Cascade Reactions

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Asymmetric Palladium(II)-Catalyzed Cascade Reaction Giving Quaternary Amino Succinimides by 1,4-Addition and a Nef-Type Reaction**

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Chiral succinimides play a vital role in pharmaceutical sciences.[1] They are typically synthesized by 1,4-additions to maleimides.[1] The pharmacologically important class of quaternary α-amino succinimides—formal derivatives of α-alkyl aspartic acid[2]—has received particular attention from both academic and industrial laboratories for its benefit for application in drug design (Figure 1). For instance, introduction of succinimides **1** in peptidomimetics results in a high preference for β-turn type-II/type-II′ conformations.[3,4] Related *N*-mesyloxysuccinimides **2** behave as irreversible mechanism-based inhibitors of serine proteases.[5] Of particular value is Ranirestat (AS-3201) which is an aldose reductase inhibitor currently in the final stage of clinical phase III trials.[6,7] α-Amino succinimide **3** is a late-stage precursor in the elegant recent total syntheses of all six amathaspiramides A–F by Fukuyama et al.[8,9]

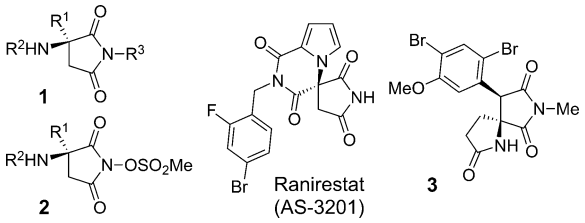
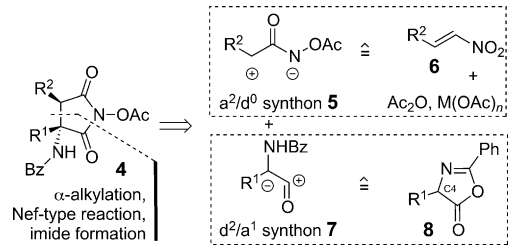


Figure 1. Examples of pharmaceutically relevant α-amino succinimides. Spiroimide **3** is a precursor to amathaspiramides A–F.

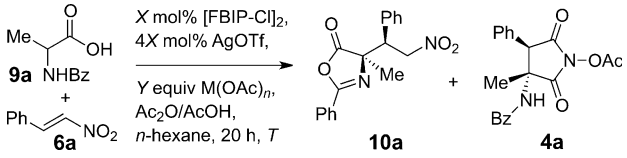
Despite the value of quaternary α-aminosuccinimides, few catalytic asymmetric methods are known for a direct catalytic asymmetric access.[10] Driven by the need for efficient approaches towards Ranirestat, methods have been developed for the asymmetric amination of α-carboxylated succinimides.[7] Here we report a new cascade reaction[11] for a rapid divergent asymmetric access to quaternary succinimides **4** using very simple starting materials. This development is based on the retrosynthetic analysis depicted in Scheme 1. The quaternary stereocenter[12] should be formed by the regio-, enantio-, and diastereoselective C4 alkylation of azlactone **8**, which acts as a synthetic equivalent for the d^2/a^1 synthon **7**.[13] We speculated that nitroolefins **6** might be suitable synthetic equivalents for the a^2/d^0 synthon **5**,[14] since they can act as Michael acceptors[15] and the nitro group might allow for a subsequent Nef-type reaction,[16] in which Ac_2O and an acetate salt would be involved.[17]



Scheme 1. Retrosynthetic analysis of *N*-acyloxy succinimides **4**.

We have recently shown that ferrocene-based palladacycles are capable of catalyzing 1,4-additions of azlactones to enones.[18] The azlactones could also be generated in situ from α-amino acid precursors and carboxylic acid anhydrides. We thus examined racemic *N*-benzoyl alanine **9a** as an azlactone source in a model reaction with 2-nitrostyrene (**6a**, Table 1).

Table 1: Development of the title reaction.



No.	X	Y M(OAc)$_n$	T [°C]	10a Yield [%][a]	10a ee [%][b]	4a Yield [%][a]	4a d.r.[c]	4a ee [%][b]
1[d]	2	0.5 NaOAc	23	46	80	17	>50:1	n.d.
2[d]	2	2 NaOAc	23	62	83	17	13:1	n.d.
3	2	2 NaOAc	23	72	85	5	9:1	n.d.
4	5	2 NaOAc	50	14	n.d.	85	6:1	72
5	5	2 KOAc	50	17	n.d.	80	7:1	66
6	5	4 CsOAc[e]	50	<2	–	91	3:1	63
7	5	2 TBAOAc	50	12	n.d.	75	4:1	61
8	5	2 $Ca(OAc)_2$	50	61	85	37	>50:1	76
9	5	2 $Zn(OAc)_2$	50	70	81	29	>50:1	69
10	5	2 $Mn(OAc)_2$	50	50	81	34	>50:1	77
11	5	5 $Mn(OAc)_2$	50	5	n.d.	95	>50:1	81

