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ASYMMETRIC CATALYTIC ALLYLIC ALKYLATION

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Abstract - An asymmetric catalytic allylic alkylation system has been developed which gives chiral substituted succinic acids in high optical yields.

The remarkable optical yields reported for asymmetric catalytic hydrogenation (Ref. 1) and asymmetric catalytic epoxidation (Ref. 2) using soluble metal complexes have not been matched in catalytic carbon-carbon bond formation reactions (Refs. 3,4,5). This is perhaps the most fundamental reaction of organic chemistry and hence it could be argued that the ultimate achievement would be to devise efficient and general asymmetric catalytic carbon-carbon bond formation reactions. From an inorganic point of view there are, at present, three viable catalytic methods for this reaction: hydroformylation (Ref. 4), cyclopropanation (Ref. 5) and allylic alkylation (Ref. 3). Of these, the last seemed to us to be most readily amenable to rational development.

The essence of catalytic alkylation is shown in Fig. 1 using palladium phosphine complexes.

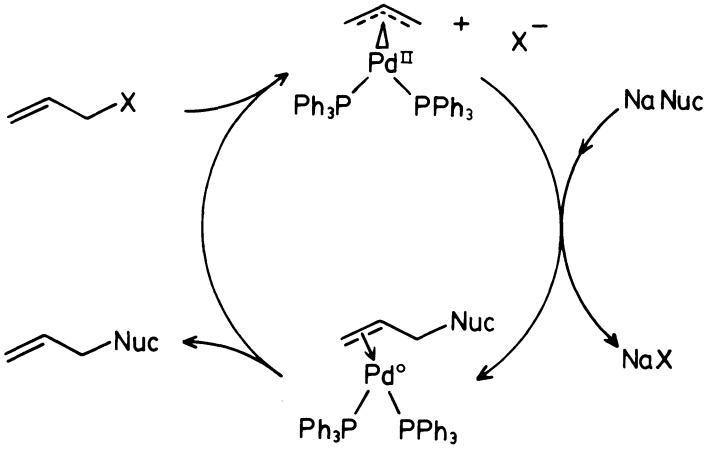


Fig. 1

The cationic Pd(II) allyl complex is susceptible to attack by a variety of nucleophiles (Nuc) including amines (Ref. 6), enamines, and soft carbon nucleophiles having pK_a's in the range 9-18 (Ref. 7). Organo-Grignard reagents can also be used but under restricted conditions (Ref. 8). After nucleophilic attack, a Pd(0) phosphine complex is produced which is capable of oxidatively adding an allylic-X compound to regenerate the π-allyl-palladium (II) species. The leaving group, X, can be any number of moieties, but for ease of oxidative addition and low reactivity with soft carbanions, allylacetates are usually used.

This reaction can be modified to give a catalytic asymmetric synthesis by incorporating chiral phosphines. Such chiral phosphine-allyl-palladium species will give diastereomeric transition states which lead to asymmetric synthesis. The nature of the substitution pattern of the allylic substrate is of central importance and our choice is based on the following considerations.

1. π-Allylic dissymmetry. Monosubstitution at the 1 or 3 positions of a coordinated π-allyl leads to a chiral system (Ref. 9). Such a system can rapidly racemize via the π-σ-π mechanism (Ref. 10). The racemization process is shown in Fig. 2 using the example of the 1-methyl-π-allyl-palladium assembly. Both of the σ-π intermediates are capable of inverting the olefin-face coordination by rotation about the carbon-carbon single bonds, but the two intermediates give different results. Path A involves inversion at the chiral centre but with retention of syn-disposition of the methyl group.

Path B transfers the methyl group to an anti-disposition but the chiral center retains its absolute configuration. Rearrangement via the more substituted end (path B) is slower than through path A and, in the absence of bulky substituents at the 2-π-allyl position, most substituents at the 1 and 3 positions strongly prefer to adopt syn-dispositions (Ref. 10).

Given that the π-σ-π rearrangement is the sole mechanism of interconversion under normal conditions, a number of important implications for asymmetric synthesis are apparent. Thus, a 1,3-unsymmetrically substituted π-allyl system can never racemize, it can only undergo a cyclic succession of epimerization reactions (Ref. 11). This is shown in Fig. 3.

