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Allylic Compounds

Dual Palladium(II)/Tertiary Amine Catalysis for Asymmetric Regioselective Rearrangements of Allylic Carbamates

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Dedicated to Professor Dieter Enders on the occasion of his 70th birthday

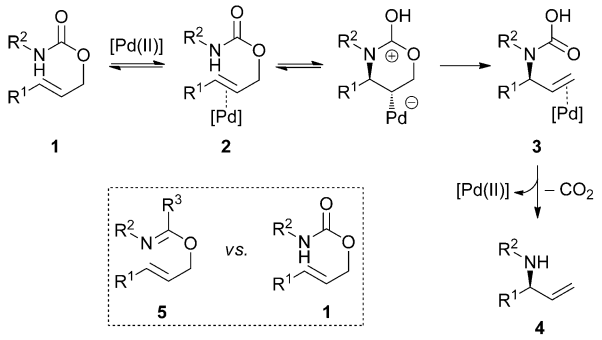
Abstract: The streamlined catalytic access to enantiopure allylic amines as valuable precursors towards chiral β- and γ-aminoalcohols as well as α- and β-aminoacids is desirable for industrial purposes. In this article an enantioselective method is described that transforms achiral allylic alcohols and *N*-tosylisocyanate in a single step into highly enantioenriched *N*-tosyl protected allylic amines via an allylic carbamate intermediate. The latter is likely to undergo a cyclisation-induced [3,3]-rearrangement catalysed by a planar chiral pentaphenylferrocene palladacycle in cooperation with a tertiary amine base. The otherwise often indispensable activation of palladacycle catalysts by a silver salt is not required in the present case and there is also no need for an inert gas atmosphere. To further improve the synthetic value, the rearrangement was used to form dimethylaminosulfonyl-protected allylic amines, which can be deprotected under non-reductive conditions.

Introduction

Enantiopure α-branched allylic amines are employed as high-value building blocks for technical scale applications[1] because the synthetically versatile amino and olefin functionalities allow for a number of subsequent synthetic manipulations. For that reason chiral allylic amines have also been used in a large number of natural product syntheses,[2] for a straightforward access towards N-containing chiral heterocycles[3] as well as α- or β-amino acids.[4] In addition, allylic amines have been described as peptide isosters with potential biological activity.[5]

As a result of the synthetic utility of chiral enantiopure allylic amines, a number of catalytic methods have been developed for the enantioselective preparation including allylic substitutions,[6] 1,2-additions of appropriate nucleophiles to imines,[7] hydrogenations of dienamines,[8] hydroaminations of allenes[9] and several types of rearrangements. The latter include [1,3]-,[10] [2,3]-[11] and [3,3]-rearrangements.[12] Predominantly allylic imidate substrates **5** (see Scheme 1, dashed box) in combination with carbophilic Lewis acids have been employed for enantioselective [3,3]-rearrangements.[12] A key feature of these reactions is a high regioselectivity, which has been explained by a cyclisation-induced rearrangement mechanism.[13]

The first enantioselective allylic imidate rearrangements were reported in 1997 by Overman et al.[14] In these initial reactions *N*-arylbenzimidates (R^3 = aryl in **5**) were used providing *N*-arylbenzamides, which are difficult to hydrolyse to the corresponding allylic amines. Further milestones were then the successful use of allylic trichloro-[15] ($R^3 = CCl_3$ in **5**) as well as *N*-aryl-[16] and *N*-alkyltrifluoroacetimidates[17] ($R^3 = CF_3$) in enantioselective rearrangements, because the trichloro- and trifluoroacetamide products can be readily transformed into primary and secondary amines, respectively. Very recently, the method could also be extended to non-halogenated acetimidates ($R^3 = CH_2R$) providing allylic acetamides, which can be deprotected under mild enzymatic conditions.[18]



Scheme 1. Comparison of allylic imidates **5** and allylic carbamates **1** and mechanistic idea of the decarboxylative Pd^{II}-catalysed rearrangement.

However, a common disadvantage of allylic imidate substrates **5** is their relatively large sensitivity towards hydrolysis, hampering their isolation and long-time storage. In addition, the preparation of trifluoro- and non-halogenated allylic imidates is tedious.

Our goal was to develop a [3,3]-rearrangement, which still provides the general advantages noted for Pd^{II}-catalysed asymmetric allylic imidate rearrangements such as high regio- and

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enantioselectivity and a broad compatibility with functional groups, but uses more robust and more readily accessible substrates. We envisioned to develop the first catalytic asymmetric allylic carbamate rearrangements, because 1) the quite stable carbamates **1** are very easily prepared by addition of alcohols to inexpensive commercial isocyanates; 2) carbamates **1** resemble allylic imidates; and 3) the initial carbaminic acid rearrangement product **3** would spontaneously decarboxylate saving an extra deprotection step (Scheme 1).

A thermal decarboxylative [3,3]-rearrangement of an *N*-phenylallylcarbamate was already reported in 1968 and accelerated by NaH, still requiring a reaction temperature of 200–240 °C.[19] In 1991, Wang and Calabrese reported that BF_3 can promote decarboxylative rearrangements for substrates with special substitution patterns to stabilise an allylic carbocation intermediate.[20] In 2000, Lei and Liu reported a non-enantioselective palladium(II)-catalysed rearrangement of *N*-tosylcarbamates.[21] High regioselectivity was accomplished by $Pd(OAc)_2$ (5 mol%) as catalyst assisted by an excess of LiBr (4 equiv) in DMF at 100 °C.[22,23] Ten years later, Xing and Yang described a gold(I) (5 mol%) catalysed reaction that made use of stoichiometric amounts of iPr_2NEt as base additive to form racemic decarboxylative rearrangement products.[24]

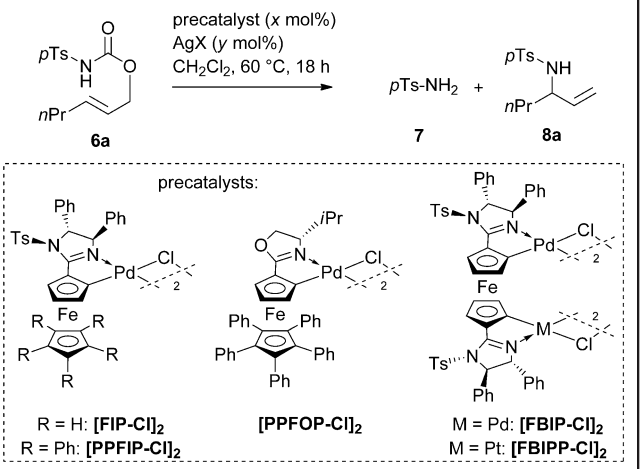
Allylic carbamates have also been employed for Pd^0-[25] and Ir^I-catalysed[26] decarboxylative allylic substitutions, in which linear products were preferentially formed in the first case and chiral branched products in the latter through electrophilic π-allyl complexes. Here we report the development of the first catalytic asymmetric decarboxylative allylic carbamate rearrangements and the translation into a domino process[27] employing achiral allylic alcohols as substrates.[28] This process is enabled by the cooperative action of Pd^{II} and a tertiary amine.[29]

