Asymmetric total synthesis of (+)-fumimycin *via* 1,2-addition to ketimines†

Patrick J. Gross,[a] Filipp Furche,[b] Martin Nieger[c] and Stefan Bräse*[a]

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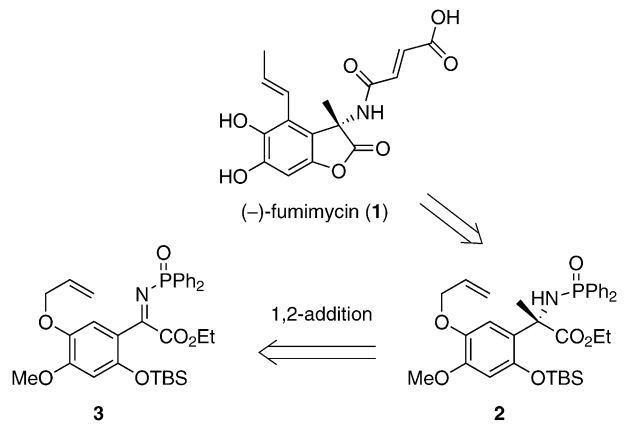
The first asymmetric total synthesis of fumimycin was accomplished. As a key step, a 1,2-addition of methyl Grignard reagents to ketimines with quinine as additive was employed. The absolute configuration of (+)-fumimycin was determined by CD-spectroscopy combined with time-dependent density functional calculations.

The mycotoxin[1] fumimycin (**1**), isolated from *Aspergillus fumisynnematus* F746, displays promising antibacterial activity.[2] It is a potent inhibitor of peptide deformylase (PDF), an enzyme essential for prokaryotic growth, but not for mammalian cells.[3] Therefore, fumimycin may represent a lead structure to a class of novel antibacterials. It displays optical activity, yet its absolute configuration was unknown.

Recently, we succeeded in accomplishing the first total synthesis of racemic fumimycin.[4] Key step for the formation of the α-trisubstituted amine **2** was the 1,2-addition of a Grignard reagent to ketimine **3** (Scheme 1).[5] Here, we report our systematic development of an enantioselective method for the 1,2-addition to ketimines resulting in the first asymmetric synthesis of (+)-fumimycin. Finally, the absolute configuration of fumimycin was elucidated by using CD-spectroscopy.



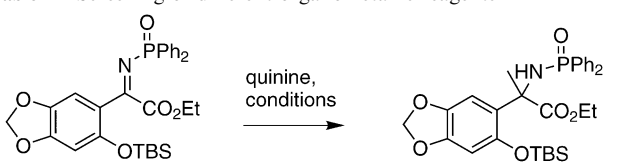
Scheme 1 Retrosynthetic strategy for fumimycin with 1,2-addition to ketimine **3** as key step. TBS = *tert*-butyldimethylsilyl.

There are only few methods for the stereocontrolled synthesis of α-trisubstituted amines by 1,2-addition to ketimines. The catalytic enantioselective 1,2-addition to ketimines is described in two examples, both employing a different substrate class.[6] Most stereocontrolled methods use chiral auxiliaries connected to the ketimine-nitrogen[7] or adjacent to the ketimine function.[8] These diastereoselective methods require a removal step of the attached auxiliary. More advantageous is the use of non-covalently-bound chiral additives. This strategy avoids the extra step of auxiliary removal and allows in principle a direct recovery and reuse of the unchanged chiral reagent.

The enantioselective 1,2-addition to ketimines by using chiral additives is described once by Huffman *et al.* They employed amino alcohol quinine to control the addition of lithium alkynylides to cyclic *N*-acyl ketimines.[9]

We envisioned a related approach for the addition of methyl organometallic reagents to acyclic *N*-phosphoryl ketimines **3**. Following Huffman *et al.*, we chose quinine as additive, which is readily available and inexpensive. Due to its amino function, quinine can be separated from the product mixture by a simple workup with NH_4Cl-solution. To generate the opposite enantiomer, we planned to use quinidine, which represents the pseudo-enantiomer of quinine. For the elaboration of such a method, we used ketimine **4** as simplified model system, yielding α-trisubstituted amine **5**. In general, we employed a solution of 5 equivalents of quinine, to which the organometallic reagent was added, followed by a solution of ketimine **4**. Initial tests with lithium, magnesium and zinc reagents showed good conversion, albeit no selectivity (Table 1, entries 1–3). It was expected that deprotonation of the alcohol function of quinine prior to the addition of the organometallic reagent might influence the selectivity. Indeed, by treating quinine with

