Asymmetric Rearrangements

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Macrocyclic Ferrocenyl–Bisimidazoline Palladacycle Dimers as Highly Active and Enantioselective Catalysts for the Aza-Claisen Rearrangement of *Z*-Configured *N-para*-Methoxyphenyl Trifluoroacetimidates**

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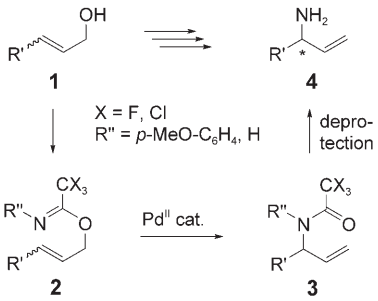
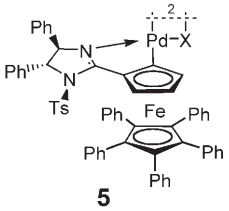
Dedicated to Professor Yoshito Kishi on the occasion of his 70th birthday

The Pd^{II}-catalyzed aza-Claisen (Overman) rearrangement[1] of allylic trichloro-[2] and *N-para*-methoxyphenyl trifluoroacetimidates[3] enables the transformation of achiral allyl imidates **2**, readily prepared from allyl alcohols **1** in a single high-yielding step, to chiral enantioenriched allyl amides **3** (Scheme 1). Since the trihaloacetamide and the *N-para*-methoxyphenyl (PMP) protecting groups can be easily removed, the overall transformation leads to allyl amines **4**, valuable building blocks for the synthesis of important compound classes such as unnatural amino acids.[2a]

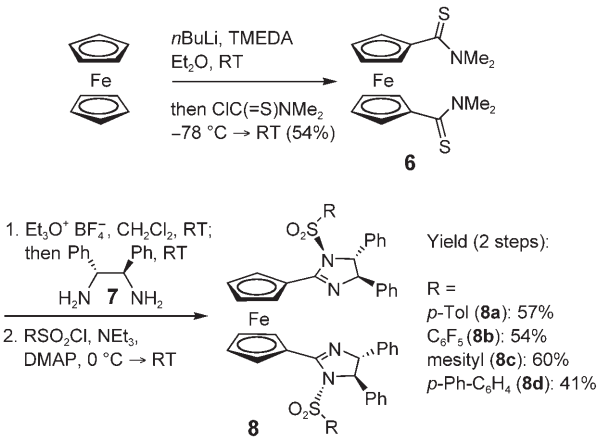


Scheme 1. The aza-Claisen (Overman) rearrangement.

Recently, we reported the first highly active chiral catalyst for the rearrangement of *E*-configured trifluoroacetimidates to provide allylic trifluoroacetamides with excellent enantioselectivities while tolerating a broad substrate scope. The catalyst **5** is a planar-chiral ferrocenyl imidazoline palladacycle (FIP) bearing a pentaphenylcyclopentadienyl (Cp^{Φ}) spectator ligand which is the key structural element responsible for both the high catalytic activity and the excellent enantioselectivity.[4,5] We assume that the enormous increase of the catalytic activity attributed to the Cp^{Φ} spectator ligand can be explained at least in part by the electron-withdrawing nature of the five phenyl substituents, which should enhance the Lewis acidity of **5**. Complex **5** showed contrastingly very low catalytic activity for the rearrangement of *Z*-configured imidates.



The electron density on the Pd^{II} center would be further decreased in a ferrocenyl–bisimidazoline system. The ligand preparation can take advantage of the possible C_2 symmetry and starts from parent ferrocene,[6] which is first transformed into the bisthioamide **6** by using a modified literature procedure (Scheme 2).[7]



Scheme 2. Synthesis of the C_2-symmetric ligands **8**.

