Catalysis Science & Technology

PAPER

View Article Online
View Journal | View Issue

Cite this: *Catal. Sci. Technol.*, 2015, 5, 2340

Catalytic asymmetric [3,3]-rearrangements of allylic acetimidates†

J. Moritz Bauer and René Peters*

Received 30th December 2014,
Accepted 27th January 2015

DOI: 10.1039/c4cy01749h

www.rsc.org/catalysis

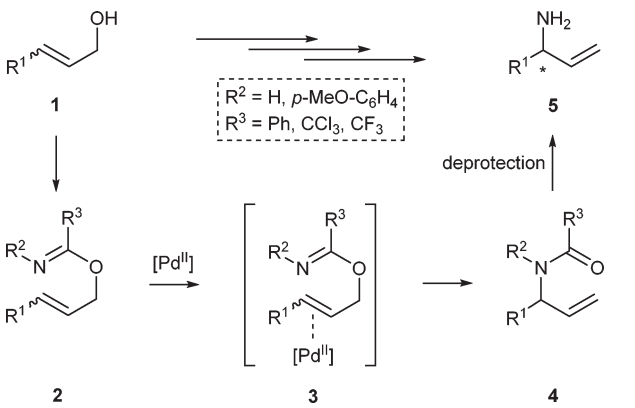
A streamlined synthetic access to enantiomerically pure allylic amines as advanced and valuable synthetic building blocks is important for pharmaceutical sciences. The rearrangement of allylic trihaloacetimidates is known as an attractive method to furnish branched chiral allylic trihaloacetamides with high levels of enantio- and regioselectivity. In the present article we report our studies on the catalytic asymmetric rearrangement of the corresponding non-halogenated acetimidates, which might provide economic advantages by avoiding CX_3 groups. The regioselective title reaction proceeds with high levels of enantioselectivity, provides high yields and requires only low catalyst loadings. In addition, the generated *N*-acetyl and *N*-phenacetyl functionalities offer the option of a subsequent mild enzymatic amide hydrolysis to get access to nearly enantiopure allylic amines.

Introduction

[3,3]-Rearrangements of allylic imidates provide a synthetic platform for a regioselective access of chiral branched allylic amines, which are masked as the corresponding amides.[1] The thermal sigmatropic [3,3]-rearrangement of allylic benzimidates was reported as early as 1937 by Mumm and Möller.[2] Allylic benzamides (**4** in Scheme 1, R^3 = aryl) are conveniently formed by this reaction type,[3] but are of restricted synthetic value, because the amide hydrolysis to release the corresponding allylic amines **5** has been reported as a difficult task.[3b] For that reason the rearrangement of allylic trichloroacetimidates **2** (Scheme 1, $R^3 = CCl_3$) has been developed as a synthetically more attractive alternative, which is commonly known as Overman rearrangement. Overman reported in 1974 that this reaction type is significantly accelerated by catalytic amounts of soft Lewis acids.[4] Based on these early studies enantioselective rearrangements of allylic trichloro-[5] and trifluoroacetimidates[6] ($R^3 = CF_3$) were later advanced, enabling a 2-step transformation of achiral allylic alcohols **1** to enantioenriched branched allylic amides **4** catalysed by chiral Pd(II)-complexes (Scheme 1). Due to the strong inductive effect of the CCl_3 or CF_3 groups, the release of the unprotected allylic amines **5** from the rearrangement products is usually readily accomplished.

In the last few years our group has developed the most active catalysts for the asymmetric rearrangement of trifluoroacetimidates,[7–9] allowing to reduce the catalyst loadings by 1–2 orders of magnitude. At the same time these catalysts enabled the highest levels of enantioselectivity achieved so far for a broad range of substrates. It became, *e.g.*, possible to generate N-substituted quaternary stereocenters with very high levels of enantioselection[7b,d] or to create a divergent access towards secondary chiral allylic amines[7c,d] by variation of the N-residue R^2 in Scheme 1. On the other hand, the preparation of the trifluoroacetimidates **2** is relatively tedious, quite expensive, usually makes use of toxic CCl_4 and generates large amounts of PPh_3 based waste.[10,11] Moreover, isolation and storage of trifluoroacetimidates is often troubled by their sensitivity towards hydrolysis.

For these reasons our goal was to develop analogous methods offering a comparable efficiency, but in which the



Scheme 1 The allylic imidate rearrangement.