Table 1 Screening of different organometallic reagents[a]



Entry	(Base); reagent	Temp/°C	Solvent	Conversion (%)	ee (%)
1	MeLi	0	THF	91	−7
2	MeMgBr	0	THF	95	<5
3	$ZnMe_2$	20	Toluene	60	−10
4	MeLi; MeMgCl	−40	THF	86	<5
5	MeLi; MeMgBr	−40	THF	98	−44
6	MeLi; MeMgI	−40	THF	76	−16

[a] Conditions: organometallic reagent (6.3 eq.) or base (5.0 eq.) and then organometallic reagent (1.3 eq.). The yields based on conversion are >90%.

[a] *Institute of Organic Chemistry, Karlsruhe Institute of Technology (KIT), Fritz-Haber-Weg 6, D-76131 Karlsruhe, Germany. E-mail: braese@kit.edu; Fax: +49 721-608-8581*
[b] *University of California, Irvine, Department of Chemistry, 1102 Natural Sciences II, Irvine, CA 92697-2025, USA. E-mail: filipp.furche@uci.edu; Fax: +1 949 824-8571*
[c] *Laboratory of Inorganic Chemistry, University of Helsinki, 00014 University of Helsinki, Finland*

† Electronic supplementary information (ESI) available: Experimental details. Crystal structure data of **4**, **7**, **8**, **8-iPrOH** and **9**. CCDC 786071 (**4**), 786072 (**7**), 786073 (**8**), 786074 (**8-iPrOH**) and 786075 (**9**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0cc03399e

methyl lithium as base and subsequent addition of methyl magnesium bromide, α-trisubstituted amine **5** was obtained in 44% ee (entry 5).

With methyl magnesium bromide as organometallic reagent, we tested other bases for the deprotonation (Table 2). In terms of selectivity and reactivity, methyl lithium proved to be the reagent of choice (entry 2).

Employing methyl magnesium bromide and methyl lithium, several β-amino alcohols were screened for their ability to induce selectivity (Table 3). Quinine and quinidine yielded the highest enantioselectivities (entries 1 and 2), and both enantiomers of amine **5** could be obtained (yet with unknown absolute configuration).

Screening of a variety of solvents indicated that polar solvents lead to better selectivity. The best results were obtained with THF.

Next we investigated the temperature dependency of the selectivity (Fig. 1). By lowering the reaction temperature to −70 °C the selectivity increased up to 61% ee. Interestingly, the selectivity decreased in the temperature range below −70 °C. This might be explained by the principle of isoinversion.[10] Below a certain temperature, the reaction proceeds partly *via* an unselective pathway. By plotting the data of both temperature ranges as Eyring plot, two linear slopes are obtained (Fig. 2). The intersection marks the isoinversion temperature T_{inv} (−69 °C), at which the highest selectivity can be obtained.

Table 2 Screening of different bases[a]

Entry	Base	Conversion (%)	ee (%)
1	*n*BuLi	76	−42
2	MeLi	>98	−44
3	LiHMDS	87	−30
4	NaHMDS	88	−49
5	NaH	86	−19
6	KHMDS	82	−25

[a] Conditions: quinine (5.0 eq.), base (5.0 eq.), THF, −40 °C; MeMgBr (1.3 eq.). The yields based on conversion are >90%.

Table 3 Screening of different chiral amino alcohols[a]

Entry	Amino alcohol	Conversion (%)	ee (%)
1	Quinine	98	−44
2	Quinidine	52	+51
4	Cinchonidine	22	−17
3	(+)-*N*-Methyl-norephedrine	35	+28
5	(*S*)-*N*-Ethylprolinol	76	<5

[a] Conditions: amino alcohol (5.0 eq.), MeLi (5.0 eq.), THF, −40 °C; MeMgBr (1.3 eq.). The yields based on conversion are >90%.