Results and Discussion

Development and optimisation of the decarboxylative carbamate rearrangement

To develop an asymmetric decarboxylative allylic carbamate rearrangement, *N*-tosyl protected allyl carbamates were chosen as substrates based on their reactivity in the previous non-enantioselective protocols.[21,24] They were readily prepared as geometrically pure isomers by addition of the corresponding *E*-configured allylic alcohols to *p*-tosylisocyanate (for details see the Supporting Information). The *n*Pr-substituted olefin **6a** was chosen as a model substrate, because the alcohol precursor is commercially available in isomerically pure form. Different ferrocene-based planar chiral pallada- and platinacycles previously developed by our research group[15e,16g,i,j] were then screened for their efficiency as asymmetric catalysts (Table 1). These metallacycles are chloride-bridged dimers, which showed almost no catalytic activity in our previous investigations on allylic imidate rearrangements without a removal of the chloride bridges. For that reason they were activated by $AgNO_3$ in CH_2Cl_2 (monopalladacycles)[15e,16i,30] and AgOTs in MeCN (bismetallacycles)[16g,j,31] according to our previously published protocols, resulting in a chloride ligand exchange. Using an excess of the silver salts per ferrocene unit, the monopalladacycles also undergo an oxidation process. In the case of pentaphenylferrocene palladacycles we have previously shown that paramagnetic Pd^{III} complexes are generated under these conditions as catalytically active species, while the ferrocene core remained intact.[16i,32]

Table 1. Investigation of the decarboxylative allylic carbamate rearrangement of model substrate **6a** under neutral reaction conditions.



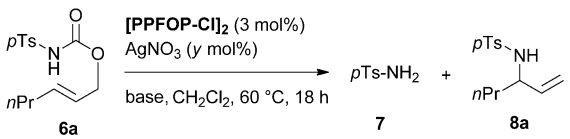
Entry	Precatalyst [x mol%]	AgX [y mol%]	Yield **7** [%][a]	Yield **8a** [%][a]	*ee* **8a** [%][b]
1	**[FIP-Cl]$_2$** (5)	$AgNO_3$ (10)	2	0	–
2	**[FIP-Cl]$_2$** (5)	$AgNO_3$ (20)	6	0	–
3	**[PPFIP-Cl]$_2$** (5)	$AgNO_3$ (10)	0	0	–
4	**[PPFIP-Cl]$_2$** (5)	$AgNO_3$ (20)	2	0	–
5	**[PPFOP-Cl]$_2$** (5)	$AgNO_3$ (10)	17	10	9
6	**[PPFOP-Cl]$_2$** (5)	$AgNO_3$ (20)	15	12	10
7	**[FBIP-Cl]$_2$** (1.5)	AgOTs (6)	0	0	–
8	**[FBIPP-Cl]$_2$** (1.5)	AgOTs (6)	0	0	–

[a] Yield determined by ^1H NMR spectroscopy using an internal standard. [b] Enantiomeric excess of isolated product (by column chromatography) determined by HPLC.

Table 1 summarises the initial results obtained with the different catalysts in CH_2Cl_2 solutions at 60 °C using small pressure tubes as reaction vials. For the monopalladacycles, the use of both non-oxidised and oxidised activated catalysts was investigated (Table 1, entries 1, 3, 5 and 2, 4, 6, respectively). In most cases, none of the desired product **8a** was obtained utilising a monopalladacycle catalyst.[33] The same result was found with both bismetallacycle catalysts (Table 1, entries 7 and 8). The only catalyst that delivered small amounts of rearrangement product **8a** (ca. 10% yield), was the pentaphenylferrocene-based oxazoline monopalladacycle **PPFOP**[15e] (Table 1, entries 5 and 6). However, the precatalyst activated by $AgNO_3$ provided only disappointing enantioselectivities (ca. 10% *ee*). In addition, relatively large amounts of sulfonamide **7** were detected as side product.

Because **PPFOP** delivered the only active system in the initial reactions, in the subsequent development we focused on this catalyst type. To increase the reactivity, the use of Brønsted base additives was studied (Table 2) to deprotonate the quite

Table 2. Investigation of different base additives.



6a 7 8a

Entry	$AgNO_3$ [*y* mol%]	Base [mol%]	Yield **7** [%][a]	Yield **8a** [%][a]	*ee* **8a** [%][b]
1	12	K_2CO_3 (100)	3	6	86
2	12	Cs_2CO_3 (100)	0	0	–
3	12	KO*t*Bu (100)	3	12	83
4	12	2,4,6-collidine (100)	3	0	–
5	12	iPr_2NEt (100)	6	88	89
6	12	PS[c] (100)	3	90	88
7	6	iPr_2NEt (100)	6	89	89
8	6	PS[c] (100)	3	96	88
9[d]	–	iPr_2NEt (100)	25	0	–
10[d]	–	PS[c] (100)	30	0	–
11	6	iPr_2NEt (25)	3	89	88
12	6	PS[c] (25)	9	86	87
13	6	iPr_2NEt (10)	6	33	92
14	6	PS[c] (10)	5	91	86
15	6	iPr_2NEt (6)	9	11	n.d.[e]
16	6	PS[c] (6)	13	27	n.d.[e]

[a] Yield determined by ^1H NMR spectroscopy using an internal standard. [b] Enantiomeric excess of isolated product (by column chromatography) determined by HPLC. [c] PS = proton sponge (1,8-bis(dimethylamino)-naphthalene). [d] The reaction was performed in the absence of a palladacycle catalyst. [e] Enantiomeric excess was not determined due to the low product yield.

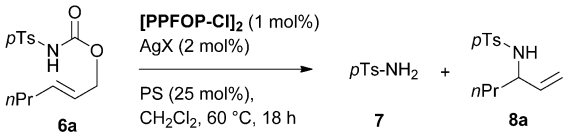
NH-acidic carbamate ($pK_a \approx 3.7$).[34] Whereas the reactivity was still low when using the O-centred bases K_2CO_3, Cs_2CO_3 and KO*t*Bu (Table 2, entries 1–3), the enantioselectivity was massively improved in the presence of the salts. The enantioselectivity was further improved by using neutral bulky organic N-bases, and the rearrangement product was obtained in high yields using either iPr_2NEt (Table 2, entry 5) or proton sponge (PS, 1,8-bis(dimethylamino)naphthalene, entry 6). In contrast, there was no reactivity with 2,4,6-collidine (Table 2, entry 4), maybe due to catalyst inhibition. In the case of iPr_2NEt or proton sponge the initial catalyst oxidation state did not play a significant role. The experiments using either the Pd^{III} catalyst (Table 2, entries 5 and 6) or the Pd^{II} catalyst (Table 2, entries 7 and 8) gave very similar results in terms of product yield, enantioselectivity and regioselectivity. The linear product of a formal [1,3]-rearrangement was only detected in trace quantities. In the absence of the catalyst no rearrangement product was detected for both N-bases, but decomposition towards sulfonamide **7** was largely increased (Table 2, entries 9 and 10).