Institut für Organische Chemie, Universität Stuttgart, Pfaffenwaldring 55, D-70569 Stuttgart, Germany. E-mail: rene.peters@oc.uni-stuttgart.de; Fax: +49 (0)711 68554330; Tel: +49 (0)711 68564330

† Electronic supplementary information (ESI) available: Experimental procedures, characterisation of all new compounds, NMR spectra, HPLC data. See DOI: 10.1039/c4cy01749h

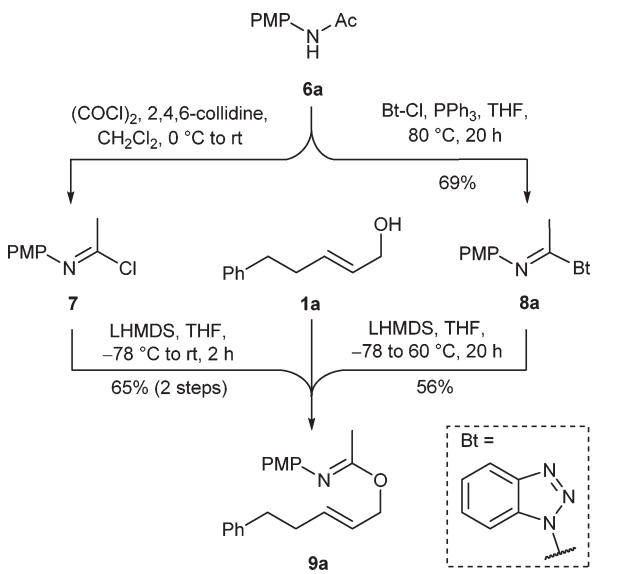
CX_3-groups would be avoided.[12] A synthetically attractive alternative might be the rearrangement of simple acetimidates ($R^3 = CH_3$ in Scheme 1), because several efficient methods for the deprotection of acetamides have been reported – either chemically[13] or by hydrolytically active enzymes.[14] Depending on the enzymes used, the latter deprotection strategy might also allow for the formation of enantiomerically pure amines by an additional kinetic resolution. This would be appealing in those cases, where the achieved enantioselectivity would not fit to the demands for a certain application, *e.g.*, as an active pharmaceutical ingredient. Moreover, the application of acetimidates would offer the advantage of an improved atom-economy.

The rearrangement of allylic non-halogenated acetimidates **2** (R^3 = alkyl) has only been scarcely reported. In 1992 Metz *et al.* reported the synthesis of racemic allylic propionylamides (R^3 = Et) which proceeded in useful yields utilising 5 mol% of $[PdCl_2(NCPh)_2]$ as catalyst.[15] Our group has reported a single enantioselective example, in which an allylic *N*-phenyl acetamide could be prepared with high enantioselectivity (ee = 94%).[7d] In our subsequent studies (see below) we found that the used reaction conditions were not generally applicable for other substrates to provide very high enantioselectivity. Herein we now report a method which (1) allows for the catalytic asymmetric synthesis of a broad range of allylic acetamides, (2) proceeds in general with excellent enantioselectivity and (3) can be executed with low catalyst loads.

Results and discussion

Optimisation

Substrate preparation. The *N*-PMP (PMP = *p*-methoxyphenyl) protected acetimidate **9a** (Scheme 2) was selected as the model substrate, because the PMP group is often used as a protecting group for amines.[16] Two alternative ways towards **9a** were developed and provided useful yields (Scheme 2). The first route is an optimisation of a previously reported method[7d] and starts from *N*-acetylated *p*-anisidine **6a**. Generation of the iminochloride **7** and subsequent treatment with the lithiated allylic alcohol formed **9a** in 65% yield over 2 steps after isolation by column chromatography. The other route used the imidoylbenzotriazole **8a** as coupling partner for the lithium alkoxide of the allylic alcohol **1a**.[17] In contrast to iminochloride **7**, **8a** is stable and can be purified without significant decomposition, but the overall yield is lower in that case (39% over 2 steps starting from **6a**) as compared to the method *via* the iminochloride **7**.

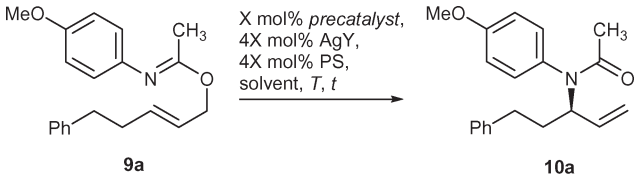


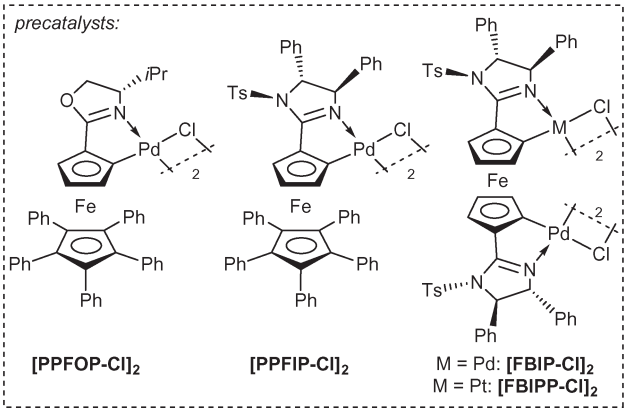
Scheme 2 Two alternative methods for the preparation of model substrate **9a**.