[a] Yield determined by ^{1}H NMR spectroscopy using an internal standard. [b] Enantiomeric excess determined by HPLC using a chiral stationary phase. [c] Diastereomeric ratio determined from the ^{1}H NMR spectrum of the crude product. [d] The reaction was performed in the absence of *n*-hexane. [e] CsOAc was generated in situ from Cs_2CO_3. n.d.: not determined.

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As a precatalyst we chose the planar–chiral ferrocene bisimidazoline bispalladacycle $[FBIP\text{-}Cl]_2$ (Figure 2).[19–21] For catalytic activity this dimeric complex must be activated by removing the otherwise inert chloro bridges. This is achieved by reaction with silver salts (AgX) in acetonitrile to form the monomeric complexes FBIP-X ($X^- =$ anionic ligand).[19]

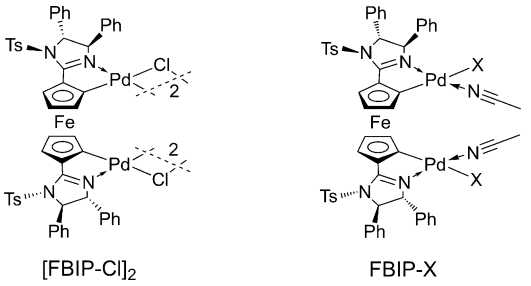


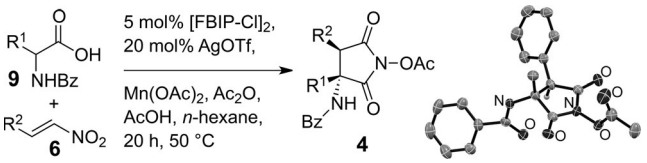
Figure 2. The dimeric precatalyst $[FBIP\text{-}Cl]_2$ and the monomeric activated catalyst species FBIP-X.

Initial attempts provided the 1,4-adduct **10a** as the major product with promising enantioselectivity (Table 1, entries 1–3).[22] Nitroolefins have already been studied in catalytic 1,4-addition reactions with azlactones, but regioselective addition at the C4 azlactone position was accomplished only for phenylglycine-derived azlactones.[23] With the FBIP catalyst only the C4 regioisomer has been detected in the present study. At room temperature, in the absence of an additional solvent, the Michael adduct was produced in moderate yield with application of 0.5 equiv of NaOAc. Gratifyingly, the imide **4a** was already found as a side product (Table 1, entry 1). An excess of NaOAc (2 equiv) provided more 1,4-adduct, but the amount of imide **4a** was not increased (Table 1, entry 2) and the larger amount of base had a negative impact on the diastereomeric ratio (d.r.) of **4a**.

When *n*-hexane was used as a cosolvent the *ee* of **10a** could be slightly increased (Table 1, entry 3). Further experimentation showed that application of higher temperatures, increased precatalyst loadings (5 mol%), and a higher excess of Ac_2O gave imide **4a** as the major product with moderate enantio- and diastereoselectivity (Table 1, entry 4). Control experiments showed that the diastereomeric ratio suffered from a base-catalyzed epimerization (see the Supporting Information). A number of alternative acetate salts were thus examined (Table 1, entries 5–10). Acetates with strong ionic character gave unsatisfactory stereoselectivity (Table 1, entries 5–7). The use of less basic metal(II) acetates resulted in diastereomerically pure imide (Table 1, entries 8–10), but only as a side product, whereas the major product was **10a**. Suitable reactivity was achieved with a larger excess of $Mn(OAc)_2$ (Table 1, entry 11). Under these conditions the cascade reaction product **4a** was produced as a single diastereomer in high yield and with good enantioselectivity.

The optimized reaction conditions are practical for different racemic *N*-benzoyl α-amino acids **9** and nitroolefins **6** (Table 2). The imides **4** were always formed as single diastereomers and isolated in useful yields. In the reaction

Table 2: Catalytic asymmetric synthesis of α-amino succinimides **4**.



