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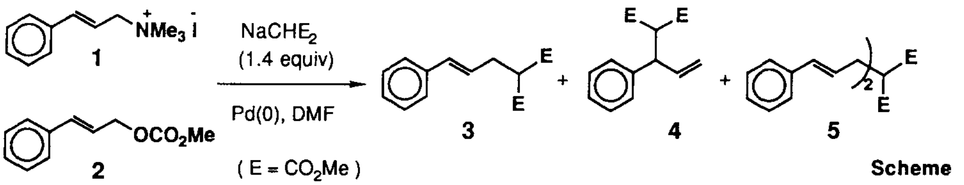
Chirality Transfer in Palladium Catalyzed Reactions of Allylammonium Salts

Takayuki Doi, Arata Yanagisawa, Masahiro Miyazawa, and Keiji Yamamoto*

Department of Chemical Engineering, Tokyo Institute of Technology
Ookayama, Meguro, Tokyo 152, JAPAN

Abstract: *Optically active 1-isobutyl-2(Z)-butenyltrimethylammonium iodide (**10**) underwent allylation with dimethyl sodiomalonate in the presence of a palladium(0) catalyst. The reaction proceeded predominantly with 1,3 transposition and with inversion of configuration due probably to a prior isomerization from anti to syn-π-allylpalladium intermediate (14→15). The stereochemistry observed in the reaction with phenylzinc chloride was opposite to that with the soft nucleophile.*

Palladium(0)-catalyzed allylations of carbon nucleophiles with a variety of allylic esters have amply been studied on both synthetic and mechanistic aspects.[1] We have recently reported that, in the Pd(0)-catalyzed carbonylation of cinnamyl *N,N*-dialkylcarbamates, an added allylamine participates in forming unsymmetric bisallylammonium salts as intermediates leading to an intriguing crossover aminocarbonylation.[2] The results show that an allylammonium salt could be a good precursor for the formation of π-allylpalladium species, there having been a few reports concerning the reaction of π-allylpalladium that arises from allylammonium salts.[3] Although a C-N chirality of allylammonium salts that may be easily obtainable from amino acids is an attractive chiral source, none of stereochemical studies but regioselective allylation with soft carbon nucleophiles has been elucidated; Alternation of the leaving group for the formation of a π-allylpalladium intermediate must effect on the reactivity as well as regio and stereoselectivities. We wish to report herein that a π-allylpalladium formed effectively from a chiral allylammonium salt undergoes fairly regioselective allylation of carbon nucleophiles and that the existing C-N chirality can be cleanly transferred into the newly created stereogenic center of the C-C bond, very similar to the case of allylic esters.[4]

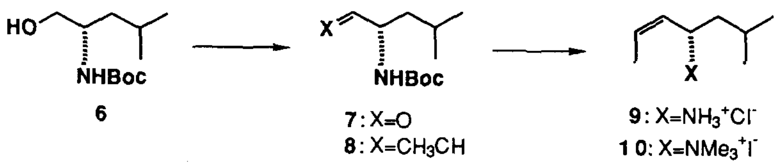


Scheme 1

Cinnamyltrimethylammonium iodide (**1**) was treated with dimethyl sodiomalonate in the presence of a palladium catalyst (1/2$Pd_2(dba)_3CHCl_3$ and 4PPh_3 ; 2 mol%) as depicted in Scheme 1.[3a] The allylation was found to be complete in 3 h at room temperature in acetonitrile, DMSO, or DMF as a solvent, though it took

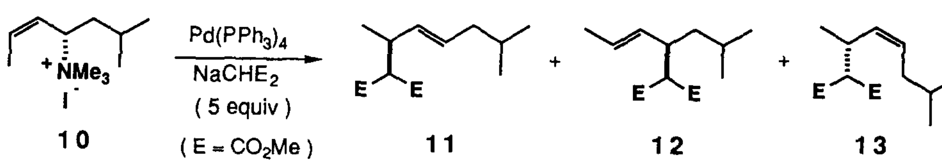
20 h in THF probably due to lack of solubility. Monoallylated product **3** with little regioisomer **4** and a considerable amount of diallylated compound **5** were obtained. The latter became much substantial when the reaction was carried out in THF. The fact that the monoallylated product is formed less selectively in the reaction of **1** than that of cinnamyl carbonate **2** indicates there is a significant influence of the amine liberated as well as the iodide ion.

In order to examine a novel chirality transfer, trimethylallylammonium iodide **10** was prepared as follows (Scheme 2): Oxidation (SO_3•Py, DMSO) of the protected aminoalcohol **6**, obtained from (*L*)-leucine, gave the labile aldehyde **7**,[5] which was immediately subjected to the Wittig reaction ($EtPPh_3I$, $KN(TMS)_2$, THF) leading to the alkene **8** (*Z*:*E* = 12:1) in 70% overall yield.[6] Deprotection of **8** (6M HCl in dioxane) provided quantitatively the allylammonium chloride **9**, which was purified by recrystallization from hexane-ethyl acetate (1:25) to an enantiomerically pure state (83%, >98%ee[7], *Z*:*E*=26:1): $[\alpha]^{25}_D$ +64.0 (*c* 1.02, $CHCl_3$), mp 141-145 °C. Methylation of **9** (MeI, K_2CO_3, EtOH) gave the desired ammonium salt (*S*)-**10** in quantitative yield: $[\alpha]^{25}_D$ +6.7 (*c* 1.04, MeOH), mp 138-139 °C (CH_2Cl_2-ether). ^1H NMR (270 MHz, $CDCl_3$) δ 0.99(d, 3H, *J*=6.6 Hz), 1.01(d, 3H, *J*=6.6 Hz), 1.5-1.6(m, 1H), 1.7-1.8(m, 1H), 1.98(dd,3H, *J*=7.0, 1.7 Hz), 3.39(s, 9H), 4.49(ddd, 1H, *J*=10.5, 10.5, 2.9 Hz), 5.32(ddq, 1H, *J*=10.9, 10.5, 1.7 Hz), 5.52(dq, 1H, *J*=10.9, 7.0 Hz). ^{13}C NMR (68 MHz, $CDCl_3$) δ 15.4 21.5 24.0 25.6 37.2 51.2 70.3 121.6 138.6. IR (cm^{-1}) 2962, 2030, 1607, 1486, 1382, 1171, 739.