Stoichiometric quantities of the N bases are not necessary because very similar reaction outcomes were also found with 25 mol% (Table 2, entries 11 and 12). The activity of PS also allowed for the use of 10 mol% (Table 2, entry 14), whereas with 10 mol% iPr_2NEt the reactivity was low (entry 13). Lower base loadings than 10 mol% were not tolerated in each case (Table 2, entries 15 and 16).

Due to the better reactivity with PS as co-catalyst, the reaction was further optimised using this base. For that purpose, different solvents were initially investigated under the conditions of Table 2, entry 12. Whereas Lewis basic solvents significantly lowered the activity (yield with DMF: 35%; MeCN: 22%), non- or weakly-coordinating solvents were tolerated, but in each case the efficiency was slightly lower than with CH_2Cl_2 (yield/*ee* with EtOAc: 86%/85%; THF: 80%/82%; toluene: 82%/84%; $CHCl_3$: 79%/84%). Nevertheless, these data demonstrate that a solvent more appropriate to a technical application than CH_2Cl_2 like for instance EtOAc can be utilised.

Different silver salts (AgX) were explored for the further optimisation (Table 3). In these trials the amount of the dimeric precatalyst was reduced to 1 mol% to facilitate the identification of differences in activity. 2 mol% of the corresponding silver salts was used for the chloride exchange.

Table 3. Investigation of different silver salts for catalyst activation.



6a 7 8a

Entry	AgX	Yield **7** [%][a]	Yield **8a** [%][a]	*ee* **8a** [%][b]
1	$AgNO_3$	8	86	77
2	AgO_2CCF_3	4	94	85
3	AgOAc	25	65	78
4	AgOTs	12	77	84
5	AgOMs	13	62	n.d.[c]
6	AgOTf	15	44	n.d.[c]
7	$AgBF_4$	16	65	82
8	$AgPF_6$	16	48	n.d.[c]
9	$AgO_2CC_3F_7$	8	86	88
10	$AgO_2CC_7F_{15}$	10	66	n.d.[c]
11[d]	AgO_2CCF_3	14	59	n.d.[c]
12[e]	AgO_2CCF_3	2	94	90
13[f]	–	13	58	86

[a] Yield determined by ^1H NMR spectroscopy using an internal standard. [b] Enantiomeric excess of isolated product (by column chromatography) determined by HPLC. [c] Enantiomeric excess was not determined. [d] 0.5 mol% of precatalyst and 1.0 mol% of the silver salt were used. [e] The reaction was performed at 50 °C. [f] The reaction was performed in the presence of the non-activated palladacycle catalyst.

Because the anionic ligand X^- has an influence on the electronic and steric properties of the catalytic centres, significant differences in catalytic activity and enantioselectivity were expected. Using $AgNO_3$ for the activation, the *ee* value decreased to 77% with the lower catalyst loading, albeit the product yield was still identical (Table 3, entry 1). Better data was obtained with silver trifluoroacetate (Table 3, entry 2), which allowed for 85% *ee* and a yield of 94%. The other silver salts tested allowed for very similar enantioselectivities, the only exception being AgOAc, which had an *ee* value smaller than 80% (Table 3, entry 3).

The amount of side product **7** formed was influenced by AgX. In particular, with AgOAc a rather large amount of **7** was found (Table 3, entry 3). The only silver salt found that allowed for an activity comparable to silver trifluoroacetate was silver

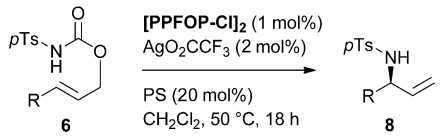
heptafluorobutyrate, which also had a slightly positive effect on the enantioselectivity (Table 3, entry 9). Nevertheless, the use of silver trifluoroacetate was more attractive to us for economic reasons.

To decrease costs, lower catalyst loadings were also studied. However, the product yield was moderate starting from 0.5 mol% of the precatalyst, partly because of the formation of more side product **7** (Table 3, entry 11). On the other hand, the *ee* value could be increased to 90% by a decrease of the reaction temperature to 50 °C (Table 3, entry 12). Surprisingly, moderate product yields could even be obtained with the non-activated catalyst (Table 3, entry 13).

Scope and limitations

The optimised conditions presented in Table 3, entry 12, were then applied to various allylic *N*-tosylcarbamates carrying different alkyl residues R at the olefin function (Table 4).

Table 4. Investigation of different carbamate substrates.



Entry	6/8	R	Yield [%][a]	*rs*[b]	*ee* [%][c]
1	**a**	*n*Pr	94	25:1	90
2	**b**	Et	88	30:1	88
3	**c**	Me	88	70:1	63
4	**d**	*n*Pent	91	24:1	88
5	**e**	$(CH_2)_2Ph$	96	34:1	92
6	**f**	$(CH_2)_2CO_2Me$	94	26:1	89
7	**g**	CH_2OTBS	77	20:1	98
8	**h**	CH_2OBn	87	20:1	98
9[d]	**i**	*i*Pr	45	8:1	86
10	**j**	*i*Bu	90	12:1	88

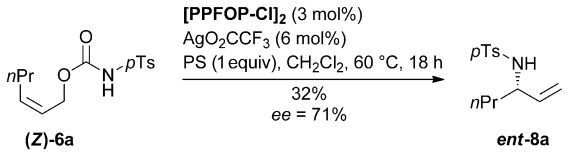
[a] Yield of isolated product. [b] Regioselectivity branched/linear product determined by ^1H NMR of the crude product. [c] Enantiomeric excess determined by HPLC. [d] $t = 48$ h at 60 °C.

In nearly all cases the products **8** were formed in good to high yields. The only exception was noted for the *i*Pr-substituted substrate **6i**. The reaction was found to be more sluggish with the sterically demanding α-branched substituent and increased formation of side products was observed (Table 4, entry 9). In contrast, in the presence of the β-branched *i*Bu substituent, the reactivity was still high. Enantiomeric excesses were usually in a range of 86 to 98% (Table 4, entry 10). The best enantioselectivities were found for two substrates with protected hydroxymethyl residues R (Table 4, entries 7 and 8). Also, an enolisable ester residue was well tolerated both in terms of reactivity and enantioselectivity (Table 4, entry 6). A moderate *ee* value was only found for substrate **6c** carrying a methyl group as the smallest residue R of the substrates investigated (Table 4, entry 3). Similarly, for allylic imidate rearrangements a methyl substituent at the olefin function was previously found to cause lower enantioselectivities, which was explained by an intrinsically more difficult differentiation of the enantiotopic olefin faces.[15,16]

Regarding the regioselectivity the branched chiral products were usually strongly favoured with ratios of ≥20:1. Lower regioselectivities of 8:1 and 12:1 were found for substrates carrying the branched *i*Pr and *i*Bu residues, respectively (Table 4, entries 9 and 10), in which the [3,3]-rearrangement is expected to be more difficult for steric reasons.