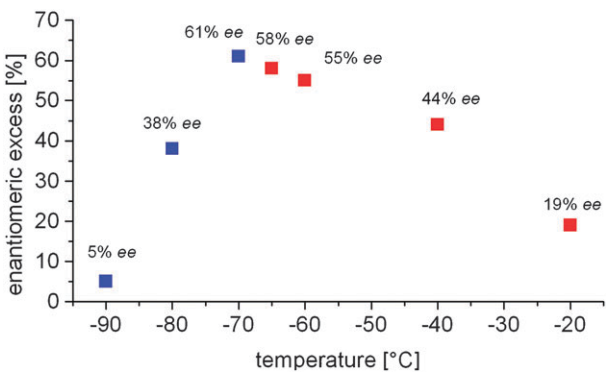


Fig. 1 Temperature dependency of the enantioselecivity.

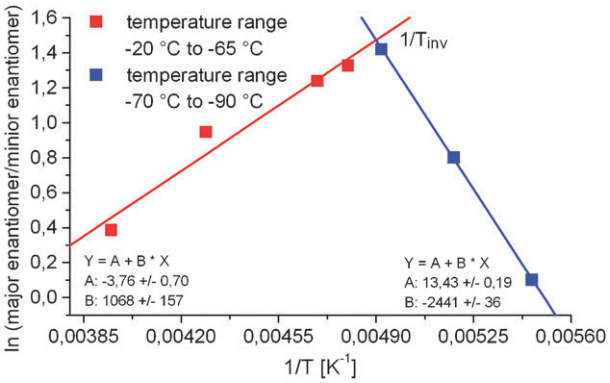
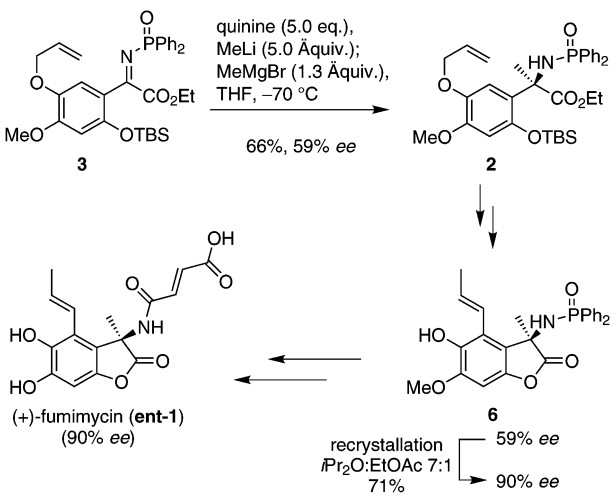


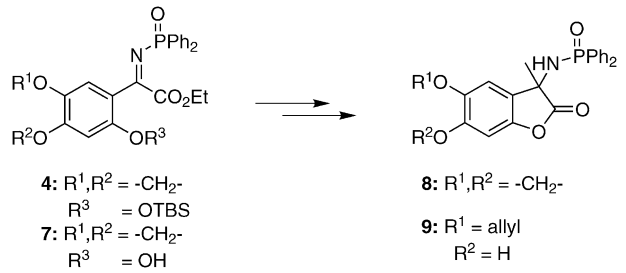
Fig. 2 Eyring plot for the determination of the isoinversion temperature.

Finally we investigated the influence of concentration on the selectivity. Higher concentration improved the selectivity, until solubility limited further increase of concentration. Thus, amine **5** could be finally obtained in 65% ee and 57% isolated yield. After the optimisation of organometallic reagent, base, amino alcohol, solvent, temperature and concentration the optimised conditions were used for the 1,2-addition to ketimine **3**, a precursor of fumimycin (Scheme 2). Amine **2** could be obtained in 59% ee. This material was transformed to lactone **6** in three steps, according to our previously described work towards racemic fumimycin.[4] Intermediate **6** could be enantioenriched: one single recrystallisation furnished **6** in 90% ee in the mother liquor. This material was further functionalised,[4] finally giving rise to (+)-fumimycin (**ent-1**).

