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Asymmetric conjugate addition of azide to α,β-unsaturated nitro compounds catalyzed by cinchona alkaloids

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Abstract—The cinchona alkaloid catalyzed asymmetric addition of azide to α,β-unsaturated nitro compounds giving optically active β-azido nitro compounds in high yields and with low enantioselectivity is presented. Subsequent modifications allow for the formation of chiral 1,2-diamines.

1. Introduction

Vicinal diamines[1] are abundant in nature and are used as important building blocks for the syntheses of a variety of useful compounds having biological activity,[1b,2] as organocatalysts,[3] and as ligands for metal complexes.[1b,4] Terminal vicinal diamines are utilized as starting compounds for the synthesis of α-amino amides, obtainable from the oxidation of vicinal diamines[5] and for the synthesis of bleomycin derivatives,[6] a family of glycopeptide antibiotics that show antitumor activity.

There are several approaches for the synthesis of the terminal 1,2-diamino scaffold. In 1913, Frankland and Smith[7] used a dihalide source as the electrophile for the reaction with two nucleophilic primary amines to form the desired product, while Dittmer et al.[8] formed vicinal diamines by an acid promoted hydrolysis of imidazolidin-2-ones. More recently, Mukaiyama et al.[9] have reported the formation of vicinal amines in a one-pot preparation by the addition of *O*-ethylhydroxylamine to vinylic nitro compounds and subsequent reduction. O'Neil et al.[10] showed that the addition of hydroxylamines to vinylic nitro compounds proceeded in excellent yield, and Enders and Wiedemann[11] have succeeded in the stereoselective addition of a nitrogen nucleophile having a C_2-symmetric *N*-aminopyrrolidine as chiral auxiliary. Optically active vicinal diamines have also been obtained using the chiral auxiliary approach as developed by Lucet et al.[12] Furthermore, the 1,2-diamino moiety can also be formed by the reduction of α-amino amides.[13]

A drawback of these approaches is that racemic adducts are obtained, so that a chiral auxiliary is needed as the source for stereoselectivity in order to obtain optically active vicinal diamines. In order to catalytically promote the formation of chiral 1,2-diamino moiety, we envisioned that the most obvious route would be the direct addition of the nitrogen source to α,β-unsaturated nitrogen-based electrophiles. Recently, MacMillan et al.[14] and Córdova et al.[15] independently reported highly enantioselective additions of an *N*-protected hydroxylamine to α,β-unsaturated aldehydes using secondary amines as chiral catalysts. For the nucleophilic addition of a nitrogen source to α,β-unsaturated electrophiles, hydrazoic acid has also proven effective as the nucleophile using organometallic and tertiary amines as catalysts. The enantioselective addition of azide to α,β-unsaturated electrophiles is a simple and easy approach to form optically active β-azido compounds.[16] Using nitrogen-based electrophiles may then lead to β-azido nitro compounds, which subsequently can be reduced to the attractive 1,2-diamines. Jacobsen and Myers[17] have reported the addition of hydrazoic acid to α,β-unsaturated imides with moderate to excellent enantioselectivity using a (salen)Al(III) complex as the catalyst, while the group of Miller presented the tertiary-amine promoted racemic addition of azide to cyclic α,β-unsaturated ketones and to an oxazolidinone.[18] The same group later developed an enantioselective variant using peptide-based catalysts.[19,20]

For the electrophilic partner in these reactions, the majority of reactions have been performed for substrates having carbonyl functionalities as the electrophilic substituent, and nitro alkenes have only received very little attention.[21] In this paper, we wish to present the unprecedented stereoselective addition of azide to α,β-unsaturated nitro compounds

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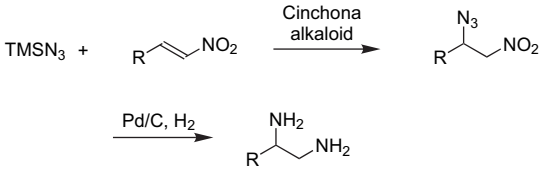
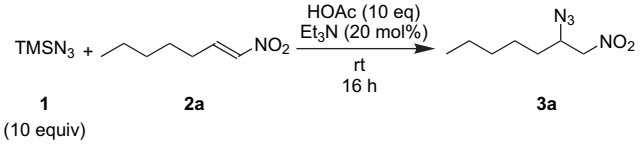
catalyzed by a dimeric cinchona alkaloid. Based on a very easy reaction procedure, the β-azido nitro products are formed in high yields with moderate enantioselectivity. It will also be shown that the subsequent reduction produces the desired 1,2-diamino adduct (Scheme 1). Moreover, to the best of our knowledge, using cinchona alkaloids as the catalyst for the nucleophilic addition of azides to vinylic electrophiles has not been reported until now.