Substrates with aryl residues R directly connected to the olefin moiety were, in general, not well tolerated and either provided no desired product (electron-rich aryl residues) or the products were formed with poor yields (as a result of side reactions) and low enantioselectivity (*ee* < 40%, data not shown). The substrate preference is thus complementary to Ir-catalysed allylic aminations, for which aromatic residues R usually provided higher regioselectivities than aliphatic groups.[6]

Moreover, we found that *Z*-configured allylic moieties are not favourable. Even using larger quantities of catalyst and base and a temperature of 60 °C the reaction was sluggish and provided the product with only moderate enantioselectivity (Scheme 2). It is noteworthy, however, that the title reaction is



Scheme 2. Rearrangement of a *Z*-configured substrate.

stereospecific, because the product was formed with opposite absolute configuration depending on the olefin geometry of the substrate. This points to a scenario in which 1) enantioface-selective olefin coordination might predetermine the configurational outcome and 2) similar to the allylic imidate rearrangement, the carbamate rearrangement might proceed through an early (half)chair-like transition state, in which *E* substituents could adopt an equatorial position, whereas *Z* substituents need to be accommodated in an axial position (see below).[15,16] The latter would explain the higher activation barriers with *Z* substrates.

The absolute configuration of **8a** was determined to be *R* by X-ray analysis (Figure 1).[35] In addition, for products **8a–d** and **8h–j** the *R* configurations could be assigned by comparison to literature data (see the Supporting Information for details).

Development and application of a domino process

Since the *N*-tosylcarbamate formation between the allylic alcohols and *N*-tosylisocyanate proceeded smoothly and provided very pure crude products, a one-pot protocol was envisioned without the need for the isolation of the carbamate substrate.[36] Stirring a solution of the allylic alcohol **9a** and *p*TsNCO for 30 min at room temperature in CH_2Cl_2 was fol-

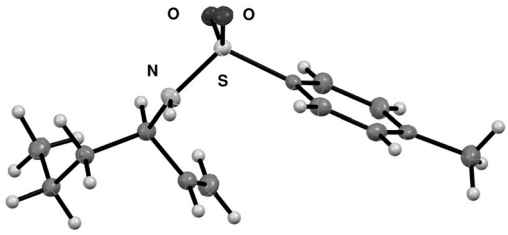
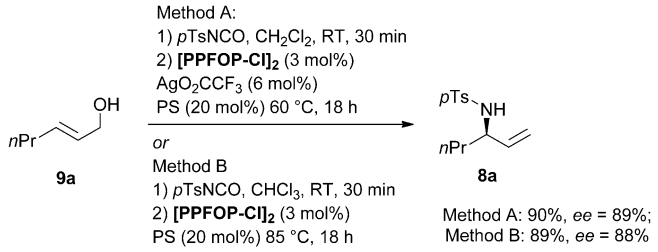


Figure 1. Determination of the absolute configuration of **8a** by X-ray crystal structure analysis.

lowed by addition of the catalyst (prepared from 3 mol% pre-catalyst and 6 mol% AgO_2CCF_3) and base (20 mol% PS). After 18 h at 60 °C the decarboxylative rearrangement product was formed in high yield with an *ee* of 89% (Scheme 3, Method A).



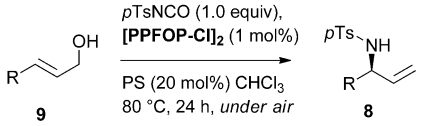
Scheme 3. Development of a one-pot protocol using activated (Method A) or non-activated catalyst (Method B).

The operational simplicity would, of course, be further improved by avoiding the catalyst activation with a silver salt. As promising results were already obtained in the initial studies (Table 3, entry 13), the carbamate rearrangement of **6a** to **8a** was reinvestigated using the non-activated catalyst in different solvents at higher temperatures to further increase the reactivity. The best results were obtained in $CHCl_3$ at 85 °C (in a sealed tube). Under conditions otherwise identical to Table 3, entry 13, compound **8a** was then obtained in 88% yield and with 90% *ee*. The one-pot version was thus repeated in $CHCl_3$ with the non-activated catalyst. After carbamate generation at room temperature, **[PPFOP-Cl]$_2$** (3 mol%) and PS (20 mol%) were added and after 18 h at 85 °C the product was isolated in 89% yield and with 88% *ee* (Scheme 3, Method B).

Due to the high efficiency of the one-pot version, the possibility of a domino reaction[37] was studied without a separate allylic carbamate preformation. All reaction components were thus mixed at once. Gratifyingly, this operationally very simple protocol also provided the rearrangement product **8a** with high yield and enantioselectivity using 1 mol% of **[PPFOP-Cl]$_2$**, even when conducted under air (Table 5, entry 1).[38]

This protocol was then used for different *E*-configured allylic alcohol substrates **9** (Table 5). Gratifyingly, the results in terms of yield, regio- and enantioselectivity for all ten substrates were very similar to those presented in Table 4, in which the isolated carbamates **6** were employed in combination with the activated catalyst. Hence, again the products were usually

Table 5. Application of the cascade title reaction.

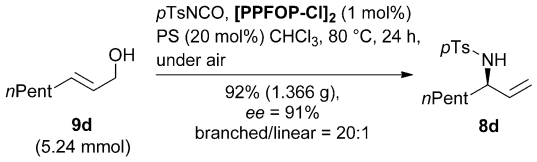


Entry	9/8	R	Yield [%][a]	*rs*[b]	*ee* [%][c]
1	**a**	*n*Pr	80	20:1	90
2	**b**	Et	88	16:1	91
3	**c**	Me	90	40:1	72
4	**d**	*n*Pent	85	22:1	93
5	**e**	$(CH_2)_2Ph$	86	25:1	92
6	**f**	$(CH_2)_2CO_2Me$	80	26:1	90
7	**g**	CH_2OTBS	83	20:1	98
8	**h**	CH_2OBn	90	20:1	98
9	**i**	*i*Pr	52	7:1	92
10	**j**	*i*Bu	79	10:1	89

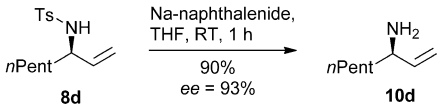
[a] Yield of isolated product. [b] Regioselectivity determined by ^{1}H NMR analysis of the crude product. [c] Enantiomeric excess determined by HPLC.

formed in good to high yields and with high enantio- and regioselectivity. For the difficult substrate **9c** carrying a Me substituent R, the *ee* could be increased from 63 to 72% applying this protocol (Table 5, entry 3). In all other examples the *ee* values ranged from 89 to 98%. Similar to the use of isolated carbamates, branched alkyl groups R had a negative impact on the regioselectivity (Table 5, entries 9 and 10). On the other hand, functional groups such as ester, ether and silyl ether moieties were well accommodated (Table 5, entries 6–8).