Activation of the thioamide groups by S-alkylation followed by treatment of the solution of the resulting bisiminium thioether with (*R*,*R*)-1,2-diphenylethane-1,2-diamine (**7**) and subsequent sulfonylation provides the ligands **8**. These ligands possess strongly pyramidalized sulfonylated N atoms similar to the sulfonylated ferrocenyl–monoimidazolines, as shown by X-ray structure analysis (Figure 1).[8,9]

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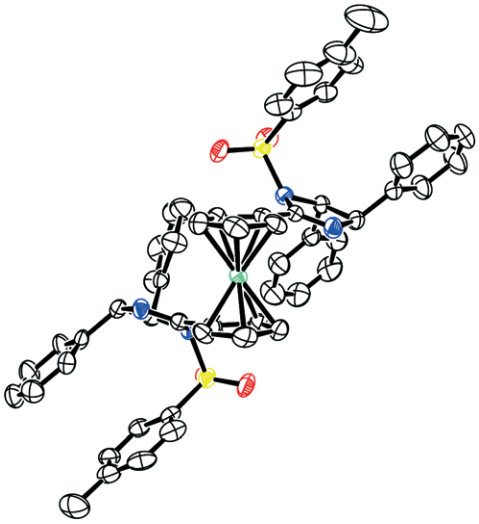
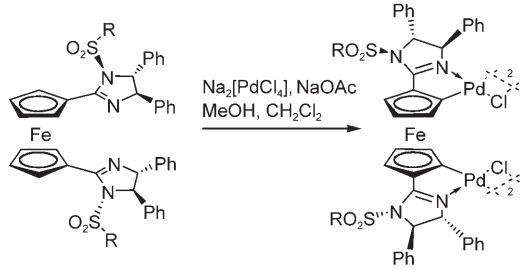


Figure 1. ORTEP representation of ligand **8a** (R = *p*-Tol) with ellipsoids set at 30% probability; C black, N blue, O red, S yellow, Fe light green. H atoms are omitted for clarity.

Steric repulsion between the phenyl group at the imidazoline 5-position and the sulfonyl group is assumed to trigger a transfer of chirality to the sulfonylated N atoms, thus resulting in a preferred conformation in which the sulfonyl residues point away from the ferrocenyl core.

This preferred conformation allowed us to perform a diastereoselective direct biscyclopalladation (Table 1), which

Table 1: Preparation of bispalladacycles **9**.



8 **9**

Entry	Product	R	Yield[a] [%]	d.r.[b]
1	**9a**	*p*-Tol	56	>100:1
2	**9b**	C_6F_5	34	>100:1
3	**9c**	mesityl	40	>100:1
4	**9d**	*p*-Ph-C_6H_4	40	>100:1

[a] Yield of isolated product after purification by silica-gel filtration. [b] Diastereomeric ratio of the product after silica-gel filtration as determined by ^{1}H NMR spectroscopy.[12]

to our knowledge is the first reaction of this kind reported in the literature.[10] Previous nonracemic ferrocenyl bispalladacycles were accessible by double *ortho* lithiation, iodination, and subsequent oxidative addition of the Pd^0 centers to the diiodoferrocenes.[11]

The resulting complexes **9** are C_2-symmetric dimers with an (S_p,S'_p,S^*_p,$S^{*\prime}_p$) configuration[13] as indicated by X-ray analysis (Figure 2).[9] The complexes can be regarded as

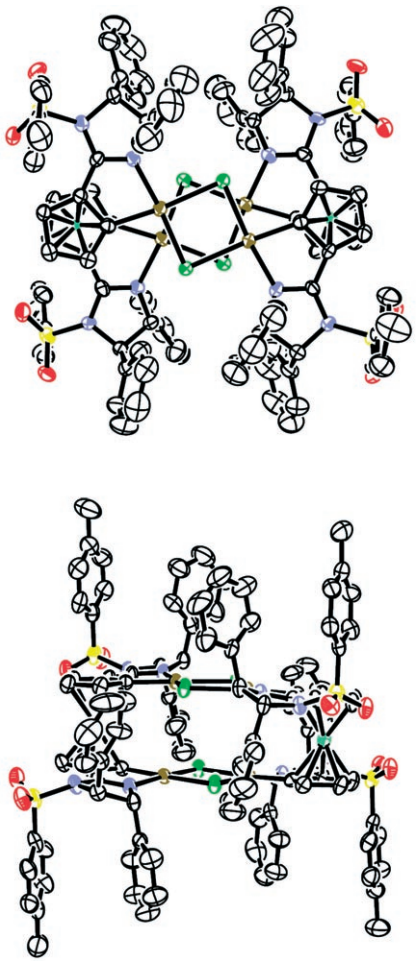


Figure 2. ORTEP representations of the dimeric bispalladacycle **9a** with ellipsoids set at 30% probability; C black, N blue, O red, S yellow, Fe light green, Pd bronze, Cl green. H atoms are omitted for clarity.

