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Chloride ion effects on kinetic resolution in Pd-catalysed allylic alkylation

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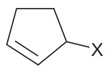
Chloride ion (5 mol%) accelerates and stabilises the oxidative addition of the slow-reacting enantiomer of cyclopentenyl pivaloate to Pd^0 complexes bearing the Trost modular ligand.

Astute chemical design and serendipity have led to a range of very effective ligands for enantioselective Pd-catalysed allylic alkylation.[1] Cyclic substrates have proven the hardest systems to substitute with high enantiomeric excess (ee) and the modular ligand systems of Trost,[2] *e.g.* (*R*,*R*)-**1**, have been almost[3] uniquely successful for this reaction type.

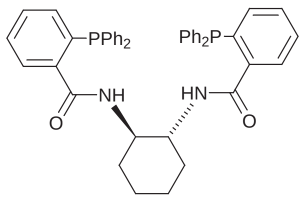


(±)-**2a**–**c**

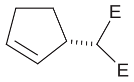
a X = O_2CMe

b X = O_2CBu^t

c X = O_2CPh

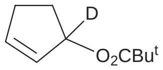


(*R*,*R*)-**1**

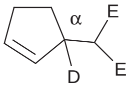


(*S*)-**3**

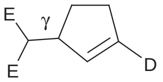
E = CO_2Me



(±)-**4b**



α-**5**



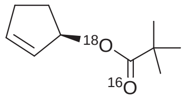
γ-**5**

We recently reported a mechanistic study[4] of the 'memory effect'[5] in the '[Pd(*R*,*R*)-**1**]'-catalysed reaction of **2a** with sodio dimethyl malonate ($NaCHE_2$; E = CO_2CH_3) in THF to give (*S*)-**3**. Herein we report on the effect of catalytic chloride ion on the kinetic resolution[6] of **2** and **4** by '[Pd(*R*,*R*)-**1**]'.

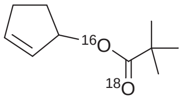
Pro-catalysts generated *in situ* from a bidentate ligand (L_2) and $[Pd(allyl)Cl]_2$ are often employed in Pd-catalysed allylic alkylation with $NaCHE_2$. Entry into the catalytic cycle is assumed to proceed *via* alkylation–reduction of $[(L_2)Pd^{II}$-π-allyl][Cl] to generate NaCl, allyl-CHE_2 and '$[Pd(L_2)]$'.[7] Using 2.25 equiv. $NaCHE_2$ and 5 mol% of '[Pd(*R*,*R*)-**1**]' generated *in situ* from (*R*,*R*)-**1** and $[Pd(allyl)Cl]_2$ (**1**/Pd = 3/2) complete conversion of both enantiomers of deuterium labelled pivaloate (±)-**4b** to a mixture of isotopomeric α- and γ-**5** occurs, in THF, within 10 min at room temp. (Table 1, entry 1).

When the reaction was quenched after 5 s, there was evidence of a moderate kinetic resolution ($k_S/k_R \approx 9$): recovered **4b** (25%) was 88% ee (*R*) and α/γ-**5** were obtained in 38% yield.† However, when the '[Pd(*R*,*R*)-**1**]' was generated under chloride-free conditions[8] from $[Pd_2dba_3.CHCl_3]$ (dba = dibenzylideneacetone) or $[Pd(allyl)(MeCN)_2][OTf]$ (**1**/Pd = 3/2) the rate of reaction was reduced and kinetic resolution enhanced. After 10 min, α-**5** and γ-**5** arising exclusively ($\geqslant$97%) from matched (*S*)-**4b** were obtained in 38–43% yield and mismatched (*R*)-**4b** had been partially resolved (47–51% ee) (Table 1, entry 2). After a further 2 h (*R*)-**4b** was recovered in 28–32% yield and $\geqslant$90% ee.‡ There was no racemisation or further conversion[9] of (*R*)-**4b** (despite a large excess of $NaCHE_2$) over a period of 48 h. However, with substoichiometric (0.5 equiv.) $NaCHE_2$ rapid ($\leqslant$60 s) partial resolution of (±)-**2c** was followed by Pd-catalysed racemisation of remaining (*R*)-**2c** (Fig. 1).