The practicality of the rearrangement protocol was examined on gram scale for substrate **9d** using a sealed pressure tube under air (Scheme 4). With 5.24 mmol of this substrate, 1.366 g of **8d** (92% yield) were obtained with 91% *ee*. A reductive sulfonamide deprotection was performed under standard conditions[39] to release the free enantioenriched allylic amine **10d** in high yield (Scheme 5). However, as these reductive conditions should not be compatible with reduction-sensitive functional groups, we were also interested in alternative protecting groups that might be removed under different conditions.



Scheme 4. Gram-scale experiment of the domino carbamate formation/decarboxylative rearrangement.

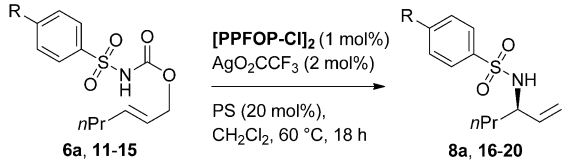


Scheme 5. Reductive sulfonamide cleavage to release a free allylic amine.

Variation of the N-protecting group

To increase the flexibility of possible protecting group strategies, a number of different allylic carbamate moieties were investigated. Unfortunately, *N*-benzyl-, *N*-carboxyl- (i.e., *N*-carbonyloxybenzyl, *N*-carbonyloxyphenyl, *N*-carbonyloxymethyl and *N*-carbonyloxytrichloromethyl) and *N*-aryl- (4-$MeOC_6H_4$, 4-$O_2NC_6H_4$, 3,5-$(F_3C)_2C_6H_3$) protected allylic carbamates failed to form the rearrangement products in more than trace quantities using the **PPFOP** catalyst system in combination with PS. Consequently, the applicability of different *N*-sulfonyl residues was investigated (Table 6).

Table 6. Investigation of the electronic effect of different *N*-sulfonyl residues.



Entry	R	Starting material/product	Yield [%][a]	*rs*[b]	*ee* [%][c]
1	OMe	**11**/**16**	83	24:1	87
2	Me	**6a**/**8a**	94	16:1	85
3	H	**12**/**17**	84	17:1	87
4	F	**13**/**18**	93	14:1	82
5	Cl	**14**/**19**	89	19:1	82
6	NO_2	**15**/**20**	62 (80)[d]	19:1 (9:1)	73 (84)[d]

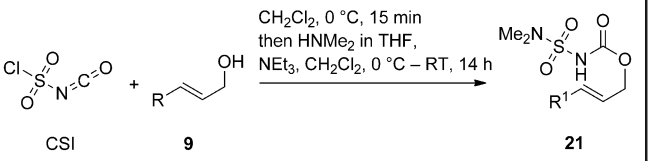
[a] Yield of isolated product. [b] Regioselectivity determined by ^{1}H NMR analysis of the crude product. [c] Enantiomeric excess determined by HPLC. [d] Data in brackets with non-activated catalyst (1 mol%) in $CHCl_3$ at 80 °C for 24 h.

The *N*-sulfonyl-substituted substrates **11**–**15** were either prepared from the allylic alcohol **9a** and the corresponding isocyanates (like with TsNCO) or using the corresponding primary sulfonamide plus CDI (1,1′-carbonyldiimidazole) as dehydrating agent (for details see the Supporting Information).

All investigated alternative sulfonyl-protected substrates **11**–**15** formed the corresponding products **16**–**20** with good regioselectivities in CH_2Cl_2 at 60 °C in a sealed tube using activated catalyst (14:1–24:1). As a trend it was observed that *N*-arylsulfonyl substrates with electron-donating residues (Table 6, entries 1 and 2) allowed for somewhat better enantioselectivities than those with electron-withdrawing residues (Table 6, entries 4–6). The NH acidity and the resultant nucleophilicity/Lewis basicity of the deprotonated substrates thus seem to be important for high enantioselection in the C–N bond-forming step. The enantioselectivity was the lowest with the *para*-nosyl N-protecting group (entry 6, 73%). However, in this case the enantioselectivity could be improved to 84% *ee* by use of the non-activated catalyst in $CHCl_3$ at 80 °C (Table 6, entry 6, data in brackets).

Due to the observed electronic effect, the more electron-rich *N*,*N*-dimethylaminosulfonyl moiety seemed to be an appropriate choice, in particular because it is also well established as a synthetically attractive protecting group as it can be removed under non-reductive conditions.[40] In our preliminary studies, this substrate type was prepared over two steps from the corresponding allylic alcohol **9**, CDI and $Me_2NSO_2NH_2$ in low overall yields (ca. 20%).[28] As anticipated, a positive influence of the strongly electron-donating amino group at the sulfonyl moiety was indeed observed in terms of enantioselectivity as shown below. For that reason a more efficient route to this substrate class was developed. In a one-pot protocol, the allylic alcohols were first treated with chlorosulfonylisocyanate (CSI) to form a chlorosulfamoyl intermediate, which was then trapped by Me_2NH (Table 7).

Table 7. Synthesis of the dimethylaminosulfonyl protected allylic substrates.



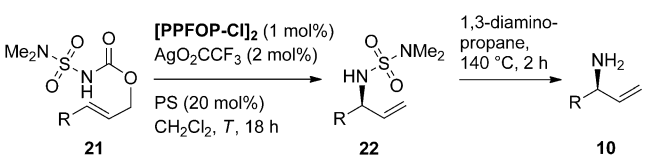
Entry	**9**/**21**	R	Yield [%][a]
1	**a**	*n*Pr	92
2	**b**	Et	99
3	**c**	Me	84
4	**d**	*n*Pent	89
5	**e**	$(CH_2)_2Ph$	90
6	**f**	$(CH_2)_2CO_2Me$	85
7	**g**	CH_2OTBS	94
8	**h**	CH_2OBn	99
9	**i**	*i*Pr	96
10	**j**	*i*Bu	97

[a] Yield of isolated product.

Different substrates **21** including those functionalised by ester, silylether or ether groups were accessible by this procedure through a smooth transformation. In general, the *N*,*N*-dimethylaminosulfonyl-protected allylic carbamates **21** showed lower reactivity in the catalytic asymmetric rearrangement than the *N*-tosyl-protected substrates **6**, therefore they required a reaction temperature of 60 °C with the **PPFOP** catalyst activated by silver trifluoroacetate (for *N*-tosyl usually 50 °C was sufficient under these conditions, see Table 4). Despite this, the products were typically formed in high yields and with improved enantioselectivities (Table 8). For instance, the substrate most difficult in terms of enantioselection equipped with a methyl residue R (**21c**) still allowed for an *ee* of 82%. For the other products the *ee* values were in the range of 92–99%.

Despite the increased reaction temperature, functional groups were well tolerated (Table 8, entries 6–8) and also the branched/linear product ratios were usually high (18–76:1) with the exception of substrate **21i** carrying the sterically more demanding *i*Pr residue as R (4:1, Table 8, entry 9). In the latter case, a reaction temperature of 80 °C was required for a useful yield after 72 h.