Catalytic model reaction. At the starting point of this investigation the conditions of the above mentioned single example for a catalytic asymmetric rearrangement of a non-halogenated allylic acetimidate[7d] were used for the rearrangement of **9a**. The chloride bridged dimeric pentaphenylferrocene oxazoline palladacycle $[PPFOP\text{-}Cl]_2$ (see Table 1) was used as precatalyst and activated by treatment with $AgNO_3$ according to the reported protocol.[7d,18] Although a higher precatalyst loading of 1.0 mol% (rather than 0.2 mol% for the reported example) was used, the enantiomeric excess of 83% was not satisfactory for the rearrangement of this substrate (entry 1). With a reduced catalyst loading of 0.5 mol% the enantiomeric excess was further decreased to 78% ee (entry 2). The change from an *N*-phenyl to a more electron-rich *N*-PMP group thus had a negative impact on the reaction outcome indicating that the previously reported conditions[7d] are not generally useful for non-halogenated acetimidates. To find a more general solution, some alternative ferrocene based catalysts, which have recently been developed in our research group, were then examined under reaction conditions that have originally been optimised for the rearrangement of allylic *N*-PMP trifluoroacetimidates.[7d,8b,9] The pentaphenylferrocene based imidazoline palladacycle $[PPFIP\text{-}Cl]_2$ (ref. 19 and 20) was thus activated by 4 equiv. (per precatalyst dimer) of AgO_2CCF_3.[7d] Earlier we have shown that 2 equiv. of a silver salt are responsible for an anion exchange of the strongly binding chloride bridges by a new anionic ligand. Another two equivalents oxidise the Pd-centers of PPFOP or PPFIP from Pd^{II} to Pd^{III}, leading to unique paramagnetic catalysts offering a significantly increased catalytic activity.[7f] Nevertheless, in the present case $[PPFIP\text{-}Cl]_2$ activated by AgO_2CCF_3 resulted in a low catalytic activity, yet promising enantioselectivity (entry 3).

For the bispalladacycle precatalyst $[FBIP\text{-}Cl]_2$ (ref. 8*b* and 21) and the mixed pallada-/platinacycle $[FBIPP\text{-}Cl]_2$ (ref. 9) an oxidation of the catalyst is usually not required for catalytic activity and activation by silver salts is just necessary for the chloride ligand exchange. In the present study the rearrangements could be done at room temperature providing high yields after reaction times of 3 days using precatalyst loadings of 1.0 or 2.0 mol% (entries 4 and 6). A reduced loading of 0.5 mol% also gave a high yield at a reaction temperature of 55 °C (entry 5). In all cases the enantioselectivity

Table 1 Investigation of different catalysts in the title reaction





#	Precatalyst	*X*	AgY	Solvent	*T* [°C]	*t* [h]	Yield[a] [%]	ee[b]
1	$[PPFOP\text{-}Cl]_2$	1.0	$AgNO_3$	CH_2Cl_2	50	24	97	83
2	$[PPFOP\text{-}Cl]_2$	0.5	$AgNO_3$	CH_2Cl_2	50	24	79	78
3	$[PPFIP\text{-}Cl]_2$	1.0	AgO_2CCF_3	CH_2Cl_2	50	24	27	93
4[c]	$[FBIP\text{-}Cl]_2$	1.0	AgOTs	$CHCl_3$	25	72	93	89
5[c]	$[FBIP\text{-}Cl]_2$	0.5	AgOTs	$CHCl_3$	55	72	93	85
6[c]	$[FBIPP\text{-}Cl]_2$	2.0	AgOTs	$CHCl_3$	25	72	87	87
7	$[PPFIP\text{-}Cl]_2$	1.0	$AgNO_3$	CH_2Cl_2	50	24	53	98
8	$[PPFIP\text{-}Cl]_2$	1.0	$AgNO_3$	CH_2Cl_2	50	72	94	98
9	$[PPFIP\text{-}Cl]_2$	1.0	$AgNO_3$	$CHCl_3$	70	24	93	98

[a] Yield of isolated product. [b] Determined by HPLC. [c] Reaction was performed in the absence of proton sponge (PS, 1,8-bis(dimethylamino)naphthalene).

was somewhat lower than for the combination $[PPFIP\text{-}Cl]_2/AgO_2CCF_3$.

Since $[PPFIP\text{-}Cl]_2$ activated by AgO_2CCF_3 gave the highest enantioselectivity and the combination of $[PPFOP\text{-}Cl]_2/AgNO_3$ provided the highest activity, we studied the activation of $[PPFIP\text{-}Cl]_2$ with $AgNO_3$ as well. Gratifyingly, this combination provided the product with excellent enantioselectivity and an improved reactivity (entry 7). Either by a prolonged reaction time or at a reaction temperature of 70 °C **10a** was finally formed in high yields and almost enantiomerically pure form (entries 8 and 9).

