Asymmetric Rearrangements

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Asymmetric Formation of Allylic Amines with N-Substituted Quaternary Stereocenters by Pd^{II}-Catalyzed Aza-Claisen Rearrangements**

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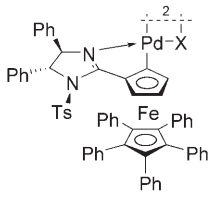
Dedicated to Professor Dieter Seebach on the occasion of his 70th birthday

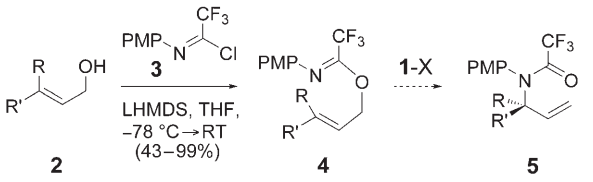
Enantiomerically pure allylic amines are valuable building blocks, as they possess two highly versatile functional groups. Two widely used methods for their preparation are the transition-metal-catalyzed allylic substitution[1] and the aza-Claisen rearrangement of trihaloacetimidates (Overman rearrangement).[2] A longstanding problem is the catalytic enantioselective formation of quaternary stereocenters by either of these methodologies. Since quaternary carbon atoms bearing a nitrogen substituent are a widespread structural motif for bioactive natural and non-natural compounds,[3] the asymmetric construction of those stereocenters by means of asymmetric catalysis is an important challenge. Enantiopure allylic amines possessing a quaternary N-substituted stereocenter are particularly attractive for the synthesis of quaternary amino acids,[4] which are important targets owing to their ability to induce helical peptide structures[5] and owing to the fact that peptides incorporating quaternary amino acid residues possess enhanced stability toward proteases.[6]



FIP-X (**1**-X)

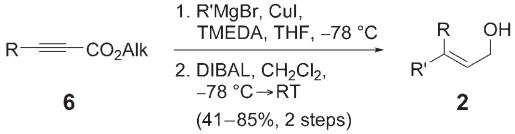
Recently, we have developed a planar-chiral ferrocenyl imidazoline palladacycle catalyst **1**-X (FIP-X), which displays unprecedented levels of activity for the highly enantioselective aza-Claisen rearrangement of *E*-configured allylic PMP-trifluoroacetimidates (PMP = *p*-methoxyphenyl).[2h] Compound **1**-X is in fact about 50–100 times more active for the rearrangement of this class of substrates than the best previously reported catalysts. The exceptionally high catalytic activity is attributed to the pentaphenylcyclopentadienyl (Cp^{Φ}) ligand and can be explained at least in part by the electron-withdrawing nature of the five phenyl substituents, which enhance the Lewis acidity of the Pd center in **1**-X.

This excellent catalytic activity has prompted us to investigate the formation of quaternary stereocenters by the rearrangement of 3,3-disubstituted allylic trifluoroacetimidates **4**, which were prepared from the corresponding allylic alcohols **2** [Eq. (1)].[7]



(1)

The isomerically almost pure 3,3-disubstituted allylic alcohols **2** were formed by CuI-mediated 1,4-additions to methyl- or ethyl-2-ynoates **6** and subsequent reduction with DIBAL [Eq. (2)].



(2)

Alk = Me, Et; R = Me, CH_2OBn;
R' = Me, Et, *n*Pr, *n*Bu, $Ph(CH_2)_2$, $TIPSO(CH_2)_3$

Functionalized derivatives were prepared starting from geranyl acetate (**7**) by regioselective epoxidation and subsequent treatment with periodic acid, leading to the corresponding aldehyde, which was reduced to alcohol **8** (Scheme 1).[8] The alcohol was then used to synthesize a silylether, carbonate, and BOC-protected amine derivative (**2d–f**). Alternatively, ester **2g** (R = Me, R′ = $(CH_2)_2CO_2Et$) was prepared by Johnson–Claisen rearrangement (see the Supporting Information). The allylic alcohols were then condensed with iminochloride **3** [Eq. (1)].

2.0 mol % of the catalyst precursor FIP-Cl (**1**-Cl, X = Cl), activated in situ with 3.75 equivalents AgTFA (relative to **1**-Cl, TFA = trifluoroacetate),[2h] was generally sufficient to give high conversion after 2.5 days at 50 °C using substrates in which one of the substituents R or R′ is a methyl group. The allylic trifluoroacetamides were formed with high to excellent *ee* values and in good yield (Table 1, entries 1–10). As expected, the rearrangement of 3,3-disubstituted substrates

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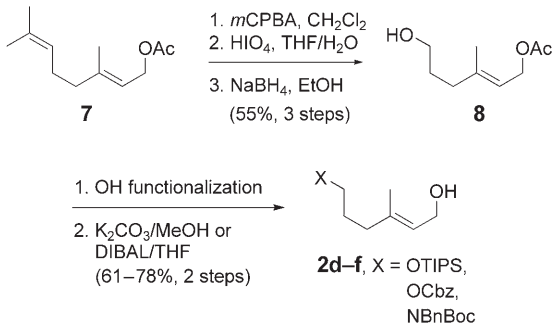
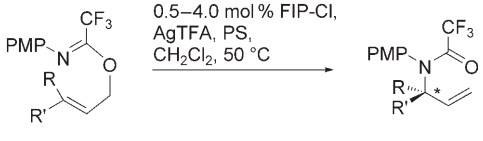


Scheme 1. Synthesis of the isomerically pure 3,3-disubstituted allylic alcohols.

