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Palladium-catalyzed Asymmetric Allylations of (S)-Proline Allyl Ester Amides

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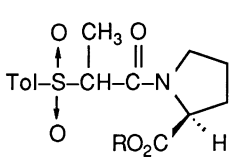
Palladium-catalyzed allylations of (S)-proline allyl ester amides are discussed, compared with the intermolecular reactions of (S)-proline methyl and ethyl ester amides with allyl acetate. (S)-Proline allyl ester amide undergoes an intramolecular allylation to demonstrate higher diastereoselectivity than the other systems, upon treatment with palladium catalysts.

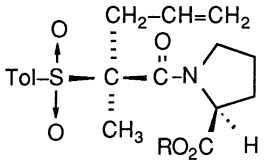
Recently much attention has been devoted to stereochemistry of palladium-catalyzed reactions in allylic systems.[1] We have reported the successful palladium-catalyzed asymmetric allylations of chiral enamines involving an allyl ester in the chiral parts.[2] We wish to communicate herein palladium-catalyzed asymmetric allylations of (S)-proline allyl ester amides via their amide enolates.

Treatment of an amide enolate, generated from amide 1a and sodium hydride, with tetrakis(triphenylphosphine)palladium [$Pd(PPh_3)_4$] (0.16 equiv.)-triphenylphosphine (PPh_3) (0.70 equiv.) in tetrahydrofuran (THF) at room temperature, 40, or 50 °C for 16-20 h followed by esterification of the produced acid 2a with diazomethane gave (2S)-2b in 84, 82, or 79% yield with 86, 65, and 50% diastereomeric excess, as shown in Table 1. The reaction at room temperature in THF led to the highest optical yield (86%) of 2b, while the reaction at lower temperature (0 °C) provided no expected product. The optical yield of the product 2b was obtained by calculation of the diastereomeric excess with the NMR spectral analysis.

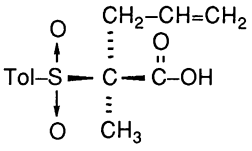
The palladium-catalyzed allylation of sodium amide enolates of 1b or 1c with allyl acetate (1.2 equiv.) was carried out in THF at 40 °C for 3-4 h in the presence of $Pd(PPh_3)_4$ (0.13 equiv.) and PPh_3 (0.57 equiv.), leading to the formation of (2S)-2b or -2c in 98 or 95% yield with 22 or 43% diastereomeric



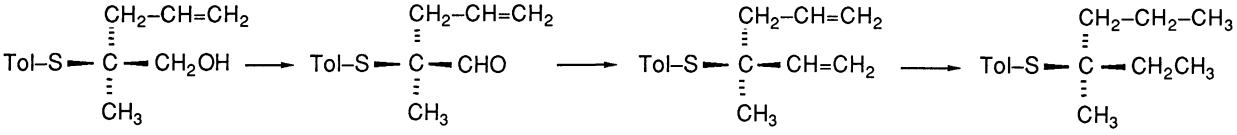
1a R=CH_2–CH=CH_2
b =CH_3
c =C_2H_5



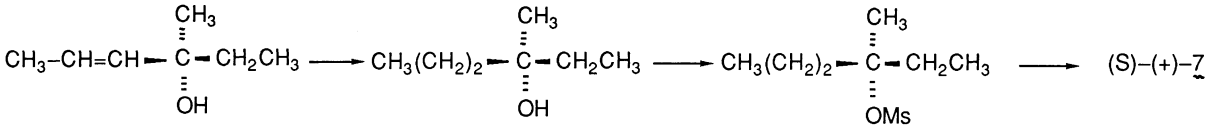
(2S)-2a R=H
b =CH_3
c =C_2H_5



(S)-(–)-3



(S)-(–)-4 (S)-(–)-5 (S)-(–)-6 (R)-(–)-7



(R)-(–)-8 (R)-(+)-9 (R)-10

excess. In consequence, it should be noted that the absolute configuration of the above newly created asymmetric carbon in 2b and 2c was (2S)-2b,c of the same configuration as that resulted from 1a and degree of the asymmetric induction was much higher from 1a than from 1b,c, as listed in Table 1.

However, the normal allylations of 1b with allyl iodide in THF produced (2R)-2b, whereas addition of HMPA in the same reaction of 1b afforded (2S)-2b.

The absolute configuration of the newly created α-asymmetric carbon in the product 2b,c was determined by chemical correlation with (R)-(-)-8 of known configuration.[3] The alcohol (-)-4, prepared by asymmetric allylation of (-)-menthyl 2-p-toluenesulfenylpropionate[4] followed by $LiAlH_4$ reduction, was oxidized with pyridinium chlorochromate to produce an aldehyde (-)-5. Condensation of the aldehyde (-)-5 with triphenylphosphonium methylide followed by reduction of the resulting olefin (-)-6 with diimide afforded (-)-7, which was chemically correlated to an optically active alcohol 8 of known absolute configuration.[3] The alcohol (R)-(-)-8, obtained by asymmetric addition of 1-propenylmagnesium bromide to ethyl methyl ketone,[3] was hydrogenated with diimide to yield (R)-(+)-9. Mesylation of the alcohol (R)-(+)-9 with methanesulfonyl chloride and triethylamine followed by substitution of the mesylate (R)-10 with sodium p-toluenethiolate in refluxing THF gave (S)-(+)-7 with inversion of configuration. Therefore the absolute configuration of 4 was determined as (S)-(-)-4.