Substrate scope

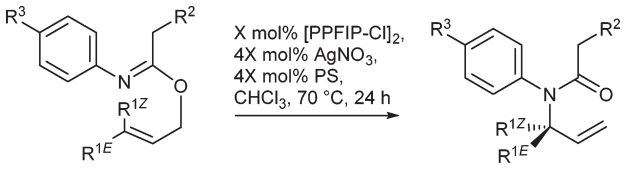
Application of $[PPFIP\text{-}Cl]_2$ as precatalyst. Under the optimised conditions various substrate modifications were studied (Table 2). Substrates **9a–d** in which R^{1E} either equals phenethyl, ethyl, *n*-propyl or *n*-pentyl all furnished the corresponding acetamides **10a–d** in high yields and with high enantioselectivity (entries 1–4).

The electronic effect of substituents R^3 on the N-aryl residues is apparently negligible as a comparison of entries 3 and 5 shows. With both *p*-OMe as an example for a π-donor and *p*-NO_2 as an example for a strong π-acceptor very similar results in terms of product yields and enantioselectivity were obtained.

In addition to the parent acetimidate substrates with R^2 = H, we also examined substrates with R^2 = Ph. A phenylacetamide product might create additional opportunities for enzymatic deprotection by the penicillin-G-amidase (PGA). It was found that the imidate substrates **9** with R^2 = Ph show a very similar behaviour (entries 6–12) compared to those with R^2 = H. Like before the electronic effect of the substituents R^3 on the N-aryl residues is of only minor importance and in each case (R_3 = NO_2, H, OMe) the products were generated in high yields and with high enantioselectivities (entries 6–8).

It was also possible to significantly reduce the catalyst loadings without a negative impact on the reaction outcome as has been demonstrated for substrate **9h**. Various precatalyst loadings ranging from 1.0 mol% to as little as 0.05 mol% were studied and they all provided almost identical results (entries 8–10). Low catalyst loadings were also examined for the phenylacetimidates **9i** and **9j** carrying different alkyl residue R^{1E} and in both cases high product yields and enantioselectivities were determined (entries 11 & 12).

Table 2 Investigation of different substrates in the PPFIP-catalysed title reaction



9 10

#	9/10	R^{1E}	R^{1Z}	R^2	R^3	*X*	Yield[a] [%]	ee[b]
1	**a**	$(CH_2)_2Ph$	H	H	OMe	1.0	93	98
2	**b**	Et	H	H	OMe	1.0	92	96
3	**c**	*n*Pr	H	H	OMe	1.0	92	96
4	**d**	*n*Pent	H	H	OMe	1.0	91	92
5	**e**	*n*Pr	H	H	NO_2	1.0	94	94
6	**f**	*n*Pr	H	Ph	NO_2	1.0	93	95
7	**g**	*n*Pr	H	Ph	H	1.0	90	97
8	**h**	*n*Pr	H	Ph	OMe	1.0	91	97
9	**h**	*n*Pr	H	Ph	OMe	0.25	94	97
10	**h**	*n*Pr	H	Ph	OMe	0.05	92	96
11	**i**	*n*Pent	H	Ph	OMe	0.25	92	94
12	**j**	Et	H	Ph	OMe	0.1	93	96
13	**k**	*i*Pr	H	Ph	OMe	1.0	84	91
14[c]	**k**	*i*Pr	H	Ph	OMe	1.0	96	95
15[d]	**l**	Ph	H	Ph	OMe	1.0	93	95
16[d]	**m**	4-NO_2–C_6H_4	H	Ph	OMe	1.0	96	90
17[c]	**n**	$(CH_2)_2CH{=}C(Me)_2$	Me	Ph	OMe	1.0	98	98

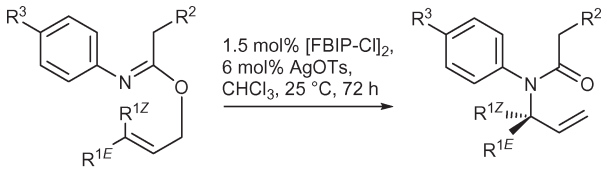
[a] Yield of isolated product. [b] Determined by HPLC. [c] Performed in CH_2Cl_2 at 50 °C for 48 h. [d] Performed in CH_2Cl_2 at 25 °C for 72 h.

Next the rearrangement of particularly challenging substrates was investigated, *e.g.* that of **9k** possessing an *i*Pr-group as R^{1E}. α-Branched alkyl residues are known to retard allylic imidate rearrangements.[1,7a,d] In the present study application of the standard conditions gave **10k** in a yield of 84% and with an ee of 91% (entry 13). The results could be further improved by decreasing the reaction temperature to 50 °C using a prolonged reaction time of 48 h (96% yield, 95% ee, entry 14).

Similarly, the rearrangement of substrates carrying aromatic residues R^{1E} required a lower reaction temperature for high enantioselectivities. Allylic imidate rearrangements of substrates of this type are in general inherently difficult, since the aryl residues accelerate a thermal background reaction.[1,7a,d] Nevertheless, at room temperature the products **10l** and **10m** were obtained in high yields and with high enantioselectivity after a reaction time of 3 days.

In addition, it is possible to form N-substituted quaternary stereocenters in excellent yield and with nearly perfect enantiocontrol as shown for substrate **9n**. Obviously, the remote olefin functionality did not have a negative impact on the reaction outcome.