Table 1: Highly enantioselective rearrangement of 3,3-disubstituted allylic imidates **4**.[a]



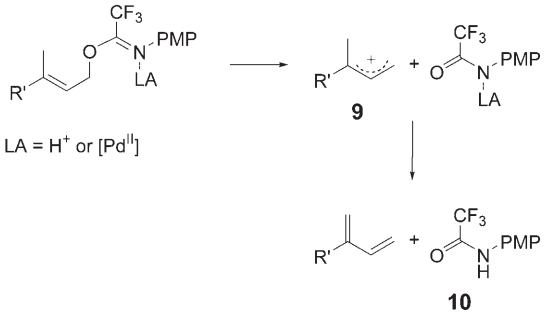
Entry	4	R′	R	Cat. [mol %]	Yield [%][b]	*ee* [%][c]
1	**a**	$(CH_2)_2Ph$	Me	2	94[d]	99.6 (*R*)
2	**a**	$(CH_2)_2Ph$	Me	0.5	79[e,f]	97 (*R*)
3	**b**	*n*Bu	Me	2	63	93 (*R*)
4	**c**	$(CH_2)_2CH{=}CMe_2$	Me	2	74	98 (*R*)
5	**d**	$(CH_2)_3OSi(iPr)_3$	Me	2	73	96 (*R*)
6	**e**	$(CH_2)_3O(CO)OBn$	Me	2	84	98 (*R*)
7	**f**	$(CH_2)_3NBnBoc$	Me	2	64	93 (*R*)
8	**g**	$(CH_2)_2CO_2Et$	Me	2	50	96 (*R*)
9	**h**	Me	$(CH_2)_3OSi(iPr)_3$	2	74	98 (*S*)
10	**i**	Me	CH_2OBn	2	84	99 (*R*)
11	**j**	Et	CH_2OBn	4	68	91 (*R*)[g]
12	**k**	*n*Pr	CH_2OBn	4	63[h]	>99.5 (*R*)
13	**l**	*n*Bu	CH_2OBn	4	61[h]	98 (*R*)
14	**m**	$(CH_2)_3OSi(iPr)_3$	CH_2OBn	4	51[h]	97 (*R*)

[a] The reactions were performed on a 0.03–0.08-mmol scale (reaction time 2.5 days) unless otherwise noted. [b] Yield of the isolated product. [c] *ee* value determined by chiral column HPLC (Daicel OD-H). [d] 0.3-mmol scale. [e] Reaction time: 10 days. [f] 1.0-mmol scale. [g] *E*/*Z* ratio of **4j** = 4:96. [h] Reaction time: 3.5 days.

4 is significantly slower than for substrates with R = H, for which only 0.05 mol % leads to full conversion after 1–3 days at 40 °C in most cases.[2h] The lower turnover frequency is attributed to the additional substituent at the C–C double bond, which hampers the attack of the imidate nitrogen atom on the olefin. Decreasing the precatalyst amount to 0.5 mol % required a reaction time of 10 days, yet provided the rearrangement product in good yield and with excellent enantioselectivity (Table 1, entry 2).

Whereas *Z*-configured 3-monosubstituted imidates had given significantly lower reaction rates than *E*-configured substrates in previous experiments with **1**-X, this difference vanishes if both R and R′ are larger than H.[2h] For example, both the *E*- and *Z*-configured substrates **4d** and **4h** bearing a bulky $(CH_2)_3OTIPS$ moiety as substituent gave practically the same yield and conversion. In both cases the product was formed under identical conditions with very high *ee* values (96 and 98 %, respectively; Table 1, entries 5 and 9), but with the opposite configuration.[9] Whenever the smaller of the two substituents R and R′ was larger than a methyl group, 4.0 mol % of **1**-Cl was employed to obtain synthetically useful yields. Excellent enantioselectivities were even obtained in those cases in which R and R′ have a similar size (Table 1, entries 12–14, for example). Gratifyingly, the rearrangement is compatible with important functional groups such as olefin, ester, carbonate, silylether, benzylether, or Boc-protected amino moieties.

