A Novel Enantioselective Reaction. Palladium-catalyzed Enantiodistinctive Reaction of Bicyclic Allylic Compounds

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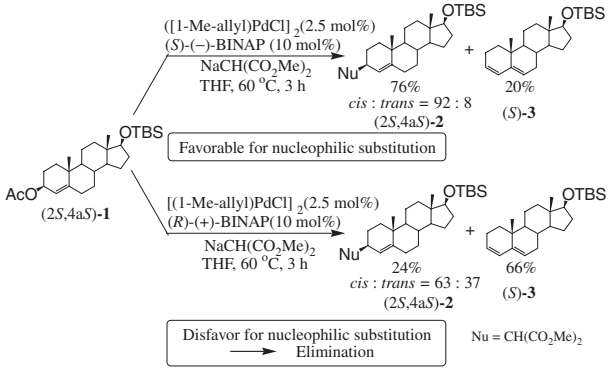
Reaction of (±)-2β-acetoxy-4aβ-methyl-2,3,4,4a,5,6,7,8-octahydronaphthalene (**4**) with dimethyl malonate anion in the presence of a catalytic amount of [(1-Me-allyl)PdCl]$_2$ and (*S*)-(−)-BINAP proceeded enantiodistinctively to give both the nucleophilic substituted product (2*S*,4a*S*)-**5** and the diene (*R*)-**6** as the elimination product in considerable enantiomeric excesses.

Catalytic enantioselective reactions to obtain enantiomerically pure molecules using chiral molecular catalysts are useful means in organic synthesis. Several catalytic kinetic resolutions have been developed as practical methods for preparation of chiral molecules from racemates.[1] However, one of significant problems of kinetic resolution method for practical application is controlling the conversion of starting materials, because it is normally recognized that the higher the conversion of the reactions, the lower enantiomeric excesses of the products. The parallel kinetic resolution recently reported is a solution for these problems.[2] In this paper, we wish to report a useful method for chiral bicyclic compounds from racemates by a palladium-catalyzed enantiodistinctive reaction.

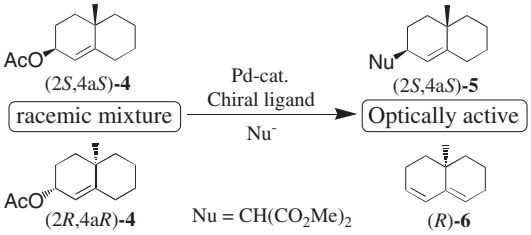
At first reaction of the acetate (2*S*,4a*S*)-**1** derived from a natural steroid using (*S*)- or (*R*)-chiral catalysts was carried out. Reaction of (2*S*,4a*S*)-**1** and dimethyl malomate anion with Pd-(*S*)-BINAP catalyst proceeded nucleophilic reaction smoothly to give (2*S*,4a*S*)-**2** in 76% yield with the diene (20%) as a minor product. On the contrary, reaction of (2*S*,4a*S*)-**1** and the malomate anion under similar conditions except for using Pd-(*R*)-BINAP catalyst instead of (*S*)-BINAP did not give (2*S*,4a*S*)-**2** in a satisfactory yield (24%), but elimination took place to give (*S*)-**3** as a major product (66%) (Scheme 1).



Scheme 1.

This interesting observation is a case that one enantiomer is a favorable catalyst for the desired reaction but the other enantiomer is unfavorable one, which converts the substrate to the product differently.

We turned attention to reactions of the racemate **4** with chiral palladium catalysts that may proceed enantio-distinctively to give an optically active nucleophilic substituted product **5** from the favorable enantiomer **4** and unfavorable enantiomer could be converted to diene which can be easily separated after the reaction (Scheme 2).



Scheme 2.

Reaction of the racemate **4** with dimethyl malonate anion was carried out in the presence of a catalytic amount of [(1-Me-allyl)PdCl]$_2$ and (*S*)-(−)-BINAP in THF at 60 °C under various conditions (Table 1). Usual kinetic resolution proceeded when 0.25 or 0.5 equivalents of dimethyl malonate was used, thus optically active **5** was obtained with high ee, although the yields are low (Runs 1 and 2).

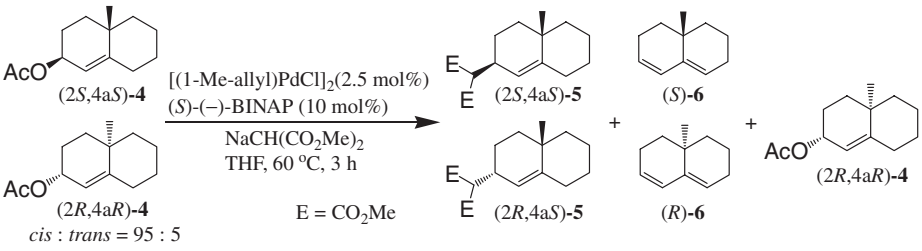
When 1.0 or 1.5 equivalents of dimethyl malonate was used in order to raise the conversion of the acetate **4**, chemical yields of **5** resulted satisfactory, but enantiomeric excesses of **5** were decreased. However the enantiomeric excesses of the nucleophilic substituted product were much higher compared with the case expected by normal kinetic resolution reaction in the same conversion (Runs 3 and 4). In addition, although stoichiometric amount of the malonate existed in the reaction, the diene **6** was obtained in considerable yields as by-product.

