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# Construction of quaternary carbon stereocentres: catalytic enantioselective allylation assisted by a bimetallic catalytic system

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**Abstract**—The asymmetric allylic alkylation of prochiral aryl cyano esters has been carried out in the presence of a bi-component catalytic system containing a palladium and a rhodium complex modified by phosphorus containing chiral auxiliaries. The allyl derivatives were isolated in up to 63% ee. The chiral pocket ligands of Trost appear the most appropriate to produce the desired chiral derivatives.


## 1. Introduction

The generation of quaternary stereocentres including catalytic asymmetric allylation, has been the subject of investigations in recent years.[1] Indeed, although many examples describe the successful introduction of chirality into a prochiral allylic substrate,[2] the enantioselective nucleophilic addition of stabilised prochiral carbon nucleophiles to a π-allylpalladium(II) complex has been fairly less explored and is quite difficult to control.[3] Nonetheless, such a reaction has proven to be a valuable tool for the construction of tetrasubstituted stereocentres.[1] Efficient catalytic systems, which are able to induce high enantiodifferentiation in the preparation of quaternary centres, have been described for specific substrates. In many cases, in order to enable a better transmission of the chiral information, the chiral auxiliary presents specific features. For example, chiral ferrocenylphosphines, which bear a functional group able to interact with the prochiral enolate while approaching the π-allyl carbon of the π-allyl palladium intermediate,[4] have been synthesised and applied successfully to the allylation of β-diketones. As another example, the chiral pocket ligands of Trost have been used successfully in the allylation of β-ketoesters,[5] β-diketones[6] and non-stabilised ketone enolates.[7]

In order to prepare highly functionalised chiral quaternary centres for further transformation, we sought to explore the allylation of cyano ester substrates. To the best of our knowledge, only one report has so far described the palladium assisted allylation of closely related substrates, that is, α-isocyanocarboxylates.[4] Another report on the use of a bimetallic Pd/Rh catalytic system for the allylation of α-cyanopropionates has also been described.[8] In the latter case, the two catalysts activate the two substrates. As such, the cyanopropionate is activated by the rhodium complex and the allyl derivative by the palladium catalyst.[8,9] In a previous study, we explored the enantioselective allylation at the benzylic position of aryl cyano esters.[10] Very high levels of enantioselectivity are difficult to reach in the presence of palladium catalysts bearing Trost-type chiral auxiliaries. This fact is most certainly related to the non-cyclic nature of the enolate nucleophile. Thus, we thought to explore the allylation of the same substrate in the presence of a bimetallic catalytic system in order to improve the selectivity of the transformation. Herein, we report on the results of the allylation of 3,4-dichlorophenyl cyano ester derivatives assisted by a catalytic mixture containing palladium and rhodium complexes modified by various chiral auxiliaries.

## 2. Results and discussion

The substrate cyano-(3,4-dichloro-phenyl)-acetic acid methyl ester **1** has been synthesised quantitatively, as

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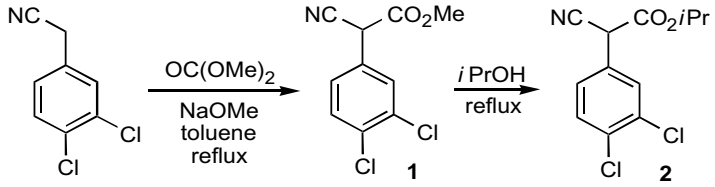
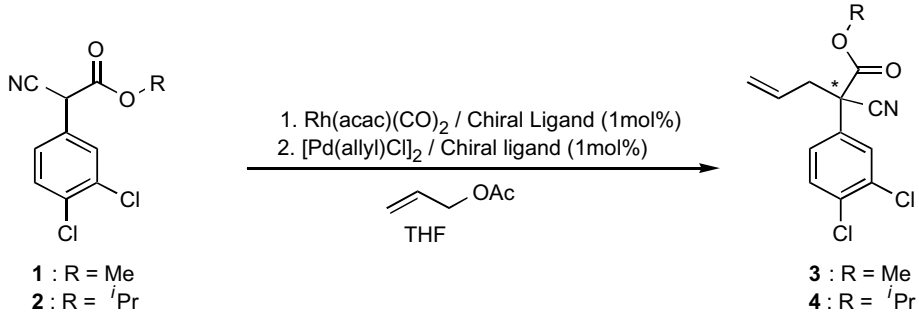
previously described, through the reaction of 3,4-dichloro benzonitrile with dimethyl carbonate in toluene in the presence of sodium malonate.[10] The corresponding isopropyl ester **2** was prepared quantitatively through a transesterification of **1** performed in isopropyl alcohol under reflux (Scheme 1).