Acid-catalyzed elimination of PMP trifluoroacetamide **10** is a significant side reaction for the 3,3-disubstituted substrates **4**, since the additional electron-donating substituent (Me in Scheme 2) leads to an additional stabilization of the



Scheme 2. Elimination as side reaction.

allylic cation **9**.[10] However, by the use of proton sponge (PS, 1,8-bis(dimethylamino)naphthalene) as a Brønsted acid scavenger this competitive reaction pathway can be suppressed to a large degree, thus allowing the preparation of allylic amides **5** in good yield.

Since the enantioselectivity of the rearrangement is apparently largely independent of the steric differentiation of the two residues R and R′ at the imidate 3-position, it appeared that the enantioselectivity-determining step is the enantioface-selective coordination of the olefin moiety to the Pd^{II} center (Figure 1).[11] Assuming that the olefin will coordinate (in analogy to PPh_3)[2h] *trans* to the imidazoline N atom owing to the *trans* effect,[12] the imidate N atom will attack the olefin at the face remote to the Pd atom. In the preferential orientation of the olefin part parallel to the ferrocene axis, the sterically undemanding C1 methylene moiety should point towards the bulky Cp^{Φ} spectator ligand to minimize unfavorable steric interactions. Coordination of the enantiotopic olefin face should be less favorable, again owing to steric crowding. Even substrates in which R and R′ have an identical size should consequently provide high enantioselectivities.

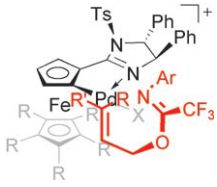
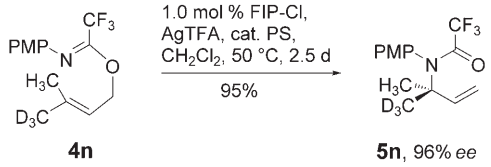


Figure 1. Explanation of the enantioselectivity by enantioface-selective olefin coordination.

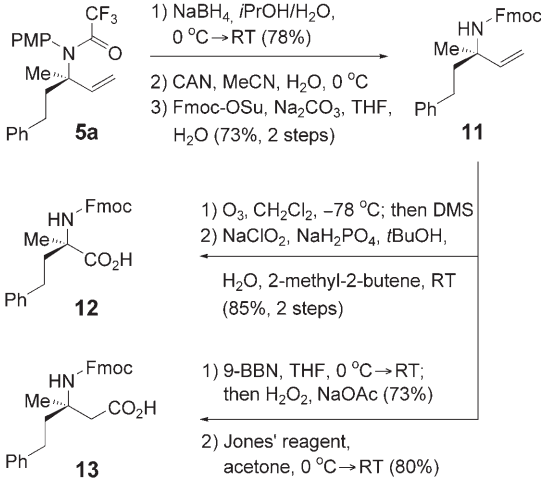
To verify this hypothesis, the use of a geometrically pure allylic imidate in which R and R′ have practically the same

size, namely CH_3 and CD_3 (Scheme 3), was investigated. Also in this case the product is formed with an *ee* value of 96%, thus confirming the mechanistic hypothesis.[13]



Scheme 3. Highly enantioselective formation of CH_3/CD_3-substitituted allylic amide **5n**.

To showcase the utility of the rearrangement products, allylic amide **5a** was employed to synthesize Fmoc-protected α,α-disubstituted α-amino acid **12** and β,β-disubstituted β-amino acid **13** (Scheme 4) by oxidative cleavage of the vinyl



Scheme 4. Use of allylic amide **5a** for the preparation of α,α-disubstituted α-amino acid **12** and β,β-disubstituted β-amino acid **13**.

system and hydroboration, respectively. The absolute configuration of α-amino acid **12** was determined after removal of the Fmoc protecting group by comparison of the specific optical rotation with reported data[14] (see the Supporting Information).[15]

In summary, we have developed a highly enantioselective and functional-group-compatible catalytic method to form allylic amines with quaternary N-substituted stereocenters. We have shown that the enantioselectivity-determining step is the enantioface-selective olefin coordination to the Pd^{II} center, allowing high enantioselectivities also for 3,3-disubstituted substrates in which the two substituents at the 3-position can even have an identical size.

Experimental Section

See the Supporting Information.

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[9] *Z*-Configured substrate **4h** was prepared in analogy to *E*-configured **4d**, but starting from neryl acetate.
[10] We assume that traces of acid may be formed in the reaction mixture by partial hydrolysis of AgTFA in the presence of traces of moisture. Whereas 3-monosubstituted imidates decompose only slowly on a slightly acidic HPLC column (less than 0.1% $(Bu_4N)HSO_4$), 3,3-disubstituted imidates **4** decompose completely to 4-methoxytrifluoroacetanilide and the corresponding diene.
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[15] Since a uniform reaction pathway can be assumed, the absolute configuration can be assigned to all rearrangement products **5**.