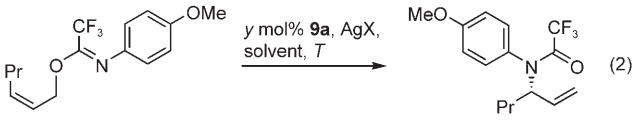
macrocycles comprising two ferrocenyl units and four chloride-bridged palladium ions. The dimeric nature of **9** forces two chloride-bridged palladium square planes to be arranged in an almost coplanar fashion. The high diastereoselectivity is remarkable, since in theory, seven different diastereomeric dimers could have been formed.[14] To our knowledge these are the first reported examples of enantio- and diastereomerically pure dimeric ferrocenyl bispalladacycles.[15]

In contrast to ferrocenyl–monoimidazoline palladacycle complexes and most other ferrocenyl palladacycles, the coordination sphere about the square-planar Pd^{II} center is dictated in the present case by the planar chirality of the bisimidazolines, which means that the (S_p,S'_p,S^*_p,$S^{*\prime}_p$)-configured complexes **9** must adopt a *trans,trans* configuration for geometric reasons.

Bispalladacycle **9a** was examined in the aza-Claisen rearrangement of *Z*-configured trifluoroacetimidates **10** since no highly active enantioselective catalyst so far existed for substrates with *Z* configuration.[16] Since the chloride-bridged dimers turned out to be unreactive as catalysts for model substrate **10a**,[17] silver trifluoroacetate was employed as an activating agent. With two equivalents of AgO_2CCF_3 (relative to dimer **9a**), the rearrangement proceeded very

slowly in CH_2Cl_2 even in the presence of 5 mol% of the bispalladacycle, yet provided (*S*)-**11a** in high yield and with 91% *ee* (Table 2, entry 1). Increasing the amount of

Table 2: Screening of conditions for the rearrangement of model substrate (*Z*)-**10a**.



(2)

10a **11a**

Entry	mol% **9a**	AgX (mol%)	*T* [°C]	Solvent	t_{act}[a] [h]	*t* [h]	Yield[b] [%]	*ee*[c] [%]
1[e]	5	AgO_2CCF_3 (10)	20	CH_2Cl_2	3	91	87	91
2[e]	5	AgO_2CCF_3 (20)	20	CH_2Cl_2	3	44	80	89
3[e]	5	AgO_2CCF_3 (30)	20	CH_2Cl_2	3	20	94	89
4[d,e]	5	AgO_2CCF_3 (30)	20	CH_2Cl_2	3	89	87	91
5[e]	5	AgOTs (30)	20	CH_2Cl_2	3	18	95	94
6[f]	5	AgOTs (30)	20	$CHCl_3$	3	24	18	94
7[f]	5	AgOTs (30)	20	$CHCl_3$	22	24	76	96
8[f]	5	AgOTs (30)	20	$CHCl_3$	46	24	83	95
9[f,h]	5	AgOTs (30)	20	$CHCl_3$	3	24	77	95
10[g]	0.5	AgOTs (3)	20	$CHCl_3$	45	24	72	97
11[g]	0.1	AgOTs (0.6)	20	$CHCl_3$	45	24	14	96
12[g]	0.1	AgOTs (0.6)	40	$CHCl_3$	46	72	80	94
13[g]	0.1	AgOTs (0.6)	55	$CHCl_3$	46	72	98	95

[a] Activation time. [b] The reactions were performed on an 8-mg scale and the yields were determined by ^{1}H NMR spectroscopy. **10a** contained 2% of the *E* isomer. [c] *ee* determined by chiral HPLC (Daicel OD-H) after hydrolysis of **11a** to the corresponding secondary amine (see the Supporting Information). [d] Reaction in the presence of 20 mol% proton sponge. [e] 200 μL of solvent was used. [f] 50 μL of solvent was used. [g] 10 μL of solvent was used. [h] The catalyst was activated at 40°C.