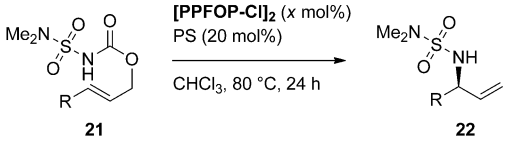
Table 8. Investigation of different dimethylaminosulfonyl protected allylic substrates **21** in the decarboxylative rearrangement followed by deprotection.



Entry	21/22/10	R	T [°C]	Yield 22 [%][a]	rs[b]	ee [%][c]	Yield 10 [%][a]
1	**a**	*n*Pr	60	85	24:1	94	75
2	**b**	Et	60	94	24:1	93	94[d]
3	**c**	Me	60	95	76:1	82	73[d]
4	**d**	*n*Pent	60	95	24:1	94	96
5	**e**	$(CH_2)_2Ph$	50	92	39:1	98[e]	98
6	**f**	$(CH_2)_2CO_2Me$	60	95	18:1	n.d.	-
7	**g**	CH_2OTBS	60	90	28:1	99	89
8	**h**	CH_2OBn	60	96	24:1	99	91
9	**i**	*i*Pr	80	45[f]	4:1	92	85[d]
10	**j**	*i*Bu	60	90[g]	18:1	94	90[d]

[a] Yield of isolated product. [b] Regioselectivity branched/linear product determined by ^1H NMR analysis of the crude product **22**. [c] Enantiomeric excess determined by HPLC after deprotection of **22** and subsequent tosylation. [d] Isolated as hydrochloride salt. [e] Enantiomeric excess of **22e** determined directly by HPLC. [f] The rearrangement was performed in $CHCl_3$ for 72 h. [g] The rearrangement was performed for 72 h.

Table 9. Investigation of different dimethylaminosulfonyl-protected allylic substrates in the decarboxylative rearrangement using **[PPFOP-Cl]$_2$**.



Entry	2	R	[PPFOP-Cl]$_2$ [x mol%]	Yield [%][a]	rs[b]	ee [%][c]
1	**a**	*n*Pr	2	82	15:1	92
2	**b**	Et	1	84	17:1	94
3	**c**	Me	1	95	37:1	84
4	**d**	*n*Pent	2	95	14:1	94
5	**e**	$(CH_2)_2Ph$	1	93	24:1	96[d]
6	**f**	$(CH_2)_2CO_2Me$	1	83	16:1	n.d.
7	**g**	CH_2OTBS	2	73	15:1	99
8	**h**	CH_2OBn	2	94	22:1	99
9	**i**	*i*Pr	2	36[e]	5:1	88
10	**j**	*i*Bu	2	66[e]	15:1	93

[a] Yield of isolated product. [b] Regioselectivity branched/linear product determined by ^1H NMR analysis of the crude product **22**. [c] Enantiomeric excess determined by HPLC after N-deprotection and subsequent tosyl protection. [d] Enantiomeric excess of **22e** determined by HPLC. [e] The rearrangement was performed for 72 h.

For the determination of the *ee* values, most substrates were deprotected, and only for **22e** were we able to determine the *ee* directly from the rearrangement product by HPLC. Deprotection was in most cases achieved in good to very high yields under standard conditions using 1,3-diaminopropane as reagent.[41] Allyl amines with low boiling points were isolated as their hydrochloride salts to avoid a loss of material. The N-deprotection of the ester-containing **22f** was problematic, resulting in decomposition. The enantiomeric excess of **22f** could not be determined thus far.

In the other cases (if not indicated otherwise) *ee* values were determined by HPLC after tosylation of the free amino group (see the Supporting Information). This revealed that the rearrangements of dimethylaminosulfonyl and tosyl-protected allylic substrates both formed the new stereocenter with identical absolute configuration (comparison of optical rotation and HPLC data). The configurational outcome was further confirmed by comparison of samples of free amine **10d** prepared by either deprotection of **8d** (Scheme 5) or **22d** (Table 8, entry 4).

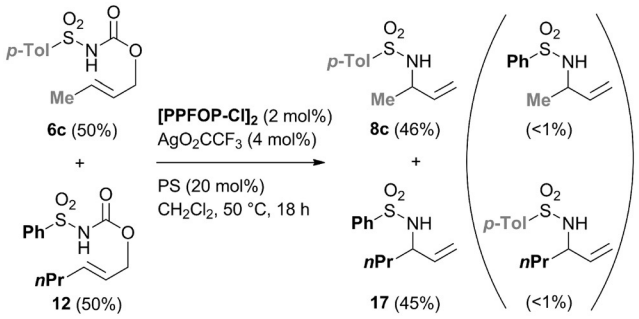
Moreover, in the case of **22e** we could show that the dimethylaminosulfonyl deprotection proceeded without significant partial racemisation; identical *ee* values were determined for **22e** itself and for the corresponding *N*-tosyl-protected **8e** obtained by deprotection of **22e** and subsequent tosylation.

To further increase the practicality of this version, the use of the non-activated catalyst was also investigated (Table 9). For comparable yields an increased catalyst loading was sometimes necessary and all reactions were performed at 80 °C in $CHCl_3$. Despite the harsher conditions, high regio- and enantioselectivities were again achieved. In fact, for the difficult substrate **22c**, the highest *ee* value for all experiments with R = Me (84%, Table 9, entry 3) was attained under these conditions (88–99% *ee* for the other residues R). The observed substitution-dependent reactivity and selectivity trends are otherwise similar as before.

Mechanistic considerations

To gain information how the title reaction proceeds, different mechanistic studies were executed. The observation that the reaction is stereospecific, providing different major product enantiomers depending on the configuration of the olefin moiety pointed to a mechanistic similarity to the Pd^{II}-catalysed allylic imidate rearrangements. For the latter, the stereospecificity has been explained by a cyclic 6-membered (half)chair-like transition state, in which differentiation of the enantiotopic olefin faces by a chiral catalyst allows for enantiocontrol.[16d,13] Different enantiomers result from an accommodation of olefin *E* residues in the equatorial position, whereas *Z* residues adopt an axial position. This would also explain the lower reactivity of the *Z* substrates in the present study by 1,3-diaxial interactions in the transition state of the C–N bond formation.

To control the assumption of a rearrangement reaction, cross-over experiments were conducted, which should provide information if the reaction proceeds through an inter- or intramolecular pathway. A 1:1 mixture of substrates **6c** and **12** differing in the *N*-sulfonyl protecting group and the olefin substituent was applied to quasi-neat reaction conditions (Scheme 6). Whereas for an intramolecular pathway only two reaction products **8c** and **17** would be expected, an intermolecular reaction should also provide two additional cross-over products. The latter were only detectable in trace amounts (<



Scheme 6. Cross-over experiment supporting an intramolecular reaction pathway.