Scheme 1.

2. Results and discussion

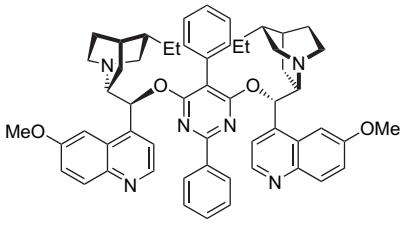
It is well known that azide salts and hydrazoic acid are toxic and it is of great interest to avoid them. Miller et al. have shown that mixing the TMS-protected azide with a carboxylic acid in the presence of a tertiary amine will form the hydrazoic acid in situ.[18] The same authors also showed that a catalytic amount of a tertiary amine could promote the addition of the in situ formed azide to α,β-unsaturated carbonyl compounds. These facts, together with the well-known ability of cinchona alkaloids to facilitate nucleophilic addition to nitro alkenes,[22] were the inspiration to add $TMSN_3$ **1** (10 equiv) to 1-nitro-hept-1-ene **2a** in the presence of catalytic amounts of Et_3N (Eq. 1). To our delight a quantitative yield of 2-azido-1-nitro-heptane **3a** was obtained after a simple purification process.



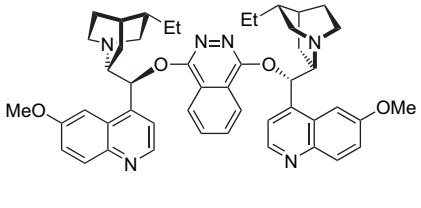
(1)

Miller et al. have proposed that mixing $TMSN_3$ and AcOH leads to hydrazoic acid and trimethylsilyl acetate during a disproportionation reaction[18] and in the present case it was observed that TMSOAc was formed as a by-product in the reaction. It was also found that in the absence of a base, the conversion was comparably very slow. Intrigued by the initial result, different commercially available cinchona alkaloids and other cinchona alkaloid derivatives were screened as chiral substitutes for Et_3N. The most promising catalysts are shown in relation to the screening results presented in Table 1.

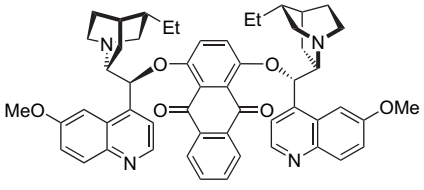
Table 1. Screening of catalysts for the β-azidation of 1-nitro-hept-1-ene **2a**



$(DHQD)_2PYR$ **4a**



$(DHQD)_2PHAL$ **4b**



$(DHQD)_2AQN$ **4c**

Entry	Catalyst	Equiv AcOH (h)	Conversion (%)	ee[a] (%)
1	—	10	25	—
2	Et_3N	10	100	—
3	Quinine	10	>95	−15
4	Quinidine	10	100	+15
5	Cinchonine	10	100	−4
6	Cinchonidine	10	100	0
7	9-*O*-Benzylcupreine	5	18	0
8	$(DHQD)_2PYR$ **4a**	10	100	−33
9	$(DHQD)_2PHAL$ **4b**	10	100	−3
10	$(DHQD)_2AQN$ **4c**	10	100	+5
11	$(DHQ)_2PYR$	10	100	+5
12	*N*-Benzylcinchonidinium chloride	10	14	n.d.

Entries 1 and 2 are conducted at rt for 16 h. Entries 3–12 are conducted at −78 °C. All reactions, except entry 7, are with 10 equiv AcOH. Entry 7 is with 5 equiv AcOH. All reactions are in Et_2O and with 0.2 equiv catalyst.

[a] Determined by GC.

The results in Table 1, entries 1–3, clearly show the rate dependence of the reaction on the presence of a base indicating that the rate-determining step is the addition of azide to the vinylic nitro compound (vide infra).[23] The application of the cinchona alkaloids, quinine and quinidine gave low yield and opposite enantioselectivity (entries 3 and 4). It was found that the cinchonines gave close to racemic products (entries 5 and 6), while the 9-*O*-benzylcupreine was catalytically inactive (entry 7). These results indicated that the monomeric alkaloids seem not to be the optimal choice for good stereoselectivity. The application of the dimeric cinchona alkaloids having the PYR-linker **4a** showed more promising results giving a moderate enantiomeric excess of 33% (entries 8–10), while both the PHAL- and AQN-linker, **4a** and **4b**, respectively, catalyzed additions with almost no face-selectivity. Similar results were obtained for a quinine dimer, $(DHQ)_2PYR$ (entry 11). As a part of the screening process, a single phase-transfer catalyst (PTC), *N*-benzylcinchonidinium chloride, was also tested; however, as shown in entry 12, very low conversion was obtained using the PTC catalyst.