Table 1. Palladium-catalyzed Asymmetric Allylations of Amides 1a-c

Amides	Base	Reaction conditions for allylation[a] Allylating agents	Reaction temp /°C	Reaction time/h	Yields/% of 2b,c[b]	d.e./% of 2b,c	Absolute confign. of 2b,c[d]
1a	NaH	-	room temp	16	84	86	S
1a	NaH	-	40	16	82	65	S
1a	NaH	-	50	16	79	50	S
1b	NaH	A	room temp	16	95	31	S
1b	NaH	A	40	4	98	22	S
1c	NaH	A	40	3	95	43	S
1b	NaH	B	room temp	12	72	32	R
1b	NaH	B	room temp	12	72[c]	-	
1b	sec-BuLi	B	-78	6	77	73	R
1b	sec-BuLi	B	-78	5	92[c]	38	S
1b	sec-BuLi	B	-20	6	79	54	R
1b	sec-BuLi	B	-20	6	95[c]	-	
1b	sec-BuLi	B	0	5	88	41	R

a) The enolates, generated from 1a-c and NaH or sec-BuLi (1.2 equiv.), were reacted in THF in the presence of $Pd(PPh_3)_4$ (0.16 equiv.) and PPh_3 (0.70 equiv.) without or with allyl acetate (A) (1.2 equiv.), or with allyl iodide (B) (1.2 equiv.) without the palladium catalyst.

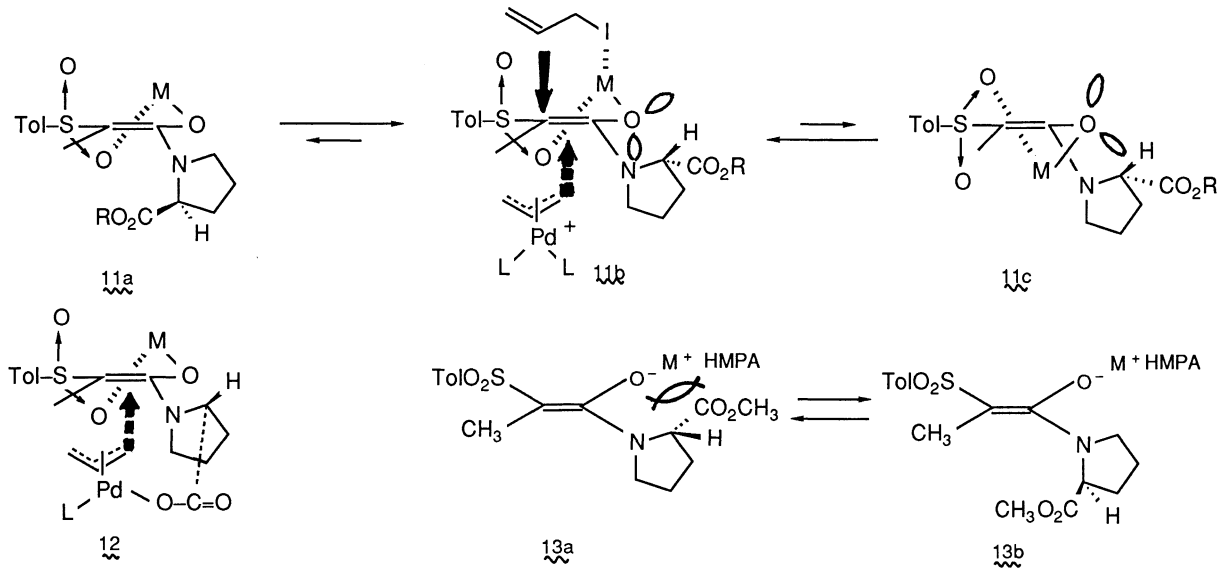
b) Yields based on the recovered starting materials.

c) Reacted in THF in the presence of HMPA.

d) The diastereomeric excess (d.e.) (%) was determined by the NMR spectral analysis of the products 2b,c.

The aforementioned allylation of the (-)-menthyl 2-p-toluenesulfenylpropionate followed by oxidation with m-chloroperbenzoic acid and hydrolysis with KOH-MeOH gave (S)-(-)-3. Amidation of this acid (S)-3 with (S)-proline methyl or ethyl ester was carried out via the acid chloride to give the corresponding amides (2S)-2b,c. Thus the absolute configuration of the above newly created asymmetric carbon in 2b,c was confirmed to be (2S)-2b,c by comparison of the NMR spectra.

Based on these stereochemical results, the mechanistic pathway for this asymmetric induction is presented as follows. The amide enolates would form six-membered transition states 11 involving a metal cation chelated with oxygen atoms of amide enolates and the sulfones. The most preferable conformation in the intermediates would be 11b, in which the ester moiety is oriented on the same side as the oxygen atom of the amide enolate, because of steric interference of the methyl group with the ester in 11a and $A^{1,3}$ strain between the ester group and the quasi-equatorial lone pair of the amide enolate oxygen in 11c.[5] In the allylation of 1b,c the allyl species formed by activation with the palladium catalyst would react to the α-carbon of the amide enolate 11b from the axial direction to give (2S)-2b,c. In the case of allyl ester 1a, an intramolecular allylation would occur via a transition state 12 to creat



(2S)-configuration in the product. However the allylation of 1b with allyl iodide would proceed from the back side of the ester group via 11b by chelation of metal cation with the iodide to yield (2R)-2b. In the presence of HMPA, the cyclic intermediate with chelation of metal cation could not be formed and the reaction would proceed via an acyclic intermediate, resulting in decrease of diastereomeric excess of the product 2b. Especially at low temperature (-78°C) participation of HMPA makes rather great contribution to preference of 13b in the equilibrium between 13a and 13b, due to steric interference of the ester group with the metal cation chelated by HMPA in 13a. Therefore the allylation (in HMPA) occurs from the backside of the ester group in 13b to furnish (2S)-2b.

Thus, this palladium-catalyzed reaction of (S)-proline allyl ester amide provided a new excellent method for diastereoselective α-allylation of carboxylic acid derivatives.

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