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A remarkable anion effect on the enantioselectivity of the Pd-catalyzed allylic amination using ferrocenyl ligands

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Abstract: The effect of several anions on the enantioselectivity of the Pd-catalyzed substitution reaction of 1,3-diphenylprop-2-enylethyl carbonate **1** with benzylamine, utilizing chiral ferrocenyl ligands such as 1-{(*R*)-1-[(*S*)-2-(diphenylphosphino)-ferrocenyl]ethyl}-3-(1-adamantyl)-1*H*-pyrazole **3a**, was investigated. Small hard anions such as F^- and BH_4^-, added in co-catalytic amounts to the catalyst, were found to enhance the ee to >99.5%. On the other hand, non-coordinating anions, e.g. PF_6^-, had a detrimental effect on the enantioselectivity (<10% ee). The beneficial effect of fluoride is discussed in terms of its establishing Curtin–Hammett conditions, by virtue of its coordination to Pd.

We present here a study of the effect exerted by anions on the enantioselectivity of the Pd-catalyzed asymmetric allylic aminations. In particular, fluoride and hexafluorophosphate (PF_6^-), either present as counterions or added as small amounts as an ammonium salt, were found to be highly beneficial (selectivity enhancement, >99.5% ee) or drastically detrimental (almost no selectivity, <10% ee), respectively. Asymmetric Pd-catalyzed allylic substitution has been the subject of considerable interest in recent years, and an increasing number of mechanistic studies of this type of reaction has been reported.[1] It is known that the substrate leaving group or the counterion contained in the catalyst complex may influence the enantioselectivity of the reaction.[2] However, neither detailed investigations and interpretations of this particular aspect have been documented, nor anion effects of such a large extent have been previously observed.

We recently reported the development of highly selective catalysts for the asymmetric allylic substitution reaction shown in Scheme 1.[3] Utilizing ferrocenyl ligands of type **3**,[4] ee's exceeding 99% were obtained.

Structural studies in solution by 2D NMR methods and in the solid state of several cationic Pd(II) π-allyl intermediates[3a,5] involved in the catalytic cycle, led to an understanding of the factors governing the nucleophilic attack of the amine *trans* to phosphorus, and hence of the origin of enantioselectivity of this particular reaction. It is important to note that the cationic Pd–allyl complexes formed during the catalytic reactions and those that have been subjected to NMR characterization differ in the nature of their counterion. Whereas the isolated complexes contained mostly PF_6^-, the anion of the *in situ* system, generated from the Pd(0) precursor $Pd_2(dba)_3 \cdot CHCl_3$ and the corresponding chiral ligand, coincided with the allylic leaving group. Experiments employing the pure π-allyl complexes as PF_6^- salts as catalyst precursors surprisingly afforded nearly racemic product, under otherwise identical reaction conditions. This unexpected observation prompted us to investigate the influence of a broader range of anions and to try to understand their mechanistic role for the standard reaction of Scheme 1. In a first series of experiments, the desired anion was added as a soluble salt (typically of tetrabutylammonium) to the *in situ* catalyst. A second set of experiments was performed using the isolated Pd(II) π-allyl complex **4a** as its PF_6^- salt, to which a second anion was added in the same way. Selected results of such catalytic reactions are listed in Table 1. It clearly turns out that

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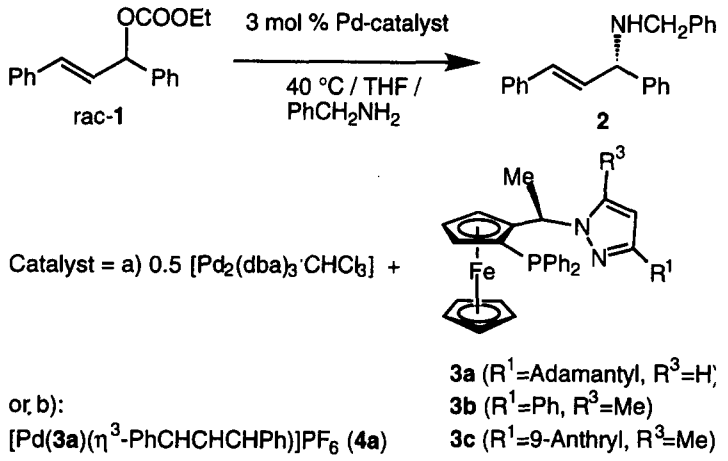


Scheme 1.