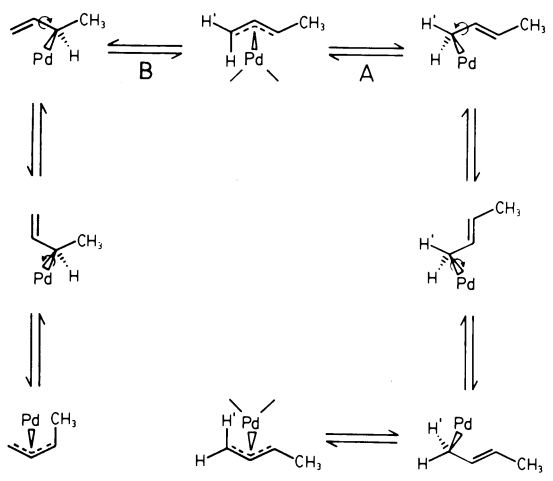


Fig. 2

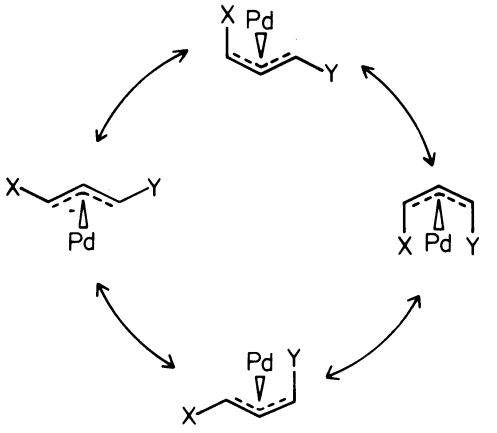


Fig. 3

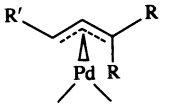


Fig. 4

Consequently, selecting a 1,3-unsymmetrically di-substituted substrate for asymmetric synthesis could lead to intractable complexity because of the diversity of species present which may undergo the alkylation. Thus a substrate is required which contains only one chiral center but is capable of rapid racemization.

2. Reaction Selectivity. Using palladium complexes, nucleophilic attack occurs exclusively at the 1 or 3 allylic position with soft carbanions. It is also generally assumed (Ref. 12) that oxidative addition of the allylic acetate substrate on the palladium (0) species occurs with inversion. There may, however, be a secondary mechanism, other than the π-σ-π rearrangement, which leads to loss of configurational integrity (Ref.13). Nucleophilic attack is also assumed to occur exclusively at the exo-allylic face when "soft" carbanions are used (Ref. 12).

Given these constraints and those implicit in the π-σ-π allyllic rearrangement mechanism, the type of chiral π-allyl system which can be used is shown in Fig. 4.

It will be noted that, whatever the R substituent is, the molecules of the type in Fig. 4 are devoid of geometric complexities. The π-σ-π isomerization can lead only to racemization and because of the absence of substituents in the 2-position the system will strongly favour a syn-disposed R'-group.

3. Regioselectivity. Regioselection in allylic alkylation has hitherto been an unsolved problem in that the nucleophile can attack either end of the π-allyl (1,3-positions) and generally mixtures of products are obtained (Ref. 14). Moreover, there did not appear to be a single characteristic of either the substrate or the nucleophile which could be used to predict the result decisively. For asymmetric synthesis we require that the nucleophile attack exclusively the less substituted end, that is, at the carbon atom bearing the R'-group (Fig. 4). Only attack at this position gives a chiral product.

We have found, however, that if the R-groups are aromatic, the allylic alkylation occurs exclusively at the chiral center of the π-allyl group. This result does not appear to depend on the nature of the R'-group and therefore represents an ideal circumstance for asymmetric synthesis. We think the major reason for this exclusive regioselectivity is the high stability of the double bond in conjugation with the two aromatic groups of the product (Fig. 5).

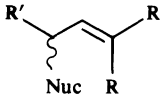


Fig. 5

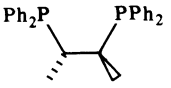


Fig. 6

4. Enantioselectivity. The final problem in asymmetric allylic alkylation is devising efficient enantioselection. Of course, optical yields are determined by the rates of reaction via diastereomeric transition states.

It is assumed that the nucleophilic attack on the π-allyl intermediates is exothermic. If this assumption is correct, then the stabilities of the diastereomeric transition states are expected to be reflected in the stabilities of the corresponding chiral phosphine-π-allyl palladium (II) diastereometers (Ref. 15). This argument is not conclusive but it does provide a reasonable starting point.

We have used S,S-chiraphos (Fig. 6) as the inducing phosphine and various palladium π-allyl systems.

The diastereomeric equilibrium shown in Fig. 7 was measured by ^{31}P NMR.