Scheme 2

To a mixture of $Pd(PPh_3)_4$ (10 mol%) and the ammonium iodide **10** (1.0 mmol) in an appropriate solvent (10 mL) was added a solution of dimethyl sodiomalonate (5 equiv) at room temperature. After being stirred at 40-80 °C until the starting material had disappeared, the reaction mixture was worked up as usual. The products were analyzed by GLC or HPLC and purified by silica-gel chromatography. The reaction in acetonitrile did proceed at 40 °C, being complete at 80 °C in 30 min to give **11** in 73% yield, in addition to **12** and **13** in 5% and 3%, respectively. Spectral data for (*S*)-**11**:[8] $[\alpha]^{25}_D$ -16.1 (*c* 1.01, $CHCl_3$) (86 %ee). ^1H NMR ($CDCl_3$) 0.84(d, 3H, *J*=6.6 Hz) 0.85(d, 3H, *J*=6.6 Hz), 1.06(d, 3H, *J*=6.6 Hz), 1.57(m, 1H), 1.85(dd, 2H, *J*=6.9, 6.3 Hz), 2.91(m, 1H), 3.28(d, 1H, *J*=9.2 Hz), 3.69(s, 3H), 3.73(s, 3H), 5.31(dd, 1H, *J*=15.2, 8.3 Hz), 5.49(dt, 1H, *J*=15.2, 6.9 Hz). ^{13}C NMR ($CDCl_3$) 18.7 22.2 28.3 37.6 41.8 52.2 52.3 58.1 130.7 132.3 168.9. IR (cm^{-1}) 2952, 1737, 1433, 1149, 1020, 972.

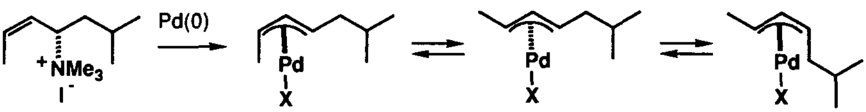


Solvent	Cat/mol%	Temp/°C	Time/h	**11** : **12** : **13** / yield	**11**/%ee	Chirality transfer /%
MeCN	10	40	22	49 4 3	82	95
	10	80	0.5	73 5 3	82	95
	2	80	1	51 2 1	84	96
DMSO	10	80	0.5	27 2 1	92	99
DMF	10	60	1	68 4 2	84	96
CH_2Cl_2	10	40	23	76 5 3	78	88

Table

On the basis of the absolute configuration as well as the enantiomeric purity of **11**, the extent of chirality transfer from **10** to **11** was found to be 95-96%[9] predominantly with 1,3-transposition and with inversion of configuration accompanied by an inversion of olefin geometry. All results of solvent effect on the reaction are given in the Table. Decrease in the catalyst from 10 to 2 mol% did not enhance the extent of chirality transfer, although it is reported that an increment of catalyst may cause the loss of stereochemical integrity.[4f,10] The reaction worked in DMF as well, but proceeded slowly in DMSO, the highest chirality transfer being observed up to 99%. Whereas the yield was moderate (76%), the chirality transfer was disadvantageous (88%) in dichloromethane.

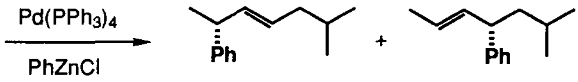
The fact that soft carbon nucleophiles, such as the malonates, attack on the face of π-allyl system opposite to that of the palladium[11] indicates the oxidative addition of (*S*)-**10** to Pd(0) to take place with inversion of configuration,[12] provided that an immediate *anti-syn*-π-allylpalladium **14** rapidly epimerizes *via* π-σ-π isomerization[13] to either *syn-syn*-**15** or even to *syn-anti*-**16** as depicted in Scheme 4. Both **14** and **15** undergo nucleophilic attack by the malonate anion at less hindered terminus with inversion of configuration leading to (*S*)-**11** as a major product. Compound **12** must arise from **15** (or **16**) by the malonate attack at its more hindered terminus. Finally, formation of the very minor product **13** would be formed from **16** present in the least amount by π-σ-π isomerization.



10 14 15 16

Scheme 3

We also examined the allylation of phenylzinc chloride, a hard carbon nucleophile, which is supposed to add to the metal of π-allylpalladium, followed by reductive elimination leading to net inverstion of stereochemistry.[14,15] In fact, treatment of (*S*)-**10** with phenylzinc chloride in the presence of $Pd(PPh_3)_4$ in THF[3b] gave a 4 : 1 mixture of **17** and **18** in 30% yield (Scheme 5).[16] The optical purity of **17** (67 %ee)[17] indicated a lower extent of chirality transfer (87%) in the reaction. Thus, (*R*)-**17** formed from **14** or **15** with retention of configuration, as a result of transmetallation followed by reductive elimination as mentioned above.

10 

Scheme 4

17 4 : 1 18

In conclusion, we have demonstrated that the C-N chirality of allylammonium salt (*S*)-**10** can be cleanly transferred to C-C chirality and that the oxidative addition of the carbon-nitrogen bond to Pd(0) takes place with inversion of configuration.

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   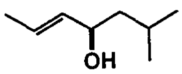

   A

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