 2H), 3.05 (q, J=6.8 Hz, 1H), 2.67 (s, 3H), 2.40 (s, 3H), 2.09 (m, 4H), 1.62 (s, 3H), 1.50 (s, 3H), 1.33 (d, J=6.8 Hz, 3H); ^{13}C NMR (C_6D_6) δ 172.6, 149.5, 131.5, 124.6, 110.7, 44.3, 36.5, 35.5, 33.6, 26.8, 25.8, 17.9, 17.7; MS 197 (M^+).
   5: IR (neat) 1642 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.86-5.72 (m, 1H), 5.57-5.47 (m, 1H), 3.36-3.24 (m, 1H), 3.01 (s, 3H), 2.88 (s, 3H), 2.05-1.30 (m, 6H); ^{13}NMR ($CDCl_3$) δ 174.5, 129.3, 124.9, 38.6, 37.2, 35.6, 25.4, 24.4, 21.0; MS 153 (M^+).
   8: IR (neat) 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.10 (qd, J=6.8, 1.4 Hz, 1H), 3.72-3.60 (m, 1H), 3.10 (s, 3H), 2.96 (s, 3H), 2.86 (dd, J=5.8, 5.8 Hz, 1H), 2.41-2.20 (m, 2H), 2.00-1.75 (m, 2H), 1.53 (dd, J=6.8, 1.4 Hz, 3H), 1.32 (d, J=9.2 Hz, 1H), 1.26 (s, 3H), 0.73 (s, 3H), Z-alkene geometry deduced from 10% N.O.E. for H-1 (hv C-1); ^{13}NMR ($CDCl_3$) δ 177.6, 141.2, 118.9, 50.1, 44.1, 40.4, 37.9, 37.8, 36.1, 29.8, 27.6, 26.3, 21.7, 12.7; MS 221 (M^+).
   9: IR (neat) 1645 cm^{-1}; ^1H NMR (C_6D_6) δ 6.10-6.00 (m, 1H), 5.90-5.75 (m, 3H), 3.22-3.15 (m, 1H), 2.65 (s, 3H), 2.32-2.20 (m, 1H), 2.25 (s, 3H), 2.10-2.00 (m, 3H); ^{13}NMR (C_6D_6) δ 173.6, 134.5, 132.9, 125.7, 125.3, 44.3, 36.5, 35.2, 31.0, 30.9; MS 165 (M^+).
   10: IR (neat) 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.21 (br d, J=9.7 Hz, 1H), 6.10 (br d, J=10.2 Hz, 1H), 5.81 (dt, J=10.9, 3.3 Hz, 1H), 5.74-5.60 (m, 1H), 5.54 (dd, J=10.2, 7.9 Hz, 1H), 5.47 (dt, J=10.7, 7.5 Hz, 1H), 4.22 (m, 1H), 2.96 (s, 3H), 2.89 (S, 3H), 2.85-2.60 (m, 1H); ^{13}NMR ($CDCl_3$) δ 172.5, 129.9, 129.4, 127.7, 127.4, 127.2, 126.9, 42.4, 38.1, 36.8, 29.2. MS 177 (M^+).
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