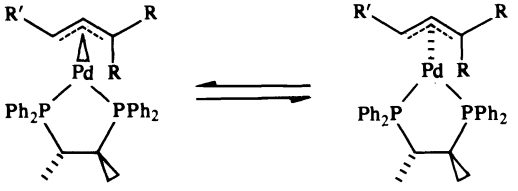


Fig. 7

The magnitude of the equilibrium constant in Fig. 7 is a measure of the chiral induction of chiraphos in enantioface selection of the π-allyl system. These internal diastereomers are intermediates in the catalytic cycle.

Tables I(a) and I(b) show the results obtained for a variety of π-allyl systems. We have taken care to ensure that equilibrium was established in all cases. In nearly all of the systems, equilibration is "instantaneous".

The errors in the ratios given in Table I vary from compound to compound but are about ± 10%. Some of the ratios are solvent dependent but provided there is not a switching in the sense of the induction, the variation is not large in most cases.

The first three entries (Table I(a)) reveal a pattern which is consistently observed, namely that, by and large, only anti-disposed groups contribute to the induction with chiraphos. Syn-disposed groups have little effect. Anti-disposed phenyl groups have a much larger induction than anti-disposed methyl groups. This induction, however, is sensitive to substituents on the phenyl groups and to a methyl group in the 2-position of the π-allyl (Table I(b)). A fused six-membered ring also contributes to the induction.

The observation that only anti-disposed groups cause significant induction with chiraphos could be an important result for asymmetric synthesis. Thus if this effect were transferable to the diastereomeric transition states, the

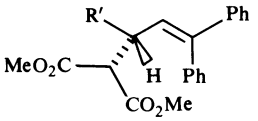


Fig. 8

π-allyl systems of the type shown in Fig. 4 would be ideal for asymmetric synthesis because the optical yields would be independent of the nature of crucial R'-group. In other words, we would have a general system which could be used to prepare homologous chiral products.

5. Organic Products. Using the π-allyl systems in Fig. 4, the product using sodium dimethylmalonate is shown in Fig. 8.

TABLE I

Diastereomer Equilibrium Ratios at 35°C of [Pd(S,S-chiraphos)allyl]ClO_4 Complexes

TABLE I(a)

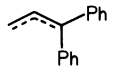
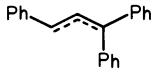
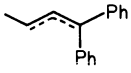
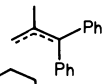
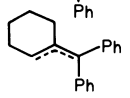
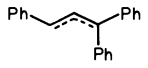
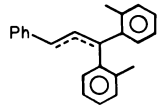
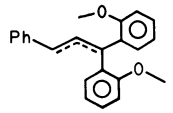
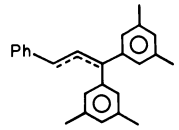
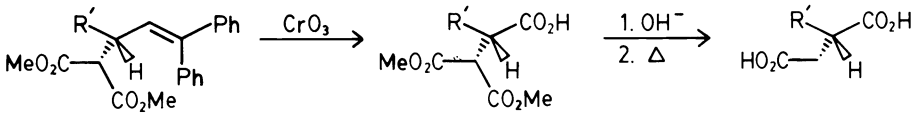
Allyl	Ratio $CDCl_3$	DMF	
	1	1	(f)
	1.7	1.8	(f)
	(a)	1.7	
	1.8	(b)	
	1	1	(f)
	6	7.5	(f)
	5.7	6	
	4	6	

TABLE I(b)

Allyl	Ratio $CDCl_3$	DMF	
	1.8		
	3.1	2.7	
	5	7.4	
	5.7	6	(3.7 in THF)
	1.5		(1.6 in DMSO)
	1.3	1.2	
	14	12	(12 in DMSO)

a) epimerizes slowly at 35°C, requires heating in DMF. f = fluxional at 30°C and the ratios given at 35°C are extrapolated from values obtained at lower temperatures. b) too much overlap of the peaks.

Such products are of little practical value unless they can be readily and efficiently transformed into useful materials. We have achieved this in the following way (Scheme 1).

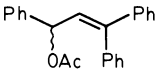
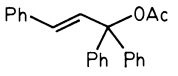
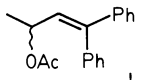
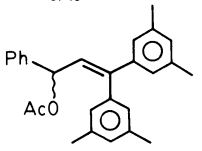


Scheme 1

The above reactions, oxidation, saponification and aqueous decarboxylation, proceed in about 70% overall chemical yield. A small amount of racemization (~ 3%) occurs in the last step. It is clear that, by switching the order of the steps in Scheme 1 and intervening with elaboration, a large array of chiral products can be obtained.

