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Mild and efficient palladium(II)-catalyzed racemization of allenes†

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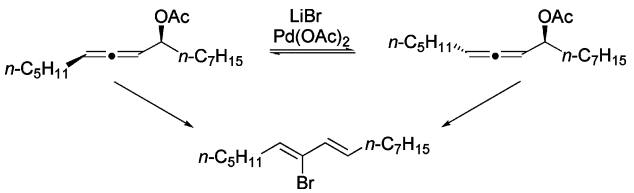
Allenes undergo racemization in the presence of catalytic amounts of $Pd(OAc)_2$/LiBr under mild conditions; the reaction proceeds *via* a bromopalladation–debromopalladation sequence and tolerates various functional groups.

Racemization is an important tool in asymmetric synthesis and has attracted considerable attention in the past few years.[1–3] Many large scale syntheses include a racemization step because the most common way in industry to obtain enantiomerically pure compounds is still *via* resolution of racemic mixtures. A major disadvantage of resolution is that only a maximum yield of 50% can be obtained; the other 50% has to be discarded or recycled. Recycling usually involves racemization of the unwanted enantiomer, often under rather harsh conditions.

Racemization also plays an important role in dynamic kinetic resolution (DKR).[3] The Pd(0)-catalyzed racemization of allylic compounds *via* π-allyl intermediates has been investigated[4] and utilized in dynamic kinetic asymmetric transformations[5] and DKR.[6] The Pd(II)-catalyzed racemization of allylic acetates *via* a 1,3-acetate shift[7] has also been utilized in DKR.[8]

During our work on the stereoselective synthesis of 2-bromo-1,3-dienes from α-acetoxy allenes we found that the starting allene epimerized during the reaction (Scheme 1).[9] Partial racemization of allenes has previously been observed in reactions with organocopper or Grignard reagents (2–5 equiv.).[10] We have now studied the palladium(II)-catalyzed racemization of allenes as a first step toward dynamic kinetic resolution of chiral allenes.

Optically active allenyl acid **1** (Chart 1) was obtained from the corresponding racemic ethyl ester[11] that was hydrolyzed and resolved with cinchonidine according to a literature method.[12] Methylation of **1** afforded **2**. Allenyl alcohols **3a–c**,[9,13,14] amines **5a**,**b** [15] and allene **7** [16] were prepared from the appropriate propargylic alcohols and organocopper reagents according to literature procedures. The acetates **4a**,**b** and amides **6a–c** were obtained from the corresponding alcohols **3a**,**b** and amines **5a**,**b**, respectively, by use of standard methods. Finally, β-allenyl ester **8** was prepared *via* an orthoester Claisen rearrangement according to a literature procedure.[17]



Scheme 1 Epimerization during the palladium-catalyzed S_N2' reaction.

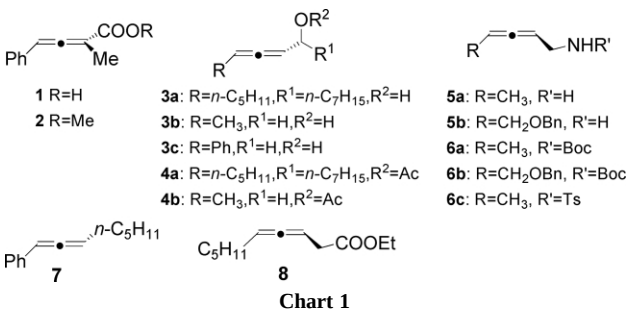


Chart 1

Our first attempt to racemize allenyl carbamate **6a** resulted in a clean but slow reaction (Table 1, entry 1). Increasing the temperature to 50 °C accelerated the reaction by one order of magnitude (entry 2). A further increase of rate was obtained by adding water to the reaction mixture (entries 3–6). This, however, turned out to be applicable only to carbamates **6a** and **6b**.