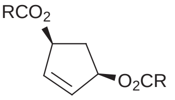
With excess nucleophile, labelled substrates were recovered unscrambled—there was no evidence of the γ-^2H isotopomer of (*R*)-**4b** and reaction of (±)-**6b** (95% ^{18}O) afforded (*R*)-**6b** ($\geqslant$90% ee) and no acyl-^{18}O isotopomer **7b**. These results suggest non-reversible Pd-allyl formation from (*R*)-**4** and (*R*)-**6** under turn-over conditions[10]§ and implicate the nucleophile in the catalyst deactivation process.



(*R*)-**6b**



7b



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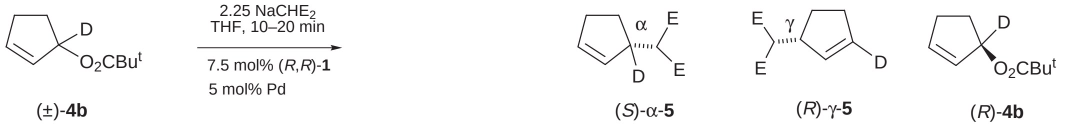
The efficient kinetic resolution of (±)-**4b** by '[Pd-(*R*,*R*)-**1**]' is not in itself surprising—the tight 'chiral pocket'[11] of (*R*,*R*)-**1** is known to effect highly enantioselective (*matched)* ionisation of *meso*-diesters **8**.[2b] More remarkable however, is that 5 mol% chloride ion increases the conversion (not *via* racemisation) of mismatched[12] (*R*)-**4b** (Table 1, compare entries 1 and 2) and inhibits catalyst deactivation. The importance of halide ions, at

Table 1 The effect of chloride on kinetic resolution with Pd^{II} *vs.* Pd^0 catalyst pre-cursors, in THF and CH_2Cl_2



		Yield (%) (*R*/*S*)		
Entry	Pd[a]	(*S*)-α-**5**	(*R*)-γ-**5**	(*R*)-**4b**
1	$[Pd(allyl)Cl]_2$	50 (42:58)	29 (36:64)	0 (—)
2	Pd^{II} [a] or Pd^0 [a]	32 (< 5:95)	11 (> 95:5)	36 (74:26)
3	Pd^{II} [a] + dba[b] + LiCl[c] or Pd^0 [a] + LiCl[c]	33 (< 5:95)	14 (> 95:5)	17–28 (> 95:5)
4	Pd^{II} [a] + LiCl[c]	46 (43:57)	31 (39:61)	0 (—)
5[d]	Pd^{II} [a]	20 (11:89)	5 (66:34)	74 (64:36)
6[d]	$[Pd(allyl)Cl]_2$	60 (33:67)	27 (19:81)	0 (—)

[a] Pd^{II} = $[Pd(allyl)(MeCN)_2][OTf]$; Pd^0 = $Pd_2dba_3{\cdot}CHCl_3$. [b] 7.5 mol% dba. [c] 5 mol% LiCl. [d] In CH_2Cl_2, 145 min.

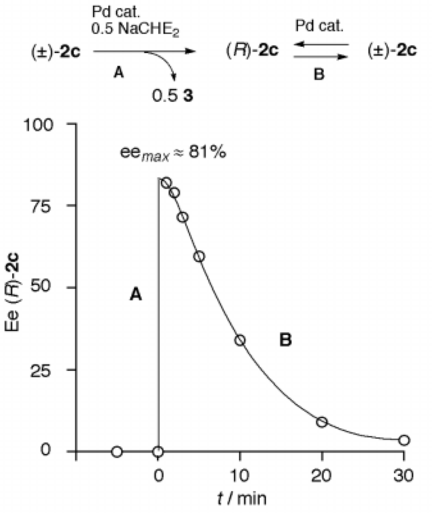


Fig. 1 Kinetic resolution (**A**) then racemisation (**B**) of (±)-**2c** on reaction with 0.5 equiv. $NaCHE_2$, catalysed by chloride-free pro-catalyst generated from 7.5 mol% (*R*,*R*)-**1** and 5 mol% $[Pd(allyl)(MeCN)_2][OTf]$.

both the Pd^0 and Pd^{II} oxidation state in cross-coupling and Heck reactions is well documented.[13] However, although a variety of halide effects have been reported in Pd-catalysed allylic substitution[14] these are all mechanistically implicated at the Pd^{II}-π-allyl stage.