AgO_2CCF_3 to four or six equivalents (relative to **9a**) significantly enhanced the rate of conversion while maintaining the high enantioselectivity (Table 2, entries 2 and 3). In contrast to previous catalysts, the presence of proton sponge (1,8-bis(dimethylamino)naphthalene) as an additive did not significantly increase the *ee* value but considerably slowed down the reaction (Table 2, entry 4). To improve the catalyst activity, various silver salts were screened. Whereas AgOTf, AgOMs, $AgNO_3$, $AgBF_4$, and $AgSbF_6$ induced little or no conversion even after extended periods of time, AgOTs led to slightly increased catalyst activity and an improved enantioselectivity, providing (*S*)-**11a** with 94% *ee* (Table 2, entry 5). By using $CHCl_3$ as the solvent for the rearrangement it was found that the catalyst activation time plays a fundamental role (Table 2, entries 6–9) since the chloride-bridged dimeric bispalladacycles are presumably kinetically much more inert than standard chloride-bridged monopalladacycle dimers for a counteranion exchange. The best results were obtained with a catalyst activation time of two days at room temperature (Table 2, entry 8) or of three hours at 40°C (entry 9). Previous reports have demonstrated that ferrocenyl–oxazoline and ferrocenyl–imidazoline monopalladacycles can be oxidized by silver salts to the corresponding ferrocenium salts, which are the catalytically active species.[18,3c,e] ^{1}H NMR experiments indicate that at least the bulk of the bispalladacycle is not oxidized by AgOTs, since the formation of a paramagnetic species is not observed even with an excess of the silver salt (6 equiv relative to **9a**). However, we cannot exclude that a ferrocenium species is formed in minute amounts and catalyzes the rearrangement. By virtue of the modified catalyst activation procedure, it was possible to reduce the catalyst amount to 0.5 mol% (Table 2, entry 10) while still obtaining reasonable conversions, whereas the reaction became very sluggish at room temperature with only 0.1 mol% catalyst activated by 0.6 mol% AgOTs (entry 11). However, the high robustness of the catalyst allowed us to perform the rearrangement at higher temperatures and concentrations (entries 12–13): at 55°C, the product was formed with 95% *ee* in almost quantitative yield after three days.

Under the optimized conditions for the model reaction, we compared the four bispalladacycles **9a–d**, which differ in the sulfonyl residue R (0.1 mol% **9**, 0.6 mol% AgOTs, 46 h catalyst activation, $CHCl_3$, 55°C, 24 h reaction time). While **9a** (78% yield, 96% *ee*) and **9b** (77% yield, 92% *ee*) gave similar catalyst activities and enantioselectivities, thereby demonstrating that the electronic influence of R is negligible, the bulkier mesityl- and biphenylsulfonyl groups in **9c** (37% yield, 90% *ee*) and **9d** (21% yield, 92% *ee*) reduced the catalyst activity considerably while still maintaining high enantioselectivities.

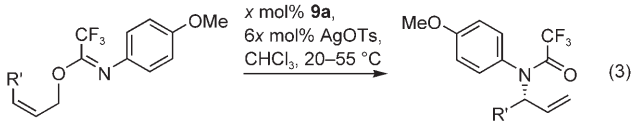
After the optimization of the reaction conditions, the scope of the rearrangement of *Z*-configured imidates **10** was studied by using catalyst precursor **9a** (Table 3). The rate of the rearrangement depends primarily on the steric bulk of the residue R′. With α-unbranched substituents (R′ = Me, *n*Pr, $(CH_2)_2$Ph, *i*Bu), (*S*)-**11** was formed in excellent yield and enantioselectivity with 1.0 mol% catalyst at room temperature (Table 3, entries 1, 4, 6, and 9). By decreasing the catalyst amount to 0.1 to 0.2 mol% and increasing the reaction temperature to 55°C, yields and enantioselectivities were only marginally affected owing to the high robustness of the catalyst against decomposition (Table 3, entries 2, 5, 7, and 10). The rearrangements were performed by using 25 mg of substrates **10**, however, working on a larger scale (2.6 to 11.6 mmol) provided similar results (Table 3, entries 3, 8, and 11).