6. Allylic Alkylation. Allylic alkylations were carried out homogeneously at 25°C. The solutions consisted of 5% [Pd(S,S-chiraphos)π-allyl]$C\ell O_4$ as catalyst precursor, two equivalents of sodium dimethylmalonate, and one equivalent of the allylacetate substrate. Chemical yields were quantitative. Some of the results are shown in Table II.

TABLE II[(a)]

	Substrate	Solvent	Optical Yield
1.		THF	84 %
2.		THF	84 %
		DMF	86 %
3.		THF	62 %
4.		THF	64 %

Note a. All of the substituted succinic acid products have the R-absolute configuration using S,S-chiraphos.

The optical yields shown in Table II are much higher than has been observed before for comparable systems and some approach practical levels of optical purity. That asymmetric synthesis is a kinetic phenomenon is evidenced by the fact that the optical yields do not correspond exactly to the diastereomeric ratios (Table I) although they reflect them if we assume that the prevailing chirality of the product originates in the major π-allyl diastereomer. It will be noted that the chiral acetate 1 and the prochiral acetate 2 give the same optical yield but despite the higher diastereomeric ratio, acetate 4 gives a lower optical yield than 1 and 2.

7. Mechanism. The asymmetric allylic alkylation reaction involves two principal steps. These are shown in Fig. 9.

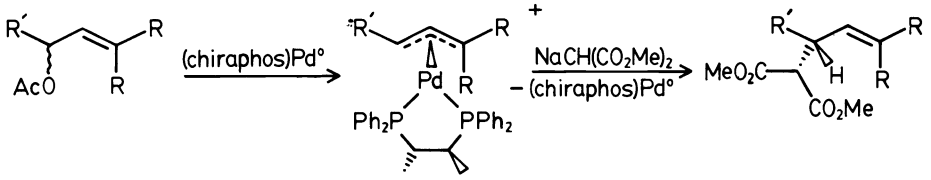


Fig. 9

Either the oxidative addition or nucleophilic attack by the carbanion could be rate determining. It is necessary to establish whether the cationic π-allyl intermediate is capable of fully epimerizing before nucleophilic attack otherwise chiral allyl acetates would give zero optical yields by a double inversion mechanism, oxidative addition followed by alkylation.

We have determined that the alkylation step is rate determining. The first indication that this is so was the observation that the allylacetates 1 and 2 (Table II) gave the same optical yields and reacted at about the same rates. More direct and conclusive evidence was provided by following the reaction in tetrahydrofuran by ^{31}P NMR. A constant spectrum was observed throughout the reaction and is shown in Fig. 10 using substrate 2 in Table II.

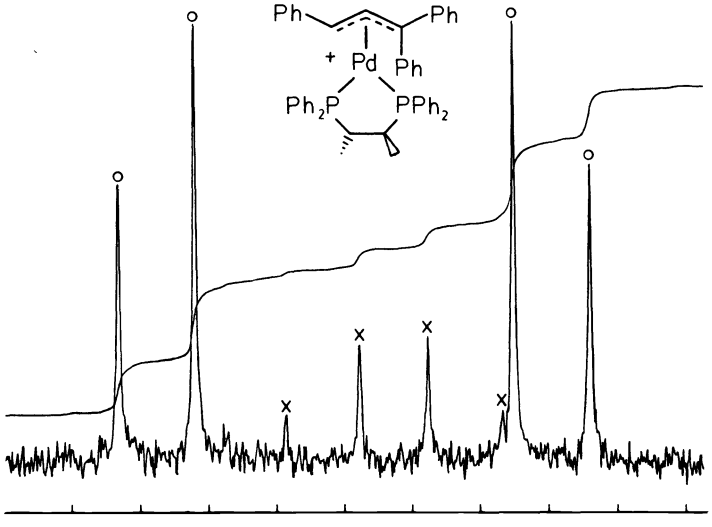


Fig. 10

The four central resonances represent the minor isomer and the four outer ones the major diastereomer. This spectrum is very similar to that observed when the pure [Pd(S,S-chiraphos)(1,3,3-triphenylallyl)]$C\ell O_4$ was used, the main difference being that the ratio under catalytic conditions is 4.7:1 rather than 3.7:1 (Table I(b)). The conclusion is clear; the rate-determining step is the alkylation and the π-allylic intermediate has time to epimerize before being attacked. It would seem, therefore, that the asymmetric synthesis is under Curtin-Hammett kinetic control and any correlation between optical yields and the ratios of the four-coordinate diastereomeric π-allylic intermediates resides in the Hammond connection for the presumably exothermic rate-determining step.