To gain further information, we compared the effect of chloride on the selectivity with different pro-catalyst systems in THF. Use of 5 mol% of the Pd^0 pro-catalyst derived from (*R*,*R*)-**1**, $[Pd_2dba_3{\cdot}CHCl_3]$ and LiCl (**1**/Pd/Cl = 3/2/2) resulted in even more effective kinetic resolution giving (*R*)-**4b** (28% yield) in ⩾95% ee in under 10 min (Table 1, entry 3). At this point (*S*)-α-**5** (⩾95% ee) and (*R*)-γ-**5** (⩾90% ee) were derived almost exclusively (>97%) from matched (*S*)-**4b** and this suggests $k_S/k_R \geqslant 100$.¶ However, complete conversion of residual (*R*)-**4b** to α/γ-**5** occurred in less than 12 h to give α/γ-**5** in 74% yield. Hence the LiCl retarded catalyst deactivation but not kinetic resolution.

With 5 mol% of the Pd^{II} pro-catalyst derived from (*R*,*R*)-**1**, $[Pd(allyl)(MeCN)_2][OTf]$ and LiCl (**1**/Pd/Cl = 3/2/2), complete conversion of (±)-**4b** to **5** occurred within 10 min (Table 1, entry 4). When dba (7.5 mol%) was also added to the pro-catalyst mixture, catalysis slowed dramatically and the system behaved similarly to that derived from a Pd^0 source (Table 1, entry 3). When the LiCl was omitted initially but added after 10 min of catalysis, powerful kinetic resolution of (±)-**4b** and catalyst deactivation occurred in the first 10 min and, on addition, the LiCl did not reactivate the catalyst.

The effect of solvent was also briefly studied. In CH_2Cl_2 reactions were slower. There was moderate kinetic resolution (k_S/k_R *ca.* 9) under chloride-(ion)-free conditions (Table 1, entry 5) and a greater 'memory effect' in the presence of 5 mol% chloride (Table 1, entry 6).

Taken together, the results suggest the following: (i) chloride coordination to Pd^0 results in a more reactive and less selective palladate-type catalyst, (ii) palladate formation is disrupted by dba, and (iii) in the absence of chloride and in the presence of $NaCHE_2$, mismatched ionisation of slower reacting (*R*)-**4b** tends to lead to catalyst decomposition.

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Notes and references

† The deuterium label and stereospecific mechanism allows the distinction of **5** arising from (*R*)- and (*S*)-**4**. Ratios were determined by NMR analysis in C_6D_6 with (+)-Eu(hfc)$_3$: (*S*)-**4b**/(*R*)-**4b** by ^1H NMR analysis and (*S*)-α-**5**/(*R*)-γ-**5**/(*R*)-α-**5**/(*S*)-γ-**5** by ^{13}C NMR analysis (see ref. 4).

‡ Analogous results were obtained with (±)-**4a** and (±)-**4c**. Pd-catalysed reaction (5 mol% [(dppf)Pd(allyl)][OTf], THF, 25 °C, 60 s) of the resultant (*R*)-**4a** with 2.25 equiv. $NaCHE_2$ afforded (*R*)-α-**5** and (*S*)-γ-**5** exclusively (>96%).

§ Reversible ionisation cannot be completely ruled out if a very tight ion-pair $\{[(\mathbf{1})\text{-Pd-}(\eta^x\text{-}c\text{-}C_5H_7)]^+[O_2CCMe_3]^-\}$ is formed and there is slow relaxation of nucleofuge orientation (*i.e.* equilibration of $^{18}O/^{16}O$) relative to exclusive internal return at the *mismatched* (α) carbon.

¶ For 98% selective conversion of (*S*)-**4b** over (*R*)-**4b** to α/γ-**5** at 43% conversion, $(k_S/k_R)_{calc}$ = 107. This calculation assumes that the slow mismatched ionisation of (*R*)-**4** gives no side products. Thus (k_S/k_R) may be much lower.

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