Particularly noteworthy is the excellent enantioselectivity obtained with imidate **10b**, which bears the small methyl substituent (94–96% *ee*; Table 3, entries 4–5). The highest literature value so far was 86% for this specific example.[3a]

For the first time *Z*-configured trifluoroacetimidates bearing α-branched substituents were also tolerated as substrates, as demonstrated for **10e** (R′ = *i*Pr; Table 3, entry 12), thus providing **11e** in 64% and with 93% *ee*. In this case 1 mol% of catalyst and a temperature of 55°C were employed to obtain preparatively useful conversions. The lower yield as compared to the α-unbranched substrates reflects the lower reaction rate, since neither substrate nor catalyst decomposition were significant issues.[19]

In conclusion, we have developed a short synthesis of enantiomerically pure ferrocenyl–bisimidazolines which have been utilized for diastereoselective biscyclopalladation reac-

Table 3: Screening of substrates **10** with different groups R′.



(3)

10

R' = Me, Pr, $(CH_2)_2Ph$, *i*Bu, *i*Pr

11

64–99%
93–99% *ee*

Entry	**10**	R′	mol% **9a**	*T* [°C]	Yield[a] [%]	*ee*[b] [%]
1[c]	**10a**	*n*Pr	1.0	20	96	98
2[c]	**10a**	*n*Pr	0.1	55	94	97
3[c,d]	**10a**	*n*Pr	0.1	55	97	97
4[e]	**10b**	Me	1.0	20	94	96
5[f]	**10b**	Me	0.1	55	97	94
6[c]	**10c**	$(CH_2)_2Ph$	1.0	20	99	96
7[c]	**10c**	$(CH_2)_2Ph$	0.2	55	90	95
8[g]	**10c**	$(CH_2)_2Ph$	0.2	55	92	97
9[c]	**10d**	*i*Bu	1.0	20	87	98
10[c]	**10d**	*i*Bu	0.1	55	86	98
11[h]	**10d**	*i*Bu	0.1	55	93	99
12[c]	**10e**	*i*Pr	1.0	55	64	93

[a] Yield of isolated product. The reactions were performed on a 25-mg scale unless otherwise noted. [b] *ee* determined by chiral HPLC (Daicel OD-H) after hydrolysis of **11** to the corresponding secondary amines (see the Supporting Information). [c] Reaction time 3 d. [d] 3.5 g of substrate **10a** (11.6 mmol) was used. [e] Reaction time 1.5 d. [f] Reaction time 1 d. [g] 0.94 g (2.59 mmol) of substrate **10c** was used. [h] 1.21 g of substrate **10d** (3.83 mmol) was used.

tions, thereby giving access to structurally fascinating dimeric macrocyclic Pd^{II} complexes. These are the first highly active enantioselective catalysts for the aza-Claisen rearrangement of *Z*-configured trifluoroacetimidates, requiring as little as 0.1 mol% of catalyst precursor for most of the substrates, whereas the best catalyst systems so far required 5 mol%. Even substrates with α-branched substituents, which could previously not be applied, rearranged with high enantioselectivity by action of only 1 mol% of catalyst precursor.