Table 3 Investigation of different substrates in the FBIP-catalysed title reaction



9 10

#	10	R^{1E}	R^{1Z}	R^2	R^3	Yield[a] [%]	ee[b]
1	**a**	$(CH_2)_2Ph$	H	H	OMe	93	89
2	**e**	*n*Pr	H	H	NO_2	90	90
3	(*ent*)-**e**	H	*n*Pr	H	NO_2	93	92
4	**h**	*n*Pr	H	Ph	OMe	95	86
5	(*ent*)-**h**	H	*n*Pr	Ph	OMe	97	89
6	(*ent*)-**f**	H	*n*Pr	Ph	NO_2	96	95
7	(*ent*)-**o**	H	*n*Pr	CH_3	OMe	84	92
8	(*ent*)-**p**	H	*n*Pr	CH_3	H	85	90

[a] Yield of isolated product. [b] Determined by HPLC.

Application of [FBIP-Cl]$_2$ as precatalyst. In addition, the FBIP-catalysed reaction was applied to substrates differing in their electronic properties of the N-aryl group and in the C,C double bond configuration (Table 3).

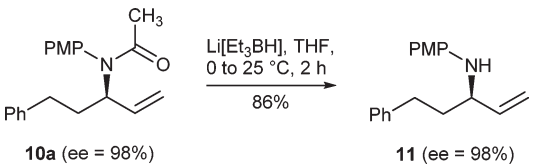
Also with this bimetallic catalyst a π-donor (*p*-OMe) and a π-acceptor (*p*-NO$_2$) on the N-aryl residue were both well tolerated and very similar results were obtained for substrates carrying these substituents (entries 1 and 2). Also less reactive[1,8] (*Z*)-configured substrates **9** provided the corresponding products in high yields and with high enantioselectivity, irrespective of the use of an electron rich or deficient N-aryl residue (entries 3 & 5–8). Using the (*Z*)-configured substrates resulted in a switch of the absolute configuration of the generated stereogenic center (determined by HPLC using a chiral stationary phase). Like other Pd(II) catalysed allylic imidate rearrangements the reaction is thus stereospecific.[1]

Amide cleavage

The release of the free amino functionality by cleavage of the amide moiety was investigated by chemical and enzymatic means.

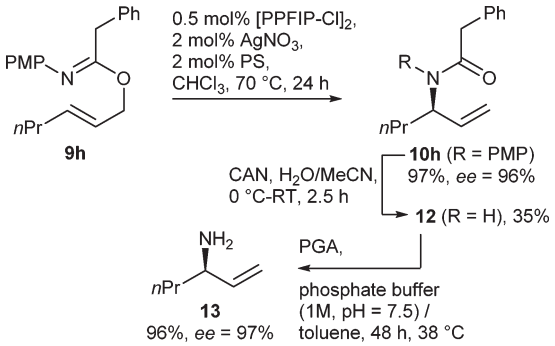
Amide cleavage by chemical means. Treatment of allylic amide **10a** with Li[Et$_3$BH] at 0–25 °C for 2 h proceeded smoothly and provided the PMP-protected amine **11** in high yield (Scheme 3).[13e] Comparison of the obtained product by HPLC using a chiral stationary phase with an authentic sample prepared by rearrangement of the corresponding trifluoroacetimidate followed by cleavage of the generated trifluoroacetamide confirmed the expected (*R*)-configuration of **10a**.[7d]

Amide cleavage by enzymatic means. To allow deprotection under very mild conditions, an enzymatic amide hydrolysis was studied. For that purpose the phenylacetimidate **9h** was rearranged on a 250 mg scale (Scheme 4). After PMP-deprotection under standard conditions the phenylacetamide **12** was applied to penicillin-G-amidase for 2 days at 38 °C. The primary amine **13** was formed in high yield (96%) and with an ee of 97% ((*R*)-configuration[12]).



10a (ee = 98%) **11** (ee = 98%)

Scheme 3 Reductive acetamide cleavage.



Scheme 4 Synthesis of the highly enantioenriched primary amine **13** *via* enzymatic phenylacetamide hydrolysis using penicillin-G-amidase.

Experimental

Procedures for the activation of pre-catalysts

a) Activation of mono-palladacycles. The corresponding palladacycle (1.0 equiv.) and the corresponding silver salt (4.0 equiv.) were suspended in dry CH_2Cl_2 (0.5 mL per 5 mg palladacycle) and ultrasonificated for 10 min. The mixture was stirred at room temperature for 14 h and then filtered through CaH_2/celite (1 : 1) under N_2. The solvent was removed by a stream of N_2 and then high vacuum was applied. A stock solution was prepared by the addition of a defined amount of the corresponding solvent.

b) Activation of [FBIP-Cl]$_2$. To a solution of AgOTs (4.0 equiv.) in dry MeCN (0.5 mL per 5 mg [FBIP-Cl]$_2$) was added [FBIP-Cl]$_2$ (1.0 equiv.). The mixture was stirred at room temperature for 14 h and then filtered through CaH_2/celite (1 : 1) under N_2. The solvent was removed by a stream of N_2 and then high vacuum was applied. A stock solution was prepared by the addition of a defined amount of the corresponding solvent.