8. Discussion. The notable features of the allylic alkylation scheme presented here is the use of the 1,1'-diaryl group and the low sensitivity of enantioselectivity with chiraphos to syn-disposed groups. Because of the latter observation, it seems probable that a wide range of products can be synthesized without a significant diminution of the optical yields.

The 1,1'-diaryl group has the following important characteristics. (1) Because the aryl groups are the same, no geometric isomerism of the π-allyl can occur to complicate the system (Fig. 3). (2) The double aryl substitution directs the nucleophilic attack exclusively to the desired chiral 3-position of the intermediate ensuring hitherto unrealized regioselectivity. (3) These aryl groups cause an enormous increase in the epimerization rate as compared to similar aliphatic trisubstituted π-allyls. Because the π-allyl intermediates can fully epimerize before nucleophilic attack occurs, either chiral or prochiral acetates (1 and 2 in Table II) can be used. We suppose that the epimerization rate enhancement is due to the formation of an intermediate where the aryl groups participate in bonding (Fig. 11). Such π-benzyls are known (Ref. 16).

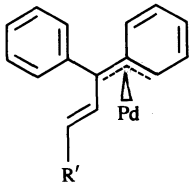


Fig. 11

(4) The 1,1'-diaryl groups also provide the enantioselection thermodynamically and probably also kinetically. It is always difficult to specify precisely origins of diatereotopic interaction but we show in Fig. 12 a pictorial representation of the two four-coordinate diastereomers formed with S,S-chiraphos.

I II

Fig. 12. A simplified edge-on view of the two diastereomers formed with a trisubstituted π-allyl (front) and S,S-chiraphos (back) in its preferred configuration.

It will be seen that the R-group interactions of the π-allyl systems and the chiral array of phenyl group (Ref. 1) of S,S-chiraphos are different for the two diastereomers. The chirality of the products corresponds to exo attack on species II. Until it is determined which of the diastereomers reacts faster, it does not seem profitable to discuss this question further.
(5) Finally, the 1,1'-diaryl moieties act as protecting groups and after completion of the reaction they can be oxidatively removed.

It seems probable, therefore, that a solution to obtaining high optical yields for allylic alkylation is at hand for the class of compounds we have described.

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REFERENCES

1. T.P. Dang and H.B. Kagan, J. Am. Chem. Soc., 94, 6429 (1972) W.S. Knowles, B.D. Vineyard, M.J. Sabacky, G.L. Backman and D.J. Weinkauff, J. Am. Chem. Soc., 99, 5946 (1977). M.D. Fryzuk and B. Bosnich, J. Am. Chem. Soc., 99, 6262 (1977). M.D. Fryzuk and B. Bosnich, J. Am. Chem. Soc., 101, 3034 (1979). P.A. MacNeil, N.K. Roberts and B. Bosnich, J. Am. Chem. Soc., 103, 2273 (1981)
2. T. Katsuki and K.B. Sharpless, J. Am. Chem. Soc., 102, 5974 (1980)
3. B.M. Trost, Accts. Chem. Research, 13, 385 (1980)
4. P. Pino and G. Consiglio, Fundamental Research in Homogeneous Catalysis, M. Tsutsui and R. Ugo, Eds., Plenum Press, New York, 1977.
5. A. Nakamura, A. Konishi, R. Tsujitani, M. Kudo and S. Otsuka, J. Am. Chem. Soc., 100, 3449 (1978)
6. K.E. Atkins, W.E. Walker, and R.M. Manyik, Tett. Letters, 3821 (1970)
7. J. Tsuji, H. Takahashi and M. Morikawa, Tett. Letters, 4387 (1965)
8. T. Hayashi, M. Konishi and M. Kumada, J. Organometallic Chem., 186, C1,(1980)
9. F. DeCandia, G. Maglio, A. Musco and G. Paiaro, Inorg. Chim. Acta, 2, 233 (1968)
10. J.W. Faller, M.E. Thomren and M.J. Mattia, J. Am. Chem. Soc., 93, 2642, (1971)
11. J.W. Faller and M.T. Tully, J. Am. Chem. Soc., 94, 2676 (1972)
12. B.M. Trost and L. Weber, J.Am. Chem. Soc., 97, 1611 (1975). B.M. Trost and T.R. Verhoeven, J. Am. Chem. Soc., 98, 603 (1976)
13. B.M. Trost, T.R. Verhoeven and J.M. Fortunak, Tett. Letters, 2301 (1979).
14. B.M. Trost, Tetrahedron, 33, 2615 (1977)
15. G.S. Hammond, J. Am. Chem. Soc., 77, 334 (1955)
16. Y. Becker and J.K. Stille, J. Am. Chem. Soc., 100, 838 and 845 (1978)