More interestingly, chirality of diene **6** obtained as a by-product depended on the amount of dimethyl malonate. (*S*) Isomer was obtained in cases with small amount of the malonate (Runs 1 and 2), whereas (*R*) isomer was obtained in those with one equivalent or more of the malonate (Runs 3 and 4).

These observations can be explained as shown in Scheme 3. At first reaction of allylic acetates, (2*S*,4a*S*)- and (2*R*,4a*R*)-**4** with Pd(0)-complex gave π-allylpalladium intermediate **7** and **8**, respectively. Reaction of **7** with dimethyl malonate anion gave (2*S*,4a*S*)-**5**. However, reaction of **8** with dimethyl malonate anion did not give allylation product (2*R*,4a*R*)-**5** smoothly, probably because the nucleophilic attack at less hindered site is restricted by the chiral ligand. It is known that the site selectivity is controlled by chiral ligands in the nucleophilic reaction of π-allylpalladium intermediates.[3,4]

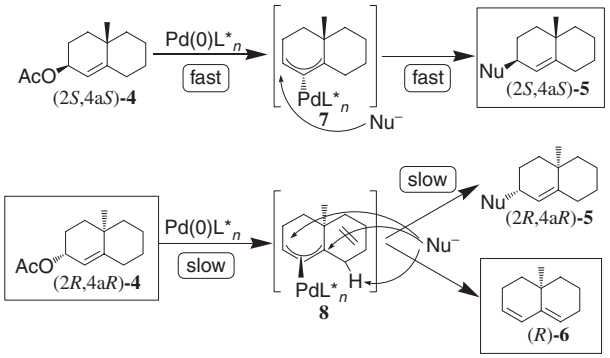
Nucleophilic attack at C2 of **7** is preferential, however, that

Table 1. Enantiodistinctive reaction of *rac*-**4** using a palladium-chiral phosphine catalyst



Run	$NaCH(CO_2Me)_2$ /equiv.	Product **5**				Product **6**			Recovered Substrate **4**		
		Yield/%[a]	*cis*:*trans*[a]	ee of *cis*/%[a]	ee of *trans*/%[a]	Yield/%[a]	ee/%[a]	Major enantiomer	Yield/%[a]	*cis*:*trans*[a]	ee of *cis*/%[a]
1	0.25	3	86:14	92	61	15	45	(*S*)	81	98:2	14
2	0.5	15	83:17	89	49	22	29	(*S*)	56	97:3	31
3	1.0	43	83:17	80	34	26	11	(*R*)	30	98:2	66
4	1.5	56	84:16	67	35	36	48	(*R*)	6	>99:<1	>99

[a]Determined by chiral GC.

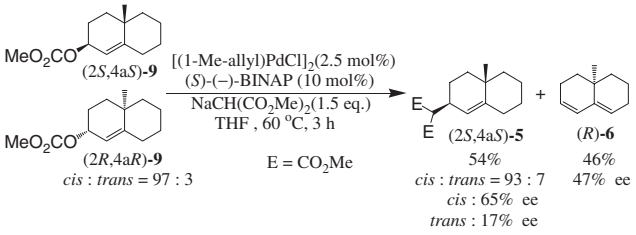


Scheme 3.

of **8** is restricted by the chiral catalyst. The chiral catalyst induces the nucleophile attack at angular carbon position (C8a) of **8**, but owing to steric effect, the nucleophile hardly attacks at C8a. In this case, elimination of **8** to the diene **6** proceeds instead of nucleophilic reaction. Indeed, (*R*)-**6** was obtained from **8** with a moderate ee even when dimethyl malonate was added more than 1.0 equiv. (Runs 3 and 4).

On the other hand, when the small amount of dimethyl malonate was used, (*S*)-**6** was obtained as a major product rather than (*R*) isomer (Runs1 and 2). In the case both nucleophilic reaction and elimination took place from **7**. These results indicate that oxidative addition of (2*S*,4a*S*)-**4** to Pd-(*S*)-BINAP complex is faster than that of (2*R*,4a*R*)-**4**. It should be noted that the recovery of **4** was dependent on the amount of the malonate, which indicates the malonate acted as a nucleophile and a base for elimination, accelerating the catalytic reaction. The rates of oxidative addition of (2*S*,4a*S*)-**4** and nucleophilc reaction of **7** were faster than those of the enantiomers, (2*R*,4a*R*)-**4** and **8**, which afforded the nucleophilic substituted product with high enantioselectivity.

Reaction of allylic carbonate **9** with dimethyl malonate proceeded similarly to that of **4** (Scheme 4). The carbonate **9** com-



Scheme 4.

pletely reacted to give the nucleophilic substituted product **5** and the eliminated product **6** in considerable enantiomeric excesses.

In conclusion, a novel enantiodistinctive reaction of bicyclic allylic compounds was observed in the palladium-catalyzed nucleophilic reaction of **4** and **9**, which will provide a useful method for preparation of optically active compounds more effectively than by normal kinetic resolution. Further development is under way.

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