These substrates were then subjected to allylation in the presence of allyl acetate catalysed by a system composed by the mixture obtained from the reaction of the two precursors $[Pd(allyl)Cl]_2$ and $Rh(acac)(CO)_2$ with various phosphorus containing auxiliaries (Schemes 2 and 3).[11] The catalytic results are summarised in Table 1.

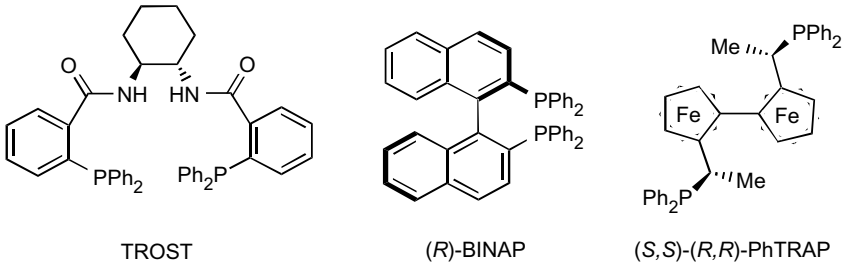
Initial experiments were carried out in the presence of the PhTRAP ligand (Scheme 3), which has already been reported as efficient in an allylic alkylation reaction of a closely related non-aryl substrate.[8] The PhTRAP ligand has been synthesised following the reported procedure.[8,12] First, allyl acetate was used as the reagent for the allylation of **1** in the presence of the two-component catalytic system obtained from the reaction of $Rh(acac)(CO)_2$ (1 mol%) and $[Pd(allyl)Cl]_2$ (1 mol% in Pd) and (*S*,*S*)-(*R*,*R*)-PhTRAP as the ligand for both rhodium and palladium complexes (entries 1 and 2). The reaction was performed in THF and no external base was introduced. The cyano ester was activated as an ester enolate coordinated to the rhodium complex through the cyano nitrogen atom [*trans*-[RhNCC(Ar)-(COOMe)(CO)(PhTRAP)]].[8] This nucleophile adds to the electrophilic π-allyl-palladium(II)–PhTRAP resulting from the reaction of allyl acetate with the palladium(0)–PhTRAP complex. The reaction proved very slow. An allyl carbonate, allyl hexafluoroisopropyl carbonate, was also used as the allyl source. The latter, which gives the advantage of releasing an anion $(CF_3)_2CHO^-$ with a lower basicity than $CH_3CO_2^-$, has been used successfully by Sawamura et al.[8] Thus, the allyl-palladium species was obtained by the decarboxylative oxidative addition of allyl hexafluoroisopropyl carbonate to the palladium(0)–PhTRAP complex. This reaction was also very slow. Even though the cyano substrate is activated and able to undergo the allylation reaction (see below), in the presence of the *trans* chelating PhTRAP ligand, the overall crowding is certainly too important to allow the addition of the rhodium–PhTRAP complexed cyano ester to the allyl-palladium–PhTRAP species.




**Scheme 1.**




**Scheme 2.**




**Scheme 3.**

**Table 1.** Asymmetric allylic alkylation[a]

| Entry | Substrate | Ligand (Pd)[b] | Ligand (Rh)[c] | Base[d] | Temp. (°C) | Time (h)[e] | Conv. (%)[f] | Ee (%)[g] |
|---|---|---|---|---|---|---|---|---|
| 1 | **1** | (*R*,*R*)-(*S*,*S*)-TRAP | (*R*,*R*)-(*S*,*S*)-TRAP | | −78 | 2 | 6 | nd[h] |
| 2[i] | | (*R*,*R*)-(*S*,*S*)-TRAP | (*R*,*R*)-(*S*,*S*)-TRAP | | 0 | 2 | 5 | nd |
| 3 | | (*R*,*R*)-(*S*,*S*)-TRAP | dppb | | rt | 2 | 100 | 32 |
| 4 | | (*R*,*R*)-(*S*,*S*)-TRAP | (*R*)-BINAP | | rt | 2 | 100 | 10 |
| 5 | | Trost | Trost | | rt | 0.5 | 100 | 32 |
| 6 | | Trost | Trost | | −78 | 0.5 | 100 | 60 |
| 7[j] | | Trost | Trost | | −78 | 1.5 | 55 | 63 |
| 8 | | Trost | Trost | (−)-Sparteine | −78 | 0.5 | 100 | 52 |
| 9[j] | | Trost | Trost | *n*-BuLi | −78 | 0.5 | 100 | 51 |
| 10[k] | | Trost | Trost | LDA | −78 | 1 | 89 | 45 |
| 11 | | Trost | dppb | | −78 | 0.5 | 100 | 50 |
| 12 | | dppb | Trost | | −78 | 0.5 | 100 | 51 |
| 13 | | | PhTRAP | | −78 | 2 | 0 | |
| 14 | | | Trost | | −78 | 1 | 80 | 45 |
| 15 | **2** | | Trost | | −78 | 0.5 | 100 | 43 |
| 16 | | Trost | Trost | | −78 | 0.5 | 100 | 53 |