1% in GC-MS), whereas both products expected for an intramolecular pathway were produced in similarly high quantities. These data are thus in agreement with a rearrangement mechanism.

A pseudo-zero-order kinetic dependence on the carbamate substrate is suggested by ^{1}H NMR monitoring at a reaction temperature of 35 °C using activated catalyst (Figure 2). There is an almost linear relationship of the product amount formed

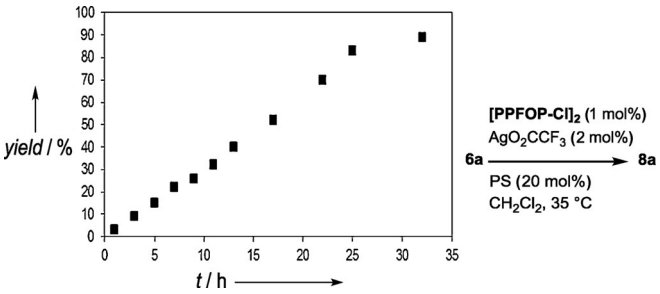


Figure 2. Relationship of product yield and time.

and the reaction time for yields up to about 80%. This is in accordance with a substrate saturation of the catalyst. Catalyst decomposition does not seem to be very critical as it would cause a decrease of the reaction rate with increasing conversion. The high affinity for the substrate to bind to the catalyst is in contrast to allylic imidate rearrangements using the same catalyst in which this behaviour was not found.[15e]

Substrate saturation for the allylic carbamate rearrangement is also in agreement with ESI-HRMS measurements. After a reaction time of 30 min at 35 °C using substrate **6a** and 5 mol% of **[PPFOP-O_2CCF_3]$_2$**, a deprotonated substrate molecule appears to be bound to the palladacycle in the dominating ferrocene palladacycle detected (not only carrying the C,N-ligand, Figure 3).

Only traces of the initially generated activated catalyst species **[PPFOP-O_2CCF_3]$_2$** were found to be present under these reaction conditions as judged from ^{19}F NMR experiments. The latter also suggest that the large majority of trifluoroacetate anions are not coordinating any more to the catalyst molecules, probably because they have been replaced by the substrate (for details see the Supporting Information).

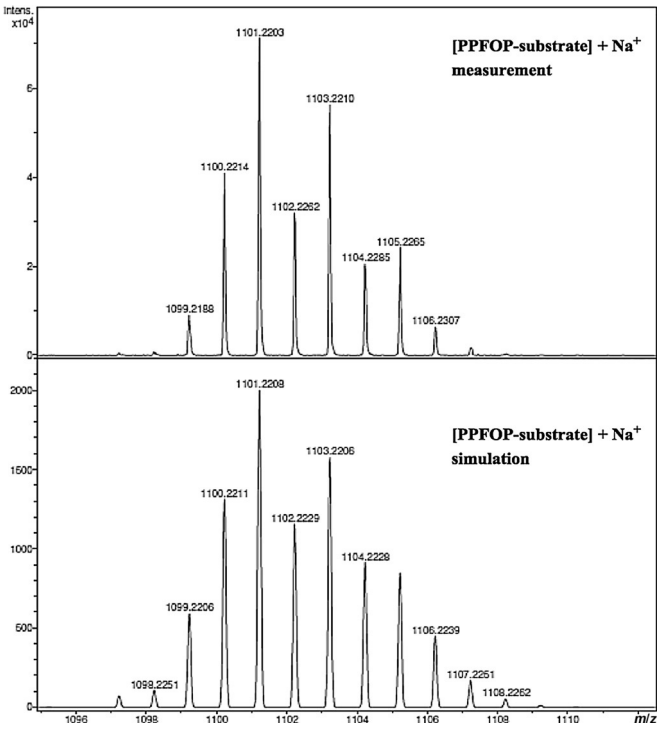
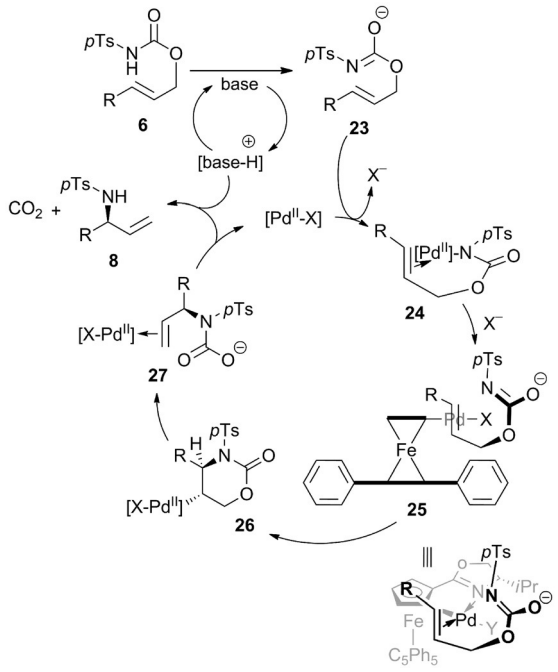


Figure 3. ESI-MS of the putative substrate catalyst adduct.

The substrate saturation and loss of the anion X^- might be explained by the formation of a chelate complex **24** as the resting state, in which both the olefin and the anionic carbamate moiety are coordinated to the palladium centre thus replacing the anionic ligand (Scheme 7).

Such a chelate might explain the observation that the anionic ligand X^- is less important for the enantioselectivity than is usually found for other applications of this catalyst type, because it is replaced by the deprotonated substrate in the enantioface-selective coordination. In this coordination the neutral olefin moiety should coordinate *trans* to the oxazoline N-donor based on the coordination behaviour typically found for ferrocene palladacycles.[15e,42] Like in other Pd^{II}-olefin complexes, the olefin moiety should be perpendicular to the Pd-square plane,[43] that is, parallel to the ferrocene axis in the present case. For steric reasons we expect that the allylic C-1 methylene points towards the massive C_5Ph_5 ligand because of its relatively low steric demand, whereas repulsive interactions between the *N*-sulfonyl residue of the substrate and the ferrocene core are minimised (Scheme 7). Also, for steric reasons the coordination of the enantiotopic olefin face is expected to be unfavourable.