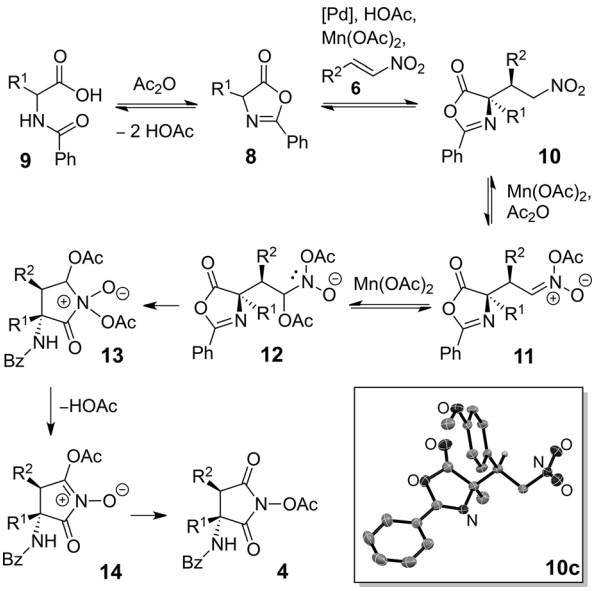
No.	4	R^1	R^2	Yield [%][a]	d.r. [%][b]	*ee* [%][c]
1	**a**	Me	Ph	95	>50:1	82
2	**b**	Me	4-Me-C_6H_4	84	>50:1	87
3	**c**	Me	4-MeO-C_6H_4	92	>50:1	78
4	**d**	Et	Ph	83	>50:1	91
5	**e**	*n*Pr	Ph	91	>50:1	93
6	**f**	*n*Pr	3-Cl-C_6H_4	78	>50:1	89
7	**g**	*n*Pr	4-Cl-C_6H_4	85	>50:1	85
8	**h**	*n*Pr	4-Br-C_6H_4	70	>50:1	85
9	**i**	*n*Pr	4-Me-C_6H_4	86	>50:1	94
10	**j**	*n*Pr	4-MeO-C_6H_4	78	>50:1	92
11	**k**	*n*Bu	Ph	85	>50:1	94
12	**l**	$(CH_2)_2CO_2Me$	3-MeO-C_6H_4	67	>50:1	93
13	**m**	*n*Pr	*n*Pr	89	>50:1	96
14	**n**	*n*Pr	*i*Pr	46	>50:1	95
15	**o**	*n*Pr	cyclohexyl	59	>50:1	94

[a] Yield of isolated product. [b] Diastereomeric ratio determined from the ^1H NMR spectrum of the crude product. [c] Enantiomeric excess determined by HPLC using a chiral stationary phase.

with β-nitrostyrene the *ee* values of **4** increased from $R^1 =$ Me (Table 2, entry 1) to Et (entry 4), *n*Pr (entry 5), and *n*Bu (entry 11). The substrate with a glutamic acid methyl ester side chain R^1 provided highly enantioenriched **4l** (Table 2, entry 12), which might serve as advanced intermediate toward the (epimeric) series of amathaspiramides A–F.[8] Regarding the nitroolefin component, electron-donating (Table 2, entries 2, 3, 9, and 10) and -withdrawing substituents (entries 6–8) in *meta* or *para* position on the aromatic residues R^2 were tolerated. *ortho* Substituents impeded the product formation. The method is also compatible with aliphatic nitroolefins (Table 2, entries 13–15), which give products **4m–o** as single diastereomers with high *ee*. When the nitroolefin was bearing an unbranched alkyl residue ($R^2 = n$-propyl), **4m** was furnished in high yield with 96% *ee*. This high efficiency was unexpected due to the considerable γ-C–H acidity of alkyl substituted nitroolefins, which is comparable to that of the azlactones. The constitution and relative and absolute configuration of **4a** have been confirmed by X-ray crystal structure analysis (see structure in Table 2).[24]

A mechanism is suggested in Scheme 2. The catalytic action of FBIP might be explained by N-coordination of the in situ generated azlactone **8** to a Pd center,[18c] which triggers the enolization required for a subsequent conjugate addition to nitroolefin **6**. It seems feasible that this conjugate addition proceeds by a bimetallic activation mode,[25] in which the nitroolefin might be simultaneously activated as a Michael acceptor by the other Pd center, because control experiments with 10 mol% of related monopalladacycles[26] gave either no product or **4a** was formed with only moderate enantioselectivity (see the Supporting Information).