[a] The catalytic reactions were carried out in THF with ligand(Pd)/Pd/ligand(Rh)/Rh/substrate ratio 1/1/1/1/100 and in the presence of allyl acetate (1.5 equiv) in the experimental conditions mentioned unless otherwise stated.
[b] The ligand was used as 1 equiv with respect to Pd. $[Pd(allyl)Cl]_2$ introduced.
[c] The ligand was used as 1 equiv with respect to Rh. $Rh(acac)(CO)_2$ introduced.
[d] Base as 1.2 equiv/substrate.
[e] The time is not optimised.
[f] Conversions were determined by $^1H$ NMR on the crude reaction mixture.
[g] Determined by $^{13}C$ NMR in the presence of [Eu(hfc)] shift reagent. The absolute configuration has not been determined. The sign of the specific rotation is (−).
[h] Not determined.
[i] The allyl hexafluoroisopropyl carbonate was used as the allylation agent.
[j] (−)-Sparteine was used. Sparteine/substrate: 1.2.
[k] $ZnCl_2$ was used. $ZnCl_2$/substrate: 2.

As demonstrated by Sawamura et al.,[8] when a catalytic system composed by Rh–PhTRAP and Pd–dppb was used in the allylation of the closely related cyano ester substrate instead of the mixture Rh–PhTRAP/Pd–PhTRAP, the selectivity remained very high. We applied the same system composed by Rh–PhTRAP and Pd–dppb (entry 3) and another one composed by Rh–PhTRAP and Pd-BINAP (entry 4). In both cases, the conversions went to completion in THF within 2 h at room temperature. The enantiomeric excesses were low, 32% and 10% ee, respectively. The fact that the reaction went to completion proves that the crowding present while using a PhTRAP ligand on both metals, inhibits the addition reaction. Also, this result shows the importance of the chiral rhodium species in the origin of the enantioselectivity of the process. Associating (*S*,*S*)-(*R*,*R*)-PhTRAP and (*R*)-BINAP provided allyl derivative **3** with 10% ee. We did not check the influence of the other BINAP enantiomer but rather turned our attention to the use of Trost-type ligands.

When applying the Trost ligand in association with the bi-component catalytic system Rh/Pd in the allylation of **1**, at room temperature, within non-optimised 30 min, the reaction went to completion and the enantiomeric purity measured for the isolated allyl derivative **3** was 32% ee (entry 5). Lowering the temperature to −78 °C led to an improvement in the selectivity of up to 60% ee (entry 6). The conversion was still complete at this temperature. When the allyl hexafluoroisopropyl carbonate was used instead of allyl acetate in the same reaction conditions (entry 7), a small increase in the ee was observed (63% ee). However, the reaction slowed down significantly as only 55% conversion was obtained in 1.5 h as compared to a total conversion reached within the non-optimised 30 min. We also examined the effect of a base associated to additives (entries 8–10). Even if the enantioselectivity decreased under such conditions (45–51% ee), the conversions were still very high.