Next the optimizing of equivalents of $TMSN_3$ and AcOH was studied. It was found that there was almost no difference in conversion or enantioselectivity when lowering the equivalents of both compounds to 5. However, lowering the amount of $TMSN_3$ to 1.5 equiv, while still having 5 equiv of AcOH reduced the conversion and gave a racemic product. Thus, having excess of acid, compared to $TMSN_3$, interfered with the catalytic cycle in a negative manner. This was further established by the fact that when lowering the amount of AcOH to 2 equiv, full conversion with an enantioselectivity of about 30% ee was observed. The reaction with 5 equiv of $TMSN_3$ and 1.5 equiv of AcOH reduced the conversion to 88%, without altering the enantioselectivity. It was concluded that 5 equiv of $TMSN_3$ and AcOH are necessary for full conversion and good enantioselectivity.

Table 2 shows the results of the solvent screening for the addition of $TMSN_3$ **1** to 1-nitro-hept-1-ene **2a** using $(DHQD)_2PYR$ **4a** as the catalyst.

It appears from results in Table 2, entries 1–5, that lower enantioselectivities (23–36% ee) were obtained in polar solvents, compared to CH_2Cl_2 and toluene where 46 and 57% ee were obtained (entry 6 and 7), while *n*-hexane, on the contrary, gave the second lowest stereoselectivity of only 28% ee (entry 8). In an attempt to account for the solvent influence on the enantioselectivity, it was found that, for the non-acidic and non-basic solvents, the Hildebrand solubility parameter[24] could explain the selectivity in the reaction.

It was also found that the acid added had a great influence on the reaction course not only on the enantiomeric excess but also on the face-selectivity. A summary of the screening of organic and inorganic proton donors, as well as other organic compounds, for the reaction of $TMSN_3$ **1** with 1-nitro-hept-1-ene **2a** using $(DHQD)_2PYR$ **4a** as the catalyst is presented in Table 3.

The results in Table 3 show a very interesting role of the additives; the addition of a proton donor not only increases the enantiomeric excess but also *inverts* the enantioselectivity (compare e.g., entry 1 with entry 2). Thus, it must be expected that the additive is part of the stereoselective step in the catalytic cycle. An enantioselectivity of 57% ee was observed for AcOH and 50% ee for benzoic acid, showing that the aliphatic carboxylic acid has a greater influence on the enantioselective step, compared to the aromatic carboxylic acid (entries 2 and 3). For the aromatic carboxylic acids, the substitution pattern influences the enantioselectivity. The highest enantioselectivity (62% ee) was obtained for 2,4,6-trimethoxy benzoic acid (entries 4–6). Compared to benzoic acid, only a slight improvement in enantioselectivity is noticed when enlarging the aromatic system to a naphthoic group (entries 3 and 7). The results in entries 8–12 showed that a carboxylic acid was not necessary as long as a proton donor is available. Surprisingly, using the insoluble $KHSO_4$ resulted in an enantioselectivity even higher than that for benzoic acid (entry 8). It is notable that a much weaker proton donor also affects the enantioselectivity as phenol results in inversion of the face-selectivity, however, low enantiomeric excess was observed (entry 9). Substituting the aromatic scaffold in phenol with two *tert*-butyl groups at the *meta*-positions greatly improved the enantioselectivity to 60% ee (entry 10) from 17% ee in the case of phenol. Even nitrogen-based proton donors were able to affect the enantioselectivity, though only low enantioselectivities are observed (entries 11 and 12). Surprisingly, using aldehydes as additives keep the same face-selectivity as when using no additive, but with better enantioselectivity compared to the absence of an additive (entry 1 vs entries 13 and 14).

Table 2. Solvent screening for the $TMSN_3$ **1** to 1-nitro-hept-1-ene **2a** catalyzed by $(DHQD)_2PYR$

Entry	Solvent	Conversion (%)	ee (%)
1	Et_2O	100	34
2	EtOAc	100	30
3	Acetone	100	36
4	THF	100	30
5	MeOH	100	23
6	CH_2Cl_2	100	46
7	Toluene	100	57
8	*n*-Hexane	100	28

All reactions are conducted for 16 h at −78 °C in toluene with 5 equiv AcOH.