General procedure for the catalytic asymmetric rearrangement of allylic imidates 9

A dry screw-cap vial was charged with the corresponding allylic imidate **9** (1.0 equiv.), then vacuum was applied and the vial was refilled with N_2 (3 times). A stock solution of proton sponge (1,8-bis-(*N*,*N*-dimethylamino)naphthalene, PS, 4× mol% [only used in the case of mono-palladacycles]) in the indicated solvent and a stock solution of the corresponding activated catalyst in the indicated solvent were added. The amount of solvent was reduced by a stream of N_2 if necessary (final concentration: 150 μL per 100 μmol of substrate). The vial was closed by a screw-cap and the mixture was stirred at the indicated temperature for the indicated time. Subsequently, the solvent was removed under reduced pressure and mesitylene (10 μL per each 50 μmol of substrate) was added to the crude product as an internal standard followed by $CDCl_3$ (1 mL) to determine conversion and yield by ^{1}H-NMR. The crude product was afterwards directly used for silicagel chromatography to isolate the corresponding allylic amide **10**. The purified samples were used to determine the ee value by HPLC.

Enzymatic deprotection: (*R*)-hex-1-en-3-amine (13)

(*R*)-*N*-(Hex-1-en-3-yl)-2-phenylacetamide **12** (92.0 μmol, 20.0 mg) was suspended in sodium phosphate buffer (1.0 mL, pH = 7.5, 1 M) and PGA (penicillin-G-amidase from *Escherichia coli*, ammonium sulfate suspension, ≥10 units per mg protein,

30 μL) and toluene (0.1 mL) were added. The flask was closed and the mixture was stirred at 38 °C for 48 h. Subsequently, H_2O (5 mL) and CH_2Cl_2 (5 mL) were added, the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic phases were dried over Na_2SO_4 and the solvent removed under reduced pressure. Mesitylene (10 μL) was added to the crude product as an internal standard followed by $CDCl_3$ (1 mL) to determine conversion and yield by ^{1}H-NMR. The crude product was afterwards dissolved in CH_2Cl_2 (10 mL) and extracted with aqueous HCl (3 × 5 mL, 1 M). The pH value of the combined aqueous phases was adjusted to pH = 14 by addition of aqueous NaOH (2 M) and the combined aqueous phases were extracted by CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure to yield **13** as a colorless oil (88.7 μmol, 8.8 mg, 96%).

$C_6H_{13}N$, MW: 99.18 g mol^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.84–5.70 (m, 1H, C*H*═CH_2), 5.13–4.95 (m, 2H, CH═CH_2), 3.32–3.22 (m, 1H, NH_2C*H*), 1.44–1.30 (m, 4H, CH_2C$H_2$$CH_3$), 1.25 (bs, 2H, N$H_2$), 0.91 (t, J = 7.1, 3H, CH_2CH_2CH_3). The analytical data are in accordance with the literature.[22] The enantiomeric excess was determined by HPLC after tosyl protection of **13** (see the ESI†).

Conclusions

In conclusion, we have identified two catalytic systems, which are very efficient for the asymmetric rearrangement of allylic non-halogenated acetimidates. This rearrangement type can be conducted with a high level of generality and enantioselectivity. At elevated temperatures it is possible to perform the title reaction using very low catalyst loadings without a decrease of enantioselectivity or yield. Also difficult substrates were found to be tolerated with a high level of efficiency. This enabled, *e.g.*, the formation of N-substituted quaternary stereocenters making use of a trisubstituted olefin moiety. Besides cleavage of the formed amide functions by known chemical methods, the products now also offer the option of enzymatic hydrolytic protocols for the access of almost enantiopure allylic amines.

Acknowledgements

This work was financially supported by the Deutsche Forschungsgemeinschaft (DFG, PE 818/4-1 & PE 818/6-1). The Fonds der Chemischen Industrie (FCI) and the Carl-Zeiss-Stiftung are acknowledged for PhD fellowships to J.M.B.

Notes and references

1 Selected reviews: (*a*) H. Nomura and C. J. Richards, *Chem. – Asian J.*, 2010, **5**, 1726; (*b*) T. K. Hollis and L. E. Overman, *J. Organomet. Chem.*, 1999, **576**, 290; (*c*) L. E. Overman and N. E. Carpenter, *Org. React.*, 2005, **66**, 1; (*d*) R. Peters, D. F. Fischer and S. Jautze, *Top. Organomet. Chem.*, 2011, **33**, 139.