Thus the first asymmetric synthesis of fumimycin could be accomplished, in 18 steps, 90% ee and 1.6% overall yield. The optical rotation of the synthesized (+)-fumimycin ($[\alpha]_D$: +109) was contrary to the optical rotation reported for the natural product ($[\alpha]_D$: −11.9) (see ESI†). (+)-Fumimycin represents



Scheme 2 Enantioselective 1,2-addition to ketimine **3**, enantioenrichment by recrystallisation and final conversion to (+)-fumimycin (**ent-1**).



Scheme 3 Precursors of fumimycin, whose structures were confirmed by X-ray analysis.

therefore the unnatural enantiomer. The natural enantiomer should be accessible by employing quinidine instead of quinine as additive (see Table 3). To determine the absolute configuration, crystallisation of several intermediates were attempted. Thus, the structures of the ketimines **4** and **7** could be confirmed, as well as the structures of the α-trisubstituted amines **8** and **9** (Scheme 3). However, enantioenriched samples of **8** and **9** furnished only racemic monocrystals (see ESI†).

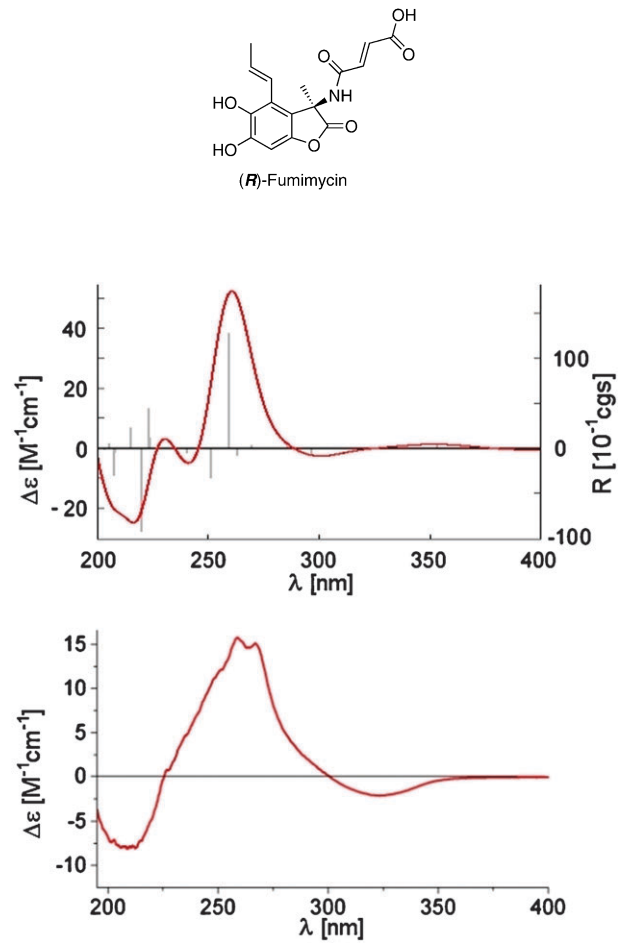


Fig. 3 Simulated CD-curve of (*R*)-fumimycin (upper panel) and measured CD-curve of (+)-fumimycin (lower panel).

Finally we used CD-spectroscopy to elucidate the absolute configuration. The CD-spectra of fumimycin was simulated using time-dependent density functional theory (TDDFT)[11] as implemented in TURBOMOLE.[12] ‡ The characteristic strong band at 255 nm arises from an n → π* transition in the fumaric acid side chain which is chirally perturbed by the lactone carbonyl chromophore (see ESI†). The simulated curve of the (*R*)-enantiomer matches with the measured CD-curve of the synthesized (+)-fumimycin (Fig. 3). It can be concluded that the natural (−)-fumimycin bears (*S*)-configuration.

The enantioselective 1,2-addition of methyl Grignard reagents, employing quinine as chiral additive, yielded α-trisubstituted amines in up to 65% ee. This novel methodology[13] and enantioenrichment by recrystallisation enabled the first asymmetric synthesis of (+)-fumimycin in 90% ee. The absolute configuration of (+)-fumimycin was assigned to be (*R*) using CD-spectroscopy and TDDFT-calculations.

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Notes and references

‡ The PBE0 hybrid functional was used with SVPD-basic sets, the structure was optimized using PBE0/TZVP. Solvent effects were treated by the COSMO continuum solvation model. See ESI† for further details.

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