The constitution and relative configuration of the 1,4-adduct **10c** have been confirmed by X-ray crystal structure

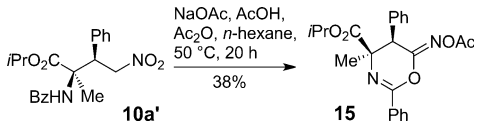


Scheme 2. Proposed mechanism of the title reaction and structural proof of the 1,4-adduct intermediate **10c** by X-ray analysis.

analysis (Scheme 2).[24] The assumption that **10** is an intermediate en route to imide **4** has been confirmed by control experiments, in which isolated **10a** was transformed to **4a** under the reaction conditions of the tandem process. When we applied the conditions listed in Table 1 (entry 4), diastereomerically pure **10a** (84% *ee*) provided the imide **4a** in 73% yield (d.r. 6:1) with 83% *ee*. *O*-Acylation of the nitronate derivative of **10** might give the dipolar species **11**, which could undergo a subsequent 1,2-addition of acetate to the C=N bond generating the nucleophilic nitrogen center in **12**. This in turn should be suitable for a subsequent intramolecular azlactone ring opening giving ammonium oxide **13**. The latter is expected to undergo elimination of acetic acid to form iminium oxide **14**. A subsequent acyl transfer would finally furnish the neutral *N*-acetoxysuccinimide **4** after a cascade of several steps.

We attempted to obtain further information about the mechanism of the reaction by continuous NMR monitoring. Since $Mn(OAc)_2$ is paramagnetic, NaOAc was used as the base. In order to increase the chances of detecting and identifying intermediates that follow the confirmed intermediate **10a**, the latter served as the starting material. During the course of this reaction only **10a** and product **4a** (including its epimer) were detected (e.g. after: 1 h: 54% **10a** and 46% **4a**; 3.5 h: 10% **10a** and 90% **4a**). This indicates that the proposed nitronate acylation arguably proceeds as the slowest step starting from **10a**.[27]

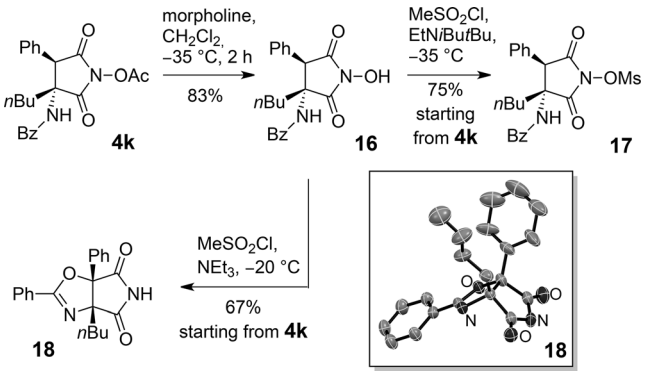
Since other intermediates were not observable by ^{1}H NMR spectroscopy, the isopropyl ester **10a′** was formed from **10a** by azlactone ring opening with *i*PrOH. This change should retard the imide formation, as the ester is less electrophilic than the azlactone carbonyl moiety. We then examined the reaction of **10a′** with NaOAc, HOAc, and Ac_2O (Scheme 3). Formation of the iminooxazine **15** (next to unreacted **10a′** and traces of **4a**) confirms a Nef-type reaction pathway. In this case the benzamide function has trapped an



Scheme 3. Confirmation of the Nef-type reactivity by formation of **15**.

electrophilic α-C atom, resulting in the transformation of a nitro group into a carboxylic acid derivative.[28]

Compounds **4** proved to be valuable synthetic building blocks providing access to interesting new product classes (Scheme 4). *N*-Hydroxyimide **16** was obtained by treatment



Scheme 4. Examples of the derivatization of title compounds **4** and the X-ray crystal structure of the bicyclic oxazoline **18**.

of **4k** with morpholine in CH_2Cl_2 at −35 °C. It could be further employed to generate the 4-substituted analogue **17** of the known suicide inhibitors **2** by *O*-sulfonylation using a sterically demanding base. The N-OMs moiety in **17** also permitted access to succinimide **18** with an annellated oxazoline featuring two adjacent quaternary stereocenters. The constitution of this novel chiral bicyclic [3.3.0] scaffold has been determined by X-ray crystal analysis.

In summary, we have developed a regio-, diastereo-, and enantioselective cascade reaction to prepare biologically interesting α-alkyl-α-aminosuccinimides from simple substrates. The formal derivatives of α-alkyl aspartic acids are generated by in situ formation of azlactones, which undergo a C4-regioselective asymmetric conjugate addition to nitroolefins. Succinimide formation proceeds through a Nef-type transformation. Crucial for high stereoselectivity is the use of a divalent acetate salt like $Mn(OAc)_2$ to avoid epimerization. We have showcased the synthetic value of the products by describing a rapid access to a suicide inhibitor analogue and a novel bicyclic [3.3.0] scaffold featuring two adjacent quaternary stereocenters.

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