2 O. Mumm and F. Möller, *Ber. Dtsch. Chem. Ges.*, 1937, **70**, 2214.

3 For efficient catalytic asymmetric rearrangements of benzimidates, see *e.g.*: (*a*) Y. Donde and L. E. Overman, *J. Am. Chem. Soc.*, 1999, **121**, 2933; (*b*) C. E. Anderson, Y. Donde, C. J. Douglas and L. E. Overman, *J. Org. Chem.*, 2005, **70**, 648; (*c*) J. Kang, T. H. Kim, K. H. Yew and W. K. Lee, *Tetrahedron: Asymmetry*, 2003, **14**, 415.

4 (*a*) L. E. Overman, *J. Am. Chem. Soc.*, 1974, **96**, 597; (*b*) L. E. Overman, *J. Am. Chem. Soc.*, 1976, **98**, 290; (*c*) L. E. Overman, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 579.

5 (*a*) C. E. Anderson and L. E. Overman, *J. Am. Chem. Soc.*, 2003, **125**, 12412; (*b*) S. F. Kirsch, L. E. Overman and M. P. Watson, *J. Org. Chem.*, 2004, **69**, 8101; (*c*) H. Nomura and C. J. Richards, *Chem. – Eur. J.*, 2007, **13**, 10216; (*d*) M. D. Swift and A. Sutherland, *Tetrahedron*, 2008, **64**, 9521.

6 (*a*) L. E. Overman, C. E. Owen, M. M. Pavan and C. J. Richards, *Org. Lett.*, 2003, **5**, 1809; (*b*) R. S. Prasad, C. E. Anderson, C. J. Richards and L. E. Overman, *Organometallics*, 2005, **24**, 77; (*c*) C. E. Anderson, Y. Donde, C. J. Douglas and L. E. Overman, *J. Org. Chem.*, 2005, **70**, 648.

7 Monopalladacycles: (*a*) M. E. Weiss, D. F. Fischer, Z.-q. Xin, S. Jautze, W. B. Schweizer and R. Peters, *Angew. Chem., Int. Ed.*, 2006, **45**, 5694; (*b*) D. F. Fischer, Z.-q. Xin and R. Peters, *Angew. Chem., Int. Ed.*, 2007, **46**, 7704; (*c*) Z.-q. Xin, D. F. Fischer and R. Peters, *Synlett*, 2008, 1495; (*d*) D. F. Fischer, A. Barakat, Z.-q. Xin, M. E. Weiss and R. Peters, *Chem. – Eur. J.*, 2009, **15**, 8722; (*e*) R. Peters, Z.-q. Xin and F. Maier, *Chem. – Asian J.*, 2010, **5**, 1770; (*f*) S. H. Eitel, M. Bauer, D. Schweinfurth, N. Deibel, B. Sarkar, H. Kelm, H.-J. Krüger, W. Frey and R. Peters, *J. Am. Chem. Soc.*, 2012, **134**, 4683.

8 Bispalladacycles: (*a*) S. Jautze, P. Seiler and R. Peters, *Angew. Chem., Int. Ed.*, 2007, **46**, 1260; (*b*) S. Jautze, P. Seiler and R. Peters, *Chem. – Eur. J.*, 2008, **14**, 1430; (*c*) T. Hellmuth, S. Rieckhoff, M. Weiss, K. Dorst, W. Frey and R. Peters, *ACS Catal.*, 2014, **4**, 1850.

9 Mixed pallada-/platinacycle: M. Weiss, W. Frey and R. Peters, *Organometallics*, 2012, **31**, 6365.

10 K. Tamura, H. Mizukami, K. Maeda, H. Watanabe and K. Uneyama, *J. Org. Chem.*, 1993, **58**, 32.

11 The preparation of trichloroacetimidates required the use of toxic trichloroacetonitrile.

12 We have recently also reported a practical asymmetric allyl carbamate rearrangement for the enantioselective synthesis of allylic amines: J. M. Bauer, W. Frey and R. Peters, *Angew. Chem., Int. Ed.*, 2014, **53**, 7634.

13 (*a*) HCl: G. A. Dilbeck, L. Field, A. A. Gallo and R. J. Gargiulo, *J. Org. Chem.*, 1978, **43**, 4593; (*b*) NaOMe: J. C. Castro-Palomino and R. R. Schmidt, *Tetrahedron Lett.*, 1995, **36**, 6871; (*c*) hydrazine: D. D. Keith, J. A. Tortora and R. Yang, *J. Org. Chem.*, 1978, **43**, 3711; (*d*) Bu_4NF/TFA: P. Carato, S. Yous, D. Sellier, J. H. Poupaert, N. Lebegue and P. Berthelot, *Tetrahedron*, 2004, **60**, 10321; (*e*) super-hydride: H. Tanaka and K. Ogasawara, *Tetrahedron Lett.*, 2002, **43**, 4417.