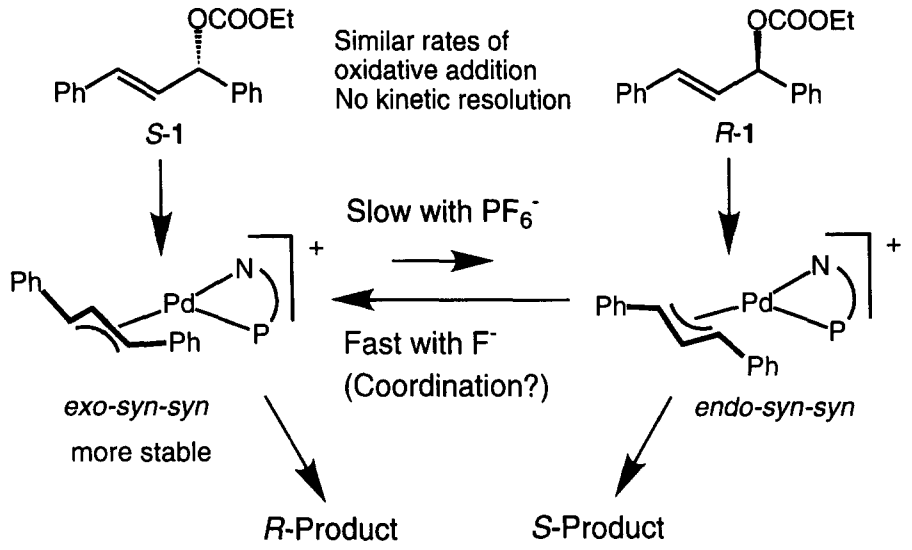
Table 1. Results of catalytic aminations of allylic carbonate **1** in the presence of anions[a)]

Ligand (catalyst)	salt added	*S*-**2**/*R*-**2** (%*ee*)	Ligand (catalyst)	salt added	*S*-**2**/*R*-**2** (%*ee*)
3a (in situ)	–	221 (99.1)	**3a** (in situ)	2 eq $[NBu_4]Br$	73 (97.3)
3a (complex **4a**)	–	1.14 (6.7)	**3a** (in situ)	2 eq $[NBu_4][BF_4]$	19 (90)
3a (in situ)	2 eq $[NBu_4]F$[b)]	>400 (>99.5)	**3a** (in situ)	2 eq $[NBu_4](OTf)$	15.7(88)
3a (in situ)	10 eq $[NBu_4]F$[b)]	>400 (>99.5)[c)]	**3a** (in situ)	2 eq $[NBu_4][ClO_4]$	15.7 (88)
3a (complex **4a**)	2 eq $[NBu_4]F$[b)]	153 (98.7)	**3a** (in situ)	2 eq $[NBu_4][PF_6]$	5.25 (68)
3a (complex **4a**)	10 eq $[NBu_4]F$[b)]	166 (98.8)[c)]	**3a** (in situ)	10 eq $[NBu_4][PF_6]$	2 (33)[c)]
3a (in situ)	1 eq $[NBu_4][BH_4]$	>400 (>99.5)	**3b** (in situ)	–	50 (96.1)
3a (complex **4a**)	1 eq $[NBu_4][BH_4]$	>400 (>99.5)	**3b** (in situ)	2 eq $[NBu_4]F$	90 (97.8)
3a (in situ)	2 eq $[NH_4]OH$	400 (99.5)	**3c** (in situ)	–	0.41 (42)[c)]
3a (complex **4a**)	2 eq $[NH_4]OH$	2.85 (48)	**3c** (in situ)	2 eq $[NBu_4]F$	1.25(11)
3a (in situ)	2 eq $[NBu_4]Cl$	221 (99.1)	**3c** (in situ)	2 eq $[NBu_4][PF_6]$	1 (0)
3a (in situ)	2 eq $[NBu_4]I$	124 (98.4)			

