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Catalytic enantioselective allylation at the activated benzylic position of prochiral aryl cyano esters: access to quaternary stereogenic centers

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Abstract—Palladium catalyzed asymmetric allylic alkylation of prochiral aryl cyano esters has been carried out in the presence of various chiral ligands. The base and additives have been varied and allowed to produce the allyl derivative presenting a highly functionalized quaternary stereogenic center. The chiral pocket ligands of Trost appears the most appropriate to produce the desired chiral derivative.

Catalytic enantioselective allylation via a chiral π-allyl palladium(II) complex has been quite intensively investigated and remarkable success has been reported.[1] Most of the examples describe the successful introduction of the chirality into the allylic substrate.[1]

In contrast, the enantioselective nucleophilic attack of a stabilized prochiral carbon nucleophile to the π-allyl–Pd(II) complex, which is occurring at the side opposite to the chiral auxiliary, has been fairly less explored and is not easy to control.[2–7] Nonetheless, such a process is a valuable and challenging tool for the construction of quaternary stereocenters[8] and has been applied with success in total synthesis.[9]

Efficient catalytic systems, which are able to induce high enantiodifferentiation in such type of allylations, have been intented for specific substrates. They consist, for example, in using a bimetallic catalytic system for the allylation of a chiral rhodium(I) enolate of α-cyanopropionates.[4] Another approach is the allylation of α-acetamido-β-ketoesters[10] or iminoesters in order to produce new amino acid derivatives.[11] Earlier, the allylation of β-diketones has been carried out with chiral ferrocenylphosphine ligands bearing a functional group able to interact with the prochiral enolate while approaching the π-allyl carbon on the π-allyl palladium intermediate.[6,12]

The chiral pocket ligands of Trost have been used successfully in the allylation of β-ketoesters[13] and β-diketones.[14] Recently, advances have been made in the asymmetric allylation of nonstabilized ketone enolates assisted by palladium catalysts bearing chiral pocket type ligands.[15,16] In these cases, α-substituted cyclohexanones were the substrates.

We sought to prepare chirons with highly functionalized quaternary stereogenic centers via the allylation of cyano ester type substrates. To the best of our knowledge, only one report describes the palladium assisted allylation of closely related substrates, that is, α-isocyanocarboxylates, which has been carried out in the presence of a chiral ferrocenylphosphine ligand bearing an additional hydroxy function.[17] In the best case, the combination of a base (DBU) and a Lewis acid ($ZnCl_2$) allowed the formation of the allyl product with 39% ee. Here, we report on our first results of the allylation of 3,4-dichlorophenyl cyano ester derivatives.

The cyano ester **1** has been synthesized quantitatively through reaction of 3,4-dichloro benzonitrile with dimethylcarbonate in toluene in the presence of sodium methoxide (Scheme 1).[18] This substrate was then subject to allylation via asymmetric allylic substitution furnishing the allyl product **2** (Scheme 2).[19,20] Four chiral

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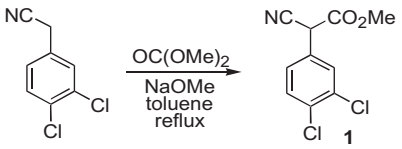
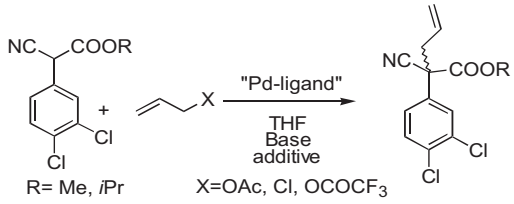


Scheme 1.



Scheme 2.