14 (*a*) Acylase: C. Simons, J. G. E. van Leeuwen, R. Stemmer, I. W. C. E. Arends, T. Maschmeyer, R. A. Sheldon and U. Hanefeld, *J. Mol. Catal. B: Enzym.*, 2008, **54**, 67; (*b*) CALB:

A. Liljeblad, P. Kallio, M. Vainio, J. Niemi and L. T. Kanerva, *Org. Biomol. Chem.*, 2010, **8**, 886; (*c*) M. V. Sergeeva, V. V. Mozhaev, J. O. Rich and Y. L. Khmelnitsky, *Biotechnol. Lett.*, 2000, **22**, 1419; (*d*) PGA: D. Kadereit and H. Waldmann, *Chem. Rev.*, 2001, **101**, 3367; (*e*) H. Waldmann and D. Sebastian, *Chem. Rev.*, 1994, **94**, 911; (*f*) B. Meseguer, D. Alonso-Díaz, N. Griebenow, T. Herget and H. Waldmann, *Angew. Chem., Int. Ed.*, 1999, **38**, 2902; (*g*) G. Cainelli, V. De Matteis, P. Galletti, D. Giacomini and P. Orioli, *Chem. Commun.*, 2000, 2351; (*h*) N. Fadnavis, M. Sharfuddin and S. Vadivel, *Tetrahedron: Asymmetry*, 1999, **10**, 4495; (*i*) R. S. Topgi, J. S. Ng, B. Landis, P. Wang and J. R. Behling, *Bioorg. Med. Chem.*, 1999, **7**, 2221; (*j*) A. L. Margolin, *Tetrahedron Lett.*, 1993, **34**, 1239.

15 P. Metz, C. Mues and A. Schoop, *Tetrahedron*, 1992, **48**, 1071.

16 P. G. M. Wuts and T. W. Greene, *Greene's Protective Groups in Organic Synthesis*, Wiley-Interscience, 4th edn, 2006.

17 A. R. Katritzky, C. V. Stevens, G.-F. Zhang, J. Jiang and N. De Kimpe, *Heterocycles*, 1995, **40**, 231.

18 C. J. Richards, in *Chiral Ferrocenes in Asymmetric Catalysis*, ed. L.-X. Dai and X.-L. Hou, Wiley-VCH, Weinheim, 2010, pp. 337–368.

19 Selected applications of this catalyst: (*a*) M. Weber and R. Peters, *J. Org. Chem.*, 2012, **77**, 10846; (*b*) T. Hellmuth, W. Frey and R. Peters, *Angew. Chem., Int. Ed.*, 2015, **54**, DOI: 10.1002/anie.201410933R1.

20 Review about the application of imidazolines in asymmetric catalysis: (*a*) H. Liu and D.-M. Du, *Adv. Synth. Catal.*, 2009, **351**, 489; selected recent applications of bisimidazoline ligands: (*b*) S. Nakamura, K. Hyodo, Y. Nakamura, N. Shibata and T. Toru, *Adv. Synth. Catal.*, 2008, **350**, 1443; (*c*) H. Liu and D.-M. Du, *Adv. Synth. Catal.*, 2010, **352**, 1113; (*d*) L. Cheng, J. Dong, J. You, G. Gao and J. Lan, *Chem. – Eur. J.*, 2010, **16**, 6761; (*e*) M. Ohara, S. Nakamura and N. Shibata, *Adv. Synth. Catal.*, 2011, **353**, 3285; (*f*) K. Hyodo, S. Nakamura, K. Tsuji, T. Ogawa, Y. Funahashi and N. Shibata, *Adv. Synth. Catal.*, 2011, **353**, 3385; (*g*) K. Hyodo, S. Nakamura and N. Shibata, *Angew. Chem., Int. Ed.*, 2012, **51**, 10337; (*h*) K. Hyodo, M. Kondo, Y. Funahashi and S. Nakamura, *Chem. – Eur. J.*, 2013, **19**, 4128; (*i*) S. Nakamura, K. Hyodo, M. Nakamura, D. Nakane and H. Masuda, *Chem. – Eur. J.*, 2013, **19**, 7304.

21 (*a*) S. Jautze, S. Diethelm, W. Frey and R. Peters, *Organometallics*, 2009, **28**, 2001; (*b*) M. Weber, J. E. M. N. Klein, B. Miehlich, W. Frey and R. Peters, *Organometallics*, 2013, **32**, 5810; selected recent applications of FBIP in catalysis with chloride ligand exchange: (*c*) M. Weber, W. Frey and R. Peters, *Angew. Chem., Int. Ed.*, 2013, **52**, 13223; (*d*) M. Weber, W. Frey and R. Peters, *Chem. – Eur. J.*, 2013, **19**, 8342; (*e*) S. H. Eitel, S. Jautze, W. Frey and R. Peters, *Chem. Sci.*, 2013, **4**, 2218; (*f*) M. Weber, S. Jautze, W. Frey and R. Peters, *Chem. – Eur. J.*, 2012, **18**, 14792; (*g*) M. Weber, W. Frey and R. Peters, *Adv. Synth. Catal.*, 2012, **354**, 1443; (*h*) M. Weiss and R. Peters, *ACS Catal.*, 2015, **5**, 310.

22 C. Grison, A. Thomas, F. Coutrot and P. Coutrot, *Tetrahedron*, 2003, **59**, 2101.