[a)] Reaction conditions, workup, and ee determination as detailed previously.[3a]

[b)] Added as 1 M $[NBu_4]F{\cdot}3\,H_2O$ in THF (Fluka). [c)] slow conversion (60h).

the presence of small hard anions is inducing high enantiomeric excesses. In the specific cases of F^-, BH_4^- and OH^-, ion addition even affords an enhanced selectivity, as compared to the reference case (*in situ* catalyst and no salt added). For all other anions tested, and more so for those with an increasing size and decreasing coordination ability, a gradually lower ee value is observed. Thus, complex **4a** (PF_6^- salt) affords virtually racemic product (6.7% ee). However, and most importantly, F^- and BH_4^- are able to compensate the deleterious effect of PF_6^-, when added to catalyst precursor **4a**. In fact, the combination of **4a** with 1 eq. of $[NBu_4][BH_4]$, or 2 eq. of $[NBu_4]F$, affords the highest known selectivity for this reaction (>99.5% ee).



Scheme 2.

Knowing that no kinetic resolution of the racemic substrate takes place under the reaction conditions of this study,[6] oxidative addition of racemic **1** to the catalyst, proceeding with inversion of configuration, generates equal amounts of diastereomeric π-allyl complexes with opposite configuration at the allylic termini. As illustrated in Scheme 2, the two diastereomeric complexes may be formulated as having *exo–syn–syn* and *endo–syn–syn* configuration,[3a] respectively, when neglecting possible *syn/anti* equilibria. Their reaction with the nucleophile at the position *trans* to phosphorus would generate opposite product enantiomers. Therefore, in order to obtain high ee's, it is important that a fast equilibrium between the diastereomers is established (Curtin–Hammett regime).[7] A possible hypothesis to account for the anion effects would assume different equilibration rates with different anions, either by virtue of ion pairing or, in the case of F^- and BH_4^-, coordination to Pd. A pentacoordinated complex would constitute a much more dynamic system, ensuring fast allyl isomerization. To test this conjecture we prepared the complexes [Pd(η^3-PhCHCHCHPh)(**3a**)]F **5a** and [Pd(η^3-PhCHCHCHPh)(**3b**)]F **5b**, from the reaction of [Pd(μ-Cl)(η^3-PhCHCHCHPh)]$_2$, the chiral ligands **3a** and **3b**, respectively, and TlF in methanol. These complexes turned out to be very unstable in the absence of MeOH or H_2O, and were found to decompose within minutes in C_6D_6 or $CDCl_3$.[8] The same fate was shown by compounds **4a** and **4b** when added of 2 eqs. of [NBu_4]F. ^{31}P NMR spectra of such solutions showed complex signal patterns in the temperature range +20°C to −70°C that could not be interpreted. Thus, no indication of a direct Pd–F interaction could be obtained. However, fluorides **5a–b** may be isolated in analytically pure form as their *stable trihydrates* by extraction from aqueous MeOH solutions.[9] These materials behave NMR spectroscopically very much like their hexafluorophosphate counterparts.

The catalytic experiments above revealed that the ee-values of the product do not change in the course of the catalytic reaction and remain constant after complete conversion, only if a "beneficial" anion such as fluoride is present in solution. In the case of the PF_6^- complex **5a**, however, ee's reach a maximum at first (ca. 65% ee, depending on catalyst concentrations), to decrease gradually after full consumption of the substrate. This puzzling finding could be traced back to a catalytic racemization of the product under reaction conditions. Indeed, when nearly enantiomerically pure product **2** was exposed to the action of complex **4a**, its ee decreased from ca. 99% (*S*) to 60% (*S*) within 24 h. On the other hand, the fluoride containing system did not affect the enantiomeric purity of the product under the same conditions. The observed racemization of enantiomerically enriched product implies that *the*