When the reaction was carried out in the presence of either the mixture Rh–dppb/Pd–Trost ligand or Rh–Trost/Pd–dppb the enantioselectivity dropped to ca. 50% ee (entries 11 and 12) although the reaction still went to completion in 0.5 h. On the other side, the control reaction performed in the presence of only the palladium–Trost ligand catalyst proceeded in an analogous manner but with a lower rate and a lower selectivity (45% ee) (entry 14). It is noteworthy that when an identical reaction was carried out in the presence of the Pd–PhTRAP catalyst alone, no addition reaction was observed. First, these results prove that the acetate released during the catalytic process from the allyl acetate is able to generate the enolate via deprotonation of the cyano ester. Second, the addition of the benzylic cyano enolate to a chiral allyl-palladium–Trost ligand complex is possible with moderate asymmetric induction. Also, the conclusion made by Sawamura considering that the rhodium catalyst bearing the chiral auxiliary is at the origin of the enantioselectivity of the process is verified here. Indeed, when the chiral auxiliary is introduced either

via the Pd complex or via the rhodium species, the enantioselectivity remained the same. Thus, there is a redistribution of the ligands between the Pd and Rh complexes. However, it is difficult to conclude that the chiral ligand is exclusively coordinated to the rhodium species, the palladium bearing only dppb after equilibration. Yet, it appears clearly that the bi-component catalytic system accelerates the reaction compared to a palladium catalyst alone and provides the allyl derivative with a higher enantioselectivity. The properties exhibited by PhTRAP and the Trost ligand are different in the reaction studied here. Also, the PhTRAP has only been studied earlier in the allylation of non-aryl cyano esters. Finally, when using isopropyl ester substrate **2** instead of the methyl ester **1**, no improvement in the selectivity of the allylation reaction was obtained (entries 15 and 16).

## 3. Conclusion

In conclusion, we have shown that the aryl cyano esters can be allylated efficiently in the presence of a bi-component Rh/Pd catalytic system with a moderate enantioselectivity. The overall balance of the steric features of the rhodium-complexed enolate nucleophile and the allylpalladium electrophile is a crucial factor affecting the rate and enantioselectivity of the addition process. Also, the Trost-type ligand appears appropriate in association with both Pd and Rh to assist efficiently in the allylation of aryl cyano ester enolates and behave quite differently compared to PhTRAP. Further research is currently in progress in order to study the scope of the process.

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11. Representative experimental procedure for the allylation reaction: in a Schlenk tube equipped with a stirrer bar, $Rh(acac)(CO)_2$ (2.6 mg, 0.01 mmol) and the chiral auxiliary (0.021 mmol) were introduced with THF (2 mL). The resulting mixture was stirred for 5 min. The latter was then added to the cyano ester substrate (1 mmol) and dissolved in freshly distilled THF (4 mL). In a second Schlenk tube equipped with a stirrer bar, the palladium complex $[Pd(allyl)Cl]_2$ (3.7 mg, 0.01 mmol) and chiral auxiliary (0.021 mmol) were dissolved in THF (2 mL) followed by the allyl reactant (1.5 mmol). This mixture was stirred for 15 min at room temperature and then transferred via cannula onto the solution containing the substrate. The catalytic medium was stirred at the indicated temperature and the evolution of the reaction was followed by GC analysis of aliquots taken from the reaction mixture. At the end of the reaction, a saturated solution of $NH_4Cl$ (5 mL) was added and the medium stirred for 5 min before addition of water (10 mL). The allyl product was extracted with ethyl acetate ($3 \times 15$ mL). The combined organic layers were washed with saturated $NaHCO_3$ (25 mL), dried over $MgSO_4$ and concentrated under reduced pressure. If necessary, the isolated product was purified through silica gel chromatography. Compound **3**: $R_f = 0.8$ (ethyl acetate–petroleum ether 1/2). $^1H$ NMR ($CDCl_3$, $\delta$) 2.8 (m, 1H, $CHH'CHCH_2$), 3.1 (m, 1H, $CHH'CHCH_2$), 3.80 (s, 3H, $CH_3$), 5.10 (m, $H_{allyl}$), 5.3 (m, 2H, $CH_2$), 5.7 (m, 1H, $CH_{allyl}$), 7.40 (dd, $J = 2.2$ and 8.6, 1H, $H_{aro}$), 7.5 (d, $J = 8.6$ Hz, 1H, $H_{aro}$), 7.6 (d, 1H, $J = 2.2$ Hz, $H_{aro}$). $^{13}C$ NMR ($CDCl_3$, $\delta$) 42 ($CH_2$), 53 ($CH_3$), 117 (CN), 122 ($C_{allyl}$), 126 ($C_{allyl}$), 128, 130, 131, 133 and 134 ($C_{aro}$), 167 (CO). Anal. Calcd for $C_{13}H_{11}Cl_2NO_2C$: 54.95, H; 3.9, N; 4.93. Found: C, 55.07; H, 4.08; N, 4.72.
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