To find a general procedure we turned our attention to α-allenyl alcohol **3c**. The reaction at 50 °C was fast but proceeded to only about 75–80% racemization even when reaction times were prolonged. This inhibition is probably due to deactivation of the catalyst *via* dimer formations (see the mechanisms in Scheme 3 and 4). To avoid this deactivation we first screened several solvents such as ethanol, dioxane, toluene, acetone, acetic acid, dichloromethane and acetonitrile. Of these solvents acetonitrile gave the best result. We next decreased the concentration of allene to slow down the dimer formation. This simple dilution resulted in a clean but slower reaction. Finally, changing the catalyst to $Pd(OAc)_2$ and LiBr speeded up the reaction and afforded more than 90% racemization after 1.5 h (Table 1, entry 9).

To determine the scope of the reaction, racemization of several other optically active allenes was studied using the catalytic system $Pd(OAc)_2$/LiBr in acetonitrile. Our objective with this racemization is to finally couple it with a kinetic resolution process to obtain a DKR process. Since most of the published resolutions deal with allenes bearing a functional group in the α-position[12,18] our primary goal was to racemize such substrates. Reaction of allenic ester **2** with 5 mol% of $Pd(OAc)_2$ and 10 mol% of LiBr in acetonitrile at 50 °C resulted in a fast racemization with a half-time ($t_{1/2}$) of less than 1 min and with > 90% racemization within 7 min (Table 2, entry 1). The rate of racemization of the different allenes tested varied from having $t_{1/2}$ from 1 min to several hours. In general, allenes having a phenyl substituent racemized rapidly (entries 1, 3 and 9). On the

Table 1 Optimization of the racemization process[a]

Entry	Substrate	Solvent	$t_{1/2}$[b]	$t_{90\%}$[c]
1[d]	**6a**	CH_3CN	23 h	n.d.
2	**6a**	CH_3CN	110 min	n.d.
3	**6a**	CH_3CN/H_2O 99/1	75 min	n.d.
4	**6a**	CH_3CN/H_2O 95/5	65 min	[e]
5	**6a**	CH_3CN/H_2O 80/20	12 min	[e]
6	**6a**	CH_3CN/H_2O 50/50	7 min	[e]
7	**3c**	CH_3CN	6 min	[e]
8[f]	**3c**	CH_3CN	45 min	130 min
9[f,g]	**3c**	CH_3CN	15 min	90 min

[a] Unless otherwise noted the reactions were carried out in 0.05 M solution at 50 °C employing 5% $PdBr_2(PhCN)_2$. [b] $t_{1/2}$ is the time taken to reach 50% racemization. [c] Time for 90% racemization. [d] Reaction was carried out at 20 °C. [e] Reaction stopped after about 76% racemization. [f] 0.005 M solution was used. [g] 5% $Pd(OAc)_2$ and 10% LiBr was used.

† Electronic supplementary information (ESI) available: details of synthesis and characterization of all new compounds. See http://www.rsc.org/suppdata/cc/b3/b316482a/

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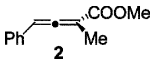
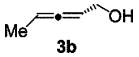
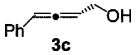
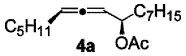
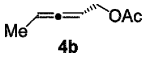
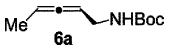
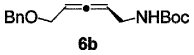
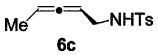
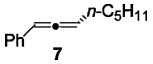
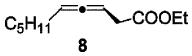
Table 2 Racemization of optically active allenes[a]

Entry	Substrate	$t_{1/2}$[b]	Time for 90% racemization
1	 **2**	< 1 min	7 min
2	 **3b**	3.3 h	n.d.
3	 **3c**	15 min	1.5 h
4[c]	 **4a**	40 min	2.3 h
5	 **4b**	21 min	1.7 h
6	 **6a**	30 min[d]	n.d.
7	 **6b**	1.3 h[d]	n.d.
8	 **6c**	2.25 h	n.d.
9	 **7**	6 min	30 min
10	 **8**	25 min	75 min