In the chelate complex **24** the deprotonated carbamate-N should be *cis* to the oxazoline N. It might then attack the olefin through an inner-sphere mechanism to generate the C–N bond. However, this possibility seems to be less likely because olefin insertions into Pd–Y bonds typically proceed by concerted mechanisms through planar 4-membered cyclic transitions states.[43] That means for the present case that in the reactive conformation the C=C double bond would need to be in the Pd^{II}-square plane necessitating a rotation of the



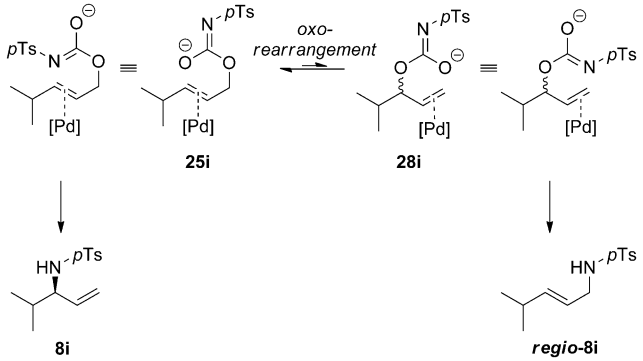
Scheme 7. Proposed mechanism of the palladacycle/base-catalysed decarboxylative allylic carbamate rearrangement.

coordinated olefin fragment by around 90°.[43] Based on the steric demand of the shielding C_5Ph_5 ligand, this is expected to cause repulsive interactions between the catalyst core and the substrate. For R = Me the smallest repulsive interaction of this type would be expected, which might at least partly explain the lower enantioselectivities in that case, because this path would be less disfavoured than with bulkier residues R. We thus favour an alternative scenario of an outer-sphere mechanism that requires a preceding dissociation of the carbamate N-atom, which might be triggered by the reversible recoordination of the anionic ligand X^-. This might also explain the influence of X^- on the reactivity. The anionic N-centre would thus attack from the face remote to the metal. For that reason, inner- and outer-sphere mechanisms should generate different enantiomers as major products assuming that the same olefin face is coordinating. Only the proposed outer-sphere pathway is in agreement with the determined *R*-configuration of the major product enantiomers based on the expected enantioface-selective olefin coordination. The lower reactivity of the more electron-rich and thus more nucleophilic dimethylaminosulfonyl-protected substrates **21** suggests that the N-decomplexation (and not the C–N bond formation) might be the rate-limiting step using activated catalysts **[PPFOP-X]$_2$**.

The subsequent C–N bond formation would provide the cyclic aminopalladated intermediate **26** featuring a σ-alkyl-Pd bond. The deprotonated carbaminic acid derivative **27** is generated by a ring-opening β-elimination. Decomplexation, decarboxylation and protonation furnish the *N*-sulfonylated allylic amine **8** and regenerate the palladium(II) and base catalysts for the next turnovers.

As shown above, the ratio of branched to linear amine is dependent on the steric bulk of the olefin substituent R. Formation of the linear isomer by a formal 1,3-rearrangement could be explained by a competing allylic substitution through a traditional π-allyl-Pd complex, which might be generated by oxidative addition from Pd^0 formed by partial decomposition of the palladacycle catalyst.[44] However, as shown above, catalyst decomposition is not likely to play a significant role as judged from the kinetic studies.

Alternatively, an oxo-rearrangement might be involved in the generation of the linear isomer (Scheme 8).



Scheme 8. Rationale for the formation of the formal 1,3-rearrangement product.

Similar oxo-rearrangements have been reported by Overman for Pd^{II}-catalysed rearrangements of allylic *N*,*N*-dialkylcarbamates.[45] Intramolecular attack of a carbamate oxygen at C=C would initially cause an isomerisation of the linear to the branched carbamate derivative like **28 i**. In the presence of a bulky branched olefin substituent such as *i*Pr, this competing reaction path might gain in importance, as the nucleophilic O-centre in **25 i** is sterically significantly less demanding than the tosyl-protected N-centre. The thus-generated branched carbamate **28 i** could then undergo a decarboxylative [3,3]-rearrangement, in which the carbamate N-atom is attacking the less-hindered terminal olefin moiety to finally form the linear allylic amine derivative *regio*-**8 i**.

Conclusion

We have reported the development and application of a step-economic enantio- and regioselective catalytic method to transform achiral allylic alcohols in a single step into tosyl-protected chiral allylic amines. These reactions are likely to proceed through a Pd^{II}/tertiary amine catalysed cyclisation-induced decarboxylative [3,3]-rearrangement of in situ-generated allylic carbamate intermediates, explaining the preference for the branched allylic product regioisomers and the observed stereospecificity. Enantioselectivity is explained in analogy to allylic imidate rearrangements using the same catalyst type by enantioface-selective olefin coordination and a subsequent outer-sphere attack of the nucleophilic deprotonated N-centre to the coordinated olefin. Our mechanistic studies have shown a substrate saturation of the catalyst up to high conversions, which can be explained by a two-point coordination of the

substrate in the resting state. The operational simplicity is notable, in particular, as there is no need for catalyst activation and an inert gas atmosphere. Whereas the allylic carbamate rearrangement could not be successfully applied to N-carbonyl-protected substrates so far, its synthetic utility was further enhanced by the effective use of *N*,*N*-dimethylaminosulfonyl-protected allylic carbamates, because this protective group can be removed under non-reductive conditions. The dimethylaminosulfonyl group thus behaves complementary to the tosyl moiety. In addition, the dimethylamino group allowed for a further improvement of the enantioselectivity. We believe that the title reaction belongs to the most practical catalytic asymmetric ways to form highly enantioenriched allylic amines.

Experimental Section

General procedure for the catalytic asymmetric decarboxylative rearrangement of *N*-sulfonyl-protected allylic carbamates by non-activated [PPFOP-Cl]$_2$

The corresponding *N*-sulfonyl protected carbamate (1 equiv), proton sponge (1,8-bis(*N*,*N*-dimethylamino)naphthalene) (0.2 equiv), and **[PPFOP-Cl]$_2$** (usually 1–2 mol%) were charged to a screw-cap vial. Vacuum was then applied and the vial was subsequently flushed with nitrogen (3 times repeated). Then $CHCl_3$ (typically 150 μL per 100 μmol) was added, the vial was closed and the mixture was stirred for the indicated time at the indicated temperature. Afterwards the mixture was diluted with CH_2Cl_2 and washed with aqueous 1 M HCl. The aqueous layer was extracted twice with CH_2Cl_2, the combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. After determination of the regioselectivity by ^{1}H NMR spectroscopy, the product was isolated by silica gel chromatography. The purified samples were used to determine the *ee* value by HPLC.

General domino procedure for the catalytic asymmetric synthesis of *N*-tosyl-protected allylic amines starting from allylic alcohols

A dry screw-cap vial was charged under air with **[PPFOP-Cl]$_2$** (1 mol%), proton sponge (1,8-bis(*N*,*N*-dimethylamino)naphthalene) (0.2 equiv), the corresponding allylic alcohol (**9**, 1 equiv) and *p*-tosylisocyanate (1.0 equiv). Subsequently, $CHCl_3$ (100 μL per 68 μmol allylic alcohol) was added. The vial was closed and the mixture stirred for 24 h at 80 °C. The solution was then diluted with CH_2Cl_2 and washed with aqueous 1 M HCl. The layers were separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and the solvent removed under reduced pressure. After determination of the regioselectivity by ^{1}H NMR spectroscopy, the product was isolated by silica gel chromatography. The purified samples were used to determine the *ee* values by HPLC.

Acknowledgements

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Keywords: allylic compounds · domino reactions · enantioselectivity · palladium · regioselectivity

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