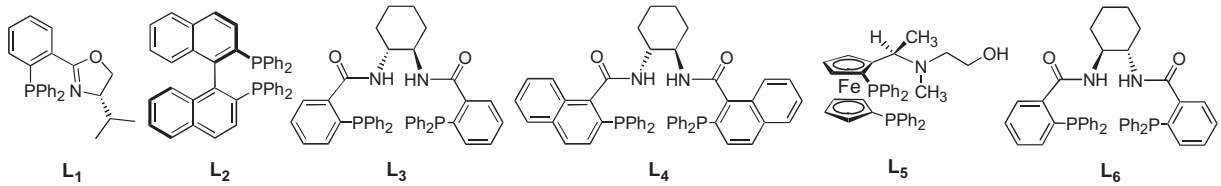
auxiliaries, that is, a phosphinooxazoline ($\mathbf{L_1}$),[21] BINAP ($\mathbf{L_2}$)[22] and the two chiral pocket ligands of Trost ($\mathbf{L_3}$ and $\mathbf{L_4}$)[23] were available commercially (Scheme 3). The functionalized ferrocenylphosphine ($\mathbf{L_5}$) (Scheme 3) has been prepared according to the reported procedure.[6]

For our first attempts, we considered the reaction of the cyano ester **1** with allylacetate using palladium complex $[PdCl(\eta^3\text{-}C_3H_5)]_2$ associated to chiral ligands $\mathbf{L_1}$, $\mathbf{L_2}$, and $\mathbf{L_5}$ in the presence of BSA/KOAc (cat),[24] LDA or $ZnEt_2$[25] at room temperature. The highest ee measured was 20% and selected examples are reported in Table 1 (entries 1–3). The beneficial effect mentioned above for the allylation of isocyano esters type substrates while using the DBU/$ZnCl_2$ combination instead of DBU alone has not been observed here for substrate **1** (entries 4 and 5).[17] Rather, the same level of enantioselectivity was observed. We turned next our attention to the use of the standard chiral pocket ligand of Trost $\mathbf{L_3}$. In the presence of a BSA/KOAc (cat) mixture, an enantiomeric excess of 45% was achieved in THF at room temperature (entry 6).

Then, reaction optimization was attempted essentially by varying the solvent and the base. The solvent had a moderate effect on the conversion and the enantioselectivity of the process. Several solvents have been examined (CH_2Cl_2, THF, toluene, DME) with THF giving the best results.

The base and the presence of additives has a stronger effect on the selectivity. As a matter of fact, the overall structure of the enolate and the size of the counterion have a notable impact on the enantioselectivity. For example, while changing the cation from Li (*n*-BuLi) (entry 7) to Na (NaH) (entry 8) and to K (KH) (entry 9), the ee was increasing from 25% to 43% (Δee = +18%). This significant ee increase can be related to the size of the cation associated to the enolate which will react with the allyl–palladium catalytic intermediate. Thus, the potassium enolate is giving the best result. With the base LDA (entry 10), an intermediate value of 38% ee is measured. This can be attributed to the amine produced during the deprotonation of the pronucleophile, which is able to remain associated to the lithium of the enolate. In consequence, an increase of the steric hindrance of the nucleophile, which is approaching the allylic moiety located within the chiral pocket furnished by the chiral ligand, will lead to an increase of the selectivity when compared to a run where *n*-Buli is used alone (Δee = +13%) (entry 7). The steric interactions between the nucleophile and the chiral ligand have thus to be improved in order to enhance the enantioselectivity. This subtle steric influence can also be apparent in the presence of sparteine. Indeed, while associating (−)-sparteine to *n*-BuLi, a significant improvement of the selectivity is observed (Δee = +29%) (entry 11). Very interestingly, the use of (−)-sparteine alone is providing the allylated product with 40% ee (entry 12). The same reaction carried out at room temperature allowed to reach an asymmetric induction of 55% (entry 13). This result is most likely associated to the presence of the protonated sparteine in the environment of the nucleophile while approaching the allylic moiety than to a selective deprotonation of the pronucleophile. Interestingly, while combining the (*S*,*S*) standard Trost ligand $\mathbf{L_6}$ with (−)-sparteine, still, the allyl product is isolated with 40% ee but with the opposite configuration (entry 14). This indicates clearly that the structure of the ion pair constituting the nucleophile has an important impact on the selectivity of the process and has to be taken into consideration more than the structure of the enolate.[15]

Zinc enolates can be generated either in the presence of $ZnEt_2$[25] or by a Li/Zn exchange process taking place while using *n*-BuLi in association with $ZnCl_2$. The outcome of the reaction involving such enolates clearly demonstrates the beneficial effect brought by the use of the latter as 50–52% ee are reached (entries 15 and 16). This is corresponding to an increase of Δee = +28% compared to the asymmetric induction obtained with the lithium enolate alone (entry 7). Generally, the reactions are fast and a total conversion is reached within nonoptimized 30 min at −78 °C and with a substrate/catalyst ratio of 150.