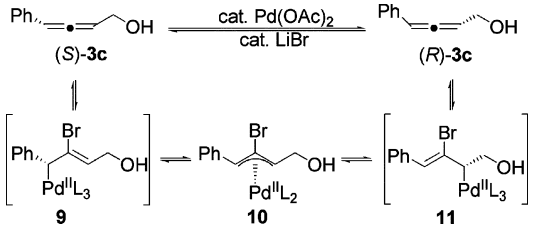
[a] Unless otherwise noted the reactions were carried out in CH_3CN at 50 °C (0.005 M) employing 5% $Pd(OAc)_2$ and 10% LiBr. [b] $t_{1/2}$ is the time taken to reach 50% racemization. [c] A single diastereomer epimerized during the reaction to afford an approximately 1:1 mixture of the diastereomers. [d] Acetonitrile:water 8:2 was used as solvent.

other hand, alcohol **3b** and tosyl derivative **6c** having a methyl group in the terminal position of the allene racemized slowly and the $t_{1/2}$ values obtained were 3.3 and 2.25 h, respectively (entries 2 and 8). The decreased reaction rate is probably due to the proposed dimer formation (in Scheme 4). Attempts to racemize amine **5a** and acid **1** under these reaction conditions resulted in complicated mixtures of products.

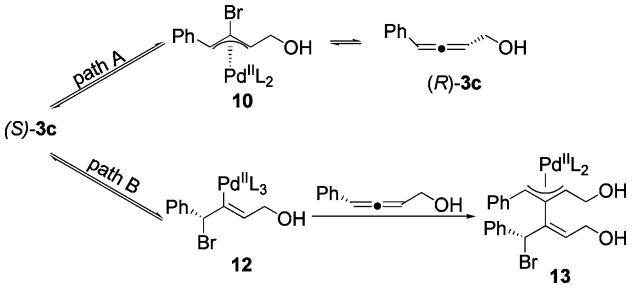
Scheme 2 shows a likely mechanism for the racemization. After *anti*-bromopalladation of one of the double bonds of (*S*)-**3c** the σ-allyl complex **9** formed rearranges to the other possible σ-allyl intermediate **11** *via* π-allyl complex **10**. *anti*-Elimination of bromide ion and palladium(II) from **11** gives the enantiomeric allene (*R*)-**3c**.

Another, less likely, pathway would involve *anti*-bromopalladation/*syn*-debromopalladation at the same double bond (or *syn*-addition/*anti*-elimination). *Syn–anti* interconversion of the four, diastereomeric π-allyl complexes does not play a role in the racemization.

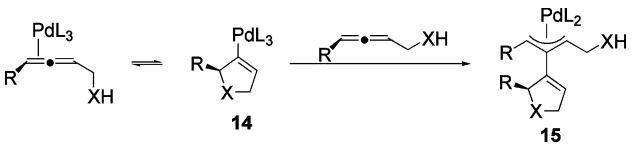
Reversible formation of a vinylpalladium intermediate **12** *via* attack by bromide on the terminal allene carbon (Scheme 3, path B) followed by irreversible insertion of a second allenic unit gives dimeric complex **13**. This pathway will tie up the catalyst in dimer **13** and decrease the rate of racemization. The deactivation can be suppressed by dilution. Although dilution does not change the ratio between the π-allyl complex **10** (path A) and vinyl complex **12** (path B) it inhibits the dimer formation by slowing down the



Scheme 2 Proposed mechanism for the racemization of allenes.



Scheme 3



Scheme 4

insertion of the second allene into the palladium–carbon bond of intermediate **12**.

If an internal nucleophile is present in the molecule a vinylpalladium species can be formed *via* an intramolecular nucleophilic attack (Scheme 4). This vinyl complex (**14**) can also insert an allene to give a dimer (**15**) that will tie up palladium and decrease the catalytic activity. Formation of dimers *via* vinylpalladium complexes such as **12** and **14** is common, and is involved in several catalytic transformations.[19] To avoid the dimerization according to Scheme 4, nucleophiles in the α-position can be protected.

In conclusion, a simple, efficient and mild method for the racemization of allenes has been developed. Various allenes were rapidly racemized in the presence of 5 mol% of palladium acetate and 10 mol% lithium bromide except when a nucleophile was present α to the cumulated double bonds. The mechanism proposed involves a bromopalladation–debromopalladation sequence. The combination of the racemization with kinetic resolution for DKR is currently being investigated in our laboratory.

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