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[7] K. Hamamura, M. Kita, M. Nonoyama, J. Fujita, *J. Organomet. Chem.* **1993**, *463*, 169. The original yield was 29% and the product isolation required two purifications by column chromatography and one by crystallization. By our modifications no column chromatography is necessary and the product is formed in 54% yield.
[8] The pyramidality at a given atom can be expressed by the difference between 360° and the sum of the three bond angles at that atom. For the present analysis, corresponding values at N(13) and N(43) are 21° and 16°, respectively. For further information of the X-ray analysis, see reference [9].
[9] X-Ray crystal structure analyses. Bruker-Nonius Kappa CCD diffractometer, $Mo_{K\alpha}$ radiation ($\lambda = 0.7107$ Å). The structures were solved by direct methods (SIR-97; A. Altomare, M. Burla, M. Camalli, G. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, G. Polidori, R. Spagna, *J. Appl. Crystallogr.* **1999**, *32*, 115) and refined by full-matrix least-squares analysis (SHELXL-97, G. M. Sheldrick, SHELXL-97, Program for the Refinement of Crystal Structures, University of Göttingen, Germany **1997**), by using an isotropic extinction correction. All non-H atoms were refined anisotropically, H atoms isotropically, whereby H positions are based on stereochemical considerations. **8a**: Crystal data at 220(2) K for $C_{54}H_{46}FeN_4O_4S_2$: $M_r = 934.92$, orthorhombic, space group $P2_12_12_1$ (no. 19), $\rho_{calcd} = 1.386\ g\,cm^{-3}$, $Z = 4$, $a = 11.1108(2)$, $b = 11.3676(2)$, $c = 35.4662(7)$ Å, $V = 4479.49(14)$ Å^3, linear crystal dimensions $0.21 \times 0.19 \times 0.17$ mm, $\mu = 0.483\ mm^{-1}$. Final $R(F) = 0.042$, $wR(F^2) = 0.097$ for 635 parameters and 6264 reflections with $I > 2\sigma(I)$ and $2.49 < \theta < 26.01°$ (corresponding *R* values based on all 7194 reflections are 0.054 and 0.105, respectively). **9a**: Crystal data at 220(2) K for $C_{108}H_{88}Cl_4Fe_2N_8O_8Pd_4S_4 \cdot 7CHCl_3$: $M_r = 3268.91$, monoclinic, space group $P2_1$ (no. 4), $\rho_{calcd} = 1.392\ g\,cm^{-3}$, $Z = 2$, $a = 15.5124(3)$, $b = 30.3423(9)$, $c = 15.8007(3)$ Å, $\beta = 118.956(1)°$, $V = 6507.4(3)$ Å^3, linear crystal dimensions $0.14 \times 0.12 \times 0.10$ mm, $\mu = 1.392\ mm^{-1}$. Final $R(F) = 0.049$, $wR(F^2) = 0.115$ for 1499 parameters, 1 restraint, and 21058 reflections with $I > 2\sigma(I)$ and $2.95 < \theta < 26.02°$ (corresponding *R* values based on all 23932 reflections are 0.059 and 0.122 respectively). CCDC-617968 (**8a**) and -617969 (**9a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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[12] Prior to short-pad silica-gel filtration the ^1H NMR spectra were too complex for an accurate determination of the d.r. value.
[13] The stereodescriptors with regard to the planar chirality are used according to K. Schlögl, *Top. Stereochem.* **1967**, *1*, 39. We employ different superscripts to distinguish the four Cp ligands: (S'_p)

indicates the configuration of a bottom Cp ligand while an asterisk (*) indicates the second ferrocene unit.
[14] The seven diastereomers would have the following configurations: (S_p,S'_p,S^*_p,$S^{*\prime}_p$), (R_p,S'_p,S^*_p,$S^{*\prime}_p$), (R_p,R'_p,S^*_p,$S^{*\prime}_p$), (R_p,S'_p,R^*_p,$S^{*\prime}_p$), (R_p,S'_p,S^*_p,$R^{*\prime}_p$), (R_p,R'_p,R^*_p,$S^{*\prime}_p$), and (R_p,R'_p,R^*_p,$R^{*\prime}_p$).
[15] Previous nonracemic bispalladacycles are monomeric since tridentate ligand motifs were used; see reference [11].
[16] With the same enantiomerically pure catalyst, *E*- and *Z*-configured substrates generally give the opposite major enantiomers. For that reason it is important to have isomerically pure substrates to get maximum *ee* values. Precatalyst **9a** (2.5 mol%) gave *ee* values up to 91% for *E*-configured model substrate **10a** (4 equiv $AgNO_3$, CH_2Cl_2, RT, 1 d, 91% yield), but is less active than **5** for *E*-configured substrates.
[17] The same of **10a** that was used for the catalyst-screening experiments contained 2% of the *E*-configured isomer.
[18] T. P. Remarchuk, Ph.D. Dissertation, University of California, Irvine, **2003**, pp. 175–235 (Overman group).
[19] Like previous catalysts, **9a** is not a suitable catalyst for the *Z*-configured substrate bearing a phenyl substituent R′, since the rearrangement is not only exceedingly slow, but also accompanied by decomposition.