Table 3. Influence of proton donors on the conversion and enantioselectivity

Entry	Additive (5 equiv)	Conversion (%)	ee (%)
1	—	n.d.	+17
2	AcOH	100	−57
3	$PhCO_2H$	100	−50
4	2,4,6-Trihydroxy benzoic acid	100	−55
5	3,4,5-Trihydroxy benzoic acid	100	−6
6	2,4,6-Trimethoxy benzoic acid	100	−62
7	1-Naphthoic acid	100	−55
8	$KHSO_4$	100	−52
9	Phenol	90	−17
10	3,5-Di-*tert*-butyl phenol	100	−60
11	Aniline	n.d.	−27
12	Benzamide	n.d.	−33
13	Acetaldehyde	n.d.	+20
14	Benzaldehyde	60	+28

All reactions are performed in toluene at −78 °C for 16 h using 5 equiv of **1**.

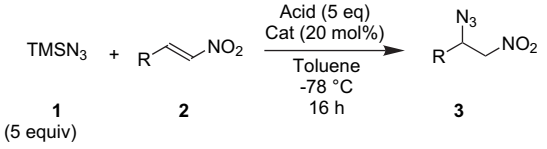
Table 4. Organocatalytic azide addition to different nitro alkenes

Entry	Substrate (R)	Catalyst	Acid	Yield (%)	ee[a] (%)
1	*n*-Pentyl—**2a**	**4a**	2,4,6-Trimethoxy benzoic acid	85	62
2	*t*-Bu—**2b**	**4c**	2,4,6-Trimethoxy benzoic acid	70	44
3	$PhCH_2CH_2$—**2c**	**4c**	AcOH	84	24[b]
4	$(CH_2)_4CO_2Me$—**2d**	**4a**	AcOH	94	35
5	Cyclohexyl—**2e**	**4c**	2,4,6-Trimethoxy benzoic acid	96	27
6	1-Cyclohexenyl—**2f**	**4a**	2,4,6-Trimethoxy benzoic acid	40	0[c]

All reactions are performed in toluene at −78 °C for 16 h.
[a] Determined by GC.
[b] Determined by HPLC.
[c] dr>99:1.

These results show that it is possible to control which enantiomer is in excess by changing the achiral additive while keeping the same catalyst.

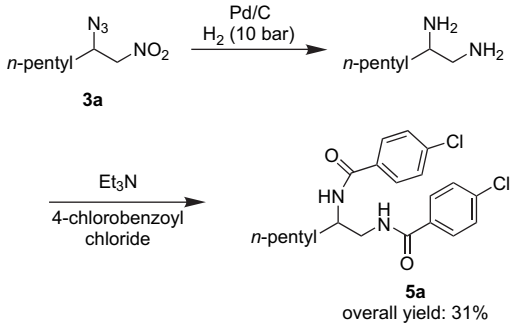
With the reaction conditions developed, different vinylic nitro compounds were reacted in the presence of AcOH and 2,4,6-trimethoxy benzoic acid as additive (Eq. 2), as the former for some substrates turned out to give better results. Furthermore, different linkers for the dimeric dihydroquinidine catalyst proved to be optimal in some cases. The results are presented in Table 4.



(2)

The results in Table 4 show that several nitro alkenes are tolerated in this reaction. Both normal and branched chains result in good yields and moderate enantiomeric excess as seen for 1-nitrohept-1-ene **2a** and 3,3-dimethyl-1-nitrobut-1-ene **2b** (entries 1 and 2). Unfortunately, having a phenyl group substituted remote from the reaction center results in a drastic lowering of the enantioselectivity when compared to the normal chain (entries 1 and 3). The result in entry 4 shows that an ester group is tolerated resulting in high yield and a moderate enantioselectivity of 35% ee. Having a cyclic aliphatic moiety substituted results in a high yield and a moderate enantioselectivity of 27% ee (entry 5). Unfortunately, addition of azide to 1-nitrocyclohex-1-ene **2f** results in a completely racemic product, though practically only one diastereomer is observed (entry 6).

A very easy approach was used in order to obtain the 1,2-diamino scaffold from the formed 2-azido-1-nitro compounds. A simple hydrogenation procedure allowed for the reduction of the azide and nitro functional groups leading to the free amines. After reduction of **3a** subsequent amidation forms product **5a** in 31% overall yield under non-optimized reaction conditions.



The suggested catalytic cycle is presented in Figure 1.

Due to the significant effect of acid (shown as AcOH in Fig. 1) on the stereoselectivity, it is proposed that the acid is a part of the catalytic cycle and probably present during