Scheme 3.

Table 1. Palladium catalyzed asymmetric allylic alkylation of **1** into **2**[a]

Entry	Allylic derivative	Ligand	Base[b]	Additive[c]	T (°C)[d]	Time (h)[e]	Conv (%)[f]	Ee (%)[g]
1	Allyl–OAc	$\mathbf{L_1}$	BSA	KOAc (0.1)	rt	0.5	100	5
2		$\mathbf{L_2}$	$ZnEt_2$	—	rt	4	100	18
3		$\mathbf{L_5}$	LDA	—	rt	1.5	100	20
4		$\mathbf{L_5}$	DBU	—	rt	1.5	100	15
5		$\mathbf{L_5}$	BDU	$ZnCl_2$	rt	1.5	100	17
6		$\mathbf{L_3}$	BSA	KOAc (0.1)	rt	1	90	45
7		$\mathbf{L_3}$	*n*-BuLi	—	−78	1.5	90	25
8		$\mathbf{L_3}$	NaH	—	−78 to rt	0.5	100	39
9		$\mathbf{L_3}$	KH	—	−78 to rt	0.5	57	43
10		$\mathbf{L_3}$	LDA	—	−78 to rt	0.5	98	38
11		$\mathbf{L_3}$	*n*-BuLi	(−)-Sparteine	−78	0.5	100	54
12		$\mathbf{L_3}$	(−)-Sparteine	—	−78	0.5	100	40
13		$\mathbf{L_3}$	(−)-Sparteine	—	rt	0.5	100	55
14		$\mathbf{L_6}$	(−)-Sparteine	—	−78	0.5	100	40
15		$\mathbf{L_3}$	$ZnEt_2$	—	−78	0.5	100	50
16		$\mathbf{L_3}$	*n*-BuLi	$ZnCl_2$	−78 to rt	1.5	100	52
17		$\mathbf{L_3}$	DBU	—	−78	0.5	100	26
18		$\mathbf{L_3}$	DBU	$ZnCl_2$	−78	1.5	100	36
19		$\mathbf{L_3}$	—	—	−78	1	80	25
20		$\mathbf{L_3}$	—	—	rt	1	80	50
21		$\mathbf{L_4}$	—	—	rt	1	90	32
22		$\mathbf{L_4}$	—	—	−78	0.5	100	15
23	Allyl–Cl	$\mathbf{L_3}$	BSA	KOAc	rt	0.5	100	34
24	Allyl–$OCOCF_3$	$\mathbf{L_3}$	—	—	−78	1.5	100	41
25	Allyl–$OCOCF_3$	$\mathbf{L_3}$	(−)-Sparteine	—	−78	0.5	100	48

[a] The catalytic reactions were carried out in THF and with ligand/Pd/substrate ratio = 1.2/1/150 in the conditions mentioned in the table.
[b] Base: 1.2 equiv/substrate.
[c] The amount of additive is relative to the substrate.
[d] For reactions performed between −78 °C and room temperature (rt), the cold bath is removed right after addition of the catalyst.
[e] The time was not optimized.
[f] Conversions were determined by ^{1}H NMR on the crude reaction mixture through integration of the methyl residue.
[g] Determined by ^{13}C NMR spectroscopy using the [Eu(hfc)] shift reagent. The absolute configuration has not been determined. The sign of the rotation is (−) except for entry 14 where it is (+).