C–N bond forming process may be reversible, under circumstances dictated by the nature of the anion present. We assume that racemization takes place via C–N oxidative addition to Pd(0). Subsequent reductive elimination by intramolecular attack of the Pd-bound amine (or amide) group at the allyl (as it is known to happen for, e.g., hydride[10a] or acetate[10b]) would result in the formation of the opposite enantiomer and thereby explain the observed racemization. However, when fluoride is present no racemization occurs, most likely because F^- is blocking a coordination site, altering charge and electronic nature of the Pd center, thus preventing an oxidative interaction with the product. Finally, the fact that turnover rates are higher with weakly coordinating anions but slow down with increasing molar ratios of added fluoride,[11] provides further indication that occupation of metal coordination sites by this anion can indeed be regarded as a subtle aspect contributing in a beneficial manner to the overall process.

Our experiments clearly indicate the eminent importance of anions in determining stereoselectivity in asymmetric reactions involving Pd(II) π-allyl intermediates, an aspect that has been rather neglected so far.

Experimental section

A general procedure for the catalysis experiments, as well as details for the determination of the enantiomeric purity of product **2** have been reported previously.[3a]

*Preparation of [Pd(η^3-PhCHCHCHPh)((R)-(S)-**3a**)]F·3H$_2$O **5a***

[Pd(η^3-PhCHCHCHPh)(μ-Cl)]$_2$ (24.4 mg, 0.037 mmol) was slurried in a solution of (*R*)-(*S*)-**3a** (48 mg, 0.08 mmol) in methanol (10 mL) and the mixture stirred at r.t. until a clear solution was obtained (ca. 15 min). Solid TlF (18.0 mg, 0.08 mmol) was added, and an immediate color change to bright yellow with concomitant formation of a fluffy white precipitate was observed. After 1 h the mixture was filtered through a pad of Celite, the filtrate diluted with an equal amount of water, and washed with hexane (10 mL) and diethyl ether (10 mL). The aqueous phase was then extracted twice with dichloromethane; to separate the layers, a few mL of saturated aqueous KF were added. The organic phases were dried (Na_2SO_4), filtered, some hexane was added and the solvents evaporated *in vacuo* to yield a yellow microcrystalline solid (61 mg, 86%). Attempts to grow single crystals from a series of solvents failed. ^{1}H NMR (250 MHz, CD_3OD, 20°C): δ 7.90 (*d*, 1 H, pz C(5)-H, *J*=2.8), 7.81–6.95 (*m*, 20 H, 18 Ph-H, C*H*Me, Allyl-H$^{trans\text{-}P}$), 6.60 (*dd*, 1 H, Allyl-H^{center}, *J*=14.1, 9.8), 6.16 (*m*, 2 H, *o*-Ph-H (PPh^{eq})), 6.07 (*d*, 1 H, pz C(4)-H, *J*=2.8), 5.33 (*d*, 1 H, Allyl-H$^{trans\text{-}N}$, *J*=9.6), 4.87 (*m*, 1 cp-H), 4.57 (*t*, 1 cp-H), 4.08 (*m*, 1 cp-H), 3.97 (s, 5 H, C_5H_5), 2.37 (*d*, 3 H, CH*Me*, *J*=7.1), 2.16–0.90 (*m*, 15 Ad-H). ^{31}P{^{1}H} NMR (101.26 MHz, CD_3OD, 20°C): δ 11.0 (*s*). IR (KBr)($\nu_{max.}$, cm^{-1}): 3054, 2902, 2847, 1624, 1510, 1482, 1435, 1354, 1306, 1242, 1163, 1100, 1000, 826, 749, 695, 620 (The IR spectrum of the water-free complex **5a** does not exhibit any absorbance that could be assigned to a Pd–F stretching vibration). MS (FAB$^+$) *m/z* 897 (M$^+$, 100%), 704 (M$^+$−PhCHCHCHPh), 307. Anal. Calcd for $C_{52}H_{52}FFeN_2PPd.3H_2O$: C, 64.30; H, 6.02; N, 2.88. Found: C, 64.39; H, 5.81; N, 2.71.

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