A beneficial effect is observed for the use of DBU/$ZnCl_2$ instead of DBU alone (Δee = +10%) (entries 17 and 18) at low temperature with a total conversion.[17]

The reaction is also feasible without a base (entries 19–22). Indeed, the substrate is allylated in neutral conditions at low as well as at room temperature. It can be suggested that the leaving group (OAc) displaced from the allylic acetate reactant during the ionization step is capable of acting as a deprotonating agent toward the pronucleophile. Giambastiani and Poli have examined very closely such base-free palladium catalyzed alkylations and showed clearly that neutral conditions are not limited to allylic carbonates, phenates, and epoxides but can also apply to allylic acetate based allylations as long as the pronucleophile presents the suitable pK_a.[26] Such neutral conditions are attractive from an atom economy standpoint as no stoichiometric amount of base is necessary. It has been noticed that the base-free reaction carried out at room temperature is providing a better selectivity (50% ee) that at low temperature (for ligand $\mathbf{L_3}$, Δee = +25%) (entries 20 and 19). While using the sterically more hindered Trost ligand $\mathbf{L_4}$, no improvement of the enantioselectivity was observed. Rather, at low temperature, a decrease to 15% ee is observed (entry 22) when compared to the standard ligand $\mathbf{L_3}$ (entry 20) (Δee = −10%). Some reactions carried out on **1** at room temperature are not going to completion (entries 19–21). This can be attributed to either a modification or a decomposition of the catalyst. Nevertheless, such a behaviour is not observed with the isopropyl based cyano ester[27]. Indeed, at room temperature the allylation in the presence of allylacetate and the auxiliary $\mathbf{L_3}$ without a base and in 30 min, the allyl product is obtained with a total conversion and in 43% ee. Thus, the steric hindrance of the ester did not bring any improvement of the enantioselectivity. Rather, the isopropyl ester substrate is allylated with a lower selectivity than **1** (Δee = −7%). Thus, the asymmetric inductions are higher when using substrate **1** and ligand $\mathbf{L_3}$ (entries 19 and 20).

Two other sources of allylic moiety, that is, allylchloride and allyl trifluoroacetate gave close results (entries 23–25).

In summary, we have shown that Pd-catalyzed allylic substitution with arylcyanoesters pronucleophiles can provide allylated derivatives with interesting levels of enantioselectivity. The actual structure of the enolate involved in the addition process is not easy to define but has a critical impact onto the selectivity. Several important points have to be taken into consideration in order to optimize the catalytic system. Beside the structure of the substrate itself, the base, eventual additives able to modify the overall steric hindrance of the enolate, and

the chiral auxiliary have to be examined very closely. In our case, the noncyclic nature of the substrate is most probably responsible for the level of enantioselectivity observed. Indeed, similar results are often obtained with pronucleophile leading to enolated which are not part of a cyclic structure.[10,16,28] Also, among the panel of chiral auxiliaries available, the chiral pocket ligand of Trost type appears the most appropriate for the targeted transformation. A further improvement of the selectivity of the allylation of **1** will certainly require the preparation of even more specific chiral auxiliaries exhibiting the chiral pocket concept. Chiral alkylated cyano esters presenting a quaternary optically pure stereogenic center are valuable synthons for asymmetric synthesis.[29] Studies in which the strategy described here is applied to the synthesis of a bio-active molecule will be reported soon.

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18. Compound **1**: ^{1}H NMR ($CDCl_3$): δ 3.82 (s, 3H, CH_3), 4.69 (s, 1H, C*H*CN), 7.31 (dd, J = 2.3 and 8.3 Hz, 1H, H_{Ar}), 7.50 (d, J = 8.3 Hz, H_{Ar}), 7.56 (d, J = 2.3 Hz, 1H, H_{Ar}). ^{13}C NMR ($CDCl_3$): δ 43 (*C*HCN), 54 (OCH_3), 115 (CN), 127, 129, 130, 131, 133, and 134 (C_{Ar}), 164,6 (CO). Anal. Calcd for $C_{10}H_7Cl_2NO_2$: C, 49.20; H, 2.89; N, 5.74. Found: C, 49.18; H, 2.81; N, 5.67.
19. Representative experimental procedure for the allylation reaction: In a Schlenk tube equipped with a stir bar, the substrate (1 mmol) is dissolved in freshly distilled THF (4 mL) and the base is added (1.2 mmol). In a second Schlenk tube equipped with a stir bar, the palladium complex $[Pd(allyl)Cl]_2$ (3.7 mg, 0.01 mmol) and the chiral auxiliary (0.021 mmol) are introduced with THF (2 mL) followed by the addition of allyl derivative (1.5 mmol). The mixture is stirred for 15 min and then transferred via cannula onto the substrate. The catalytic medium is stirred at the indicated temperature and the evolution of the reaction is followed through GC or TLC analysis of aliquots taken from the reaction mixture. At the end of the reaction, a saturated solution of NH_4Cl (5 mL) is added and the medium stirred for 5 min before addition of water (10 mL). The allylated product is extracted with ethyl acetate (3×15 mL). The organic phase is washed with a solution of saturated $NaHCO_3$ (25 mL), dried over $MgSO_4$, and concentrated under reduced pressure. If necessary, the isolated product is purified through silica gel chromatography.
20. Compound **2**: ^{1}H NMR ($CDCl_3$): δ 2.80 (dd, J = 13.8 and 6.9 Hz, 1H, C*H*H′CH=CH_2), 2,82 (dd, J = 13.8 and 6.9 Hz, 1H, CH*H*′CH=CH_2), 3.80 (s, 3H, CH_3), 5.22–5.28 (m, 2H, CH=CH_2), 5.62–5.76 (m, 1H, C*H*=CH_2), 7.39 (dd, J = 2.2 and 8.3 Hz, 1H, H_{Ar}), 7.48 (d, J = 8.3 Hz, 1H, H_{Ar}), 7.64 (d, 1H, J = 2.2 Hz, H_{Ar}). ^{13}C NMR ($CDCl_3$): δ 42.3 (CH_2), 53.3 (*C*CN), 54.2 (OCH_3), 117.1 (CN), 122.0 (CH_2=CH), 125.7 (CH_2=*C*H), 128.4, 129.8, 131.0, 133.6 and 133.9 (C_{Ar}), 167.0 (CO). Anal. Calcd for $C_{13}H_{11}Cl_2NO_2$: C, 54.95; H, 3.9; N, 4.93. Found: C, 55.07; H, 4.08; N, 4.72.
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27. Cyano-(3,4)-dichlorophenyl acetic acid isopropyl ester: this isopropyl ester was prepared quantitatively through a transesterification of **1** performed in isopropylalcohol under reflux. ^{1}H NMR ($CDCl_3$): δ 1.25 (d, J = 6.1 Hz, 6H, (CH_3)$_2$), 4.65 (s, 1H, C*H*CN), 4.97–5.10 (m, 1H, C*H*(CH_3)$_2$), 7.29 (dd, J = 8.3 and 2.2 Hz, 1H, H_{Ar}), 7.49 (d, J = 8.3 Hz, 1H, H_{Ar}), 7.54 (d, J = 2.2 Hz, 1H, H_{Ar}). ^{13}C NMR ($CDCl_3$): δ 21.4 (CH_3), 43.0 (*C*H(CH_3)$_2$), 72.1 (CN), 127.2, 129.9, 130.0, 131.2, 133.5, 133.8 (C_{Ar}), 163.6 (CO). Corresponding allyl derivative (2-cyano-2-(3,4-dichlorophenyl-pent-4-enoic acid isopropyl ester): ^{1}H NMR ($CDCl_3$): δ 1.18 (d, J = 6.1 Hz, 3H, CH_3), 1.28 (d,

J = 6.1 Hz, CH_3), 2.79 (dd, J = 13.9 and 7.1 Hz, 1H, C*H*H′CH=CH_2), 3.06 (dd, J = 13.8 and 7.2 Hz, 1H, CH*H*′CH=CH_2), 5.00–5.09 (m, 1H, C*H*(CH_3)), 5.22–5.28 (m, 2H, CH=C*H*$_2$), 5.64–5.72 (m, 1H, C*H*=CH_2), 7.39 (dd, J = 8.3 and 2.0 Hz, 1H, H_{Ar}), 7.48 (d, J = 8.6 Hz, 1H, H_{Ar}), 7.64 (d, J = 2.0 Hz, 1H, H_{Ar}). ^{13}C NMR ($CDCl_3$): δ 21.2 (CH_3), 21.4 (CH_3), 42.2 (CH_2), 53.5 (CCN), 72.0 (OCH), 117,2 (CN), 121.8 (*C*H_2=CH), 125.6 (CH_2=*C*H), 128.4, 130.0, 131.0, 133.4, 133.5, 134.2 (C_{Ar}), 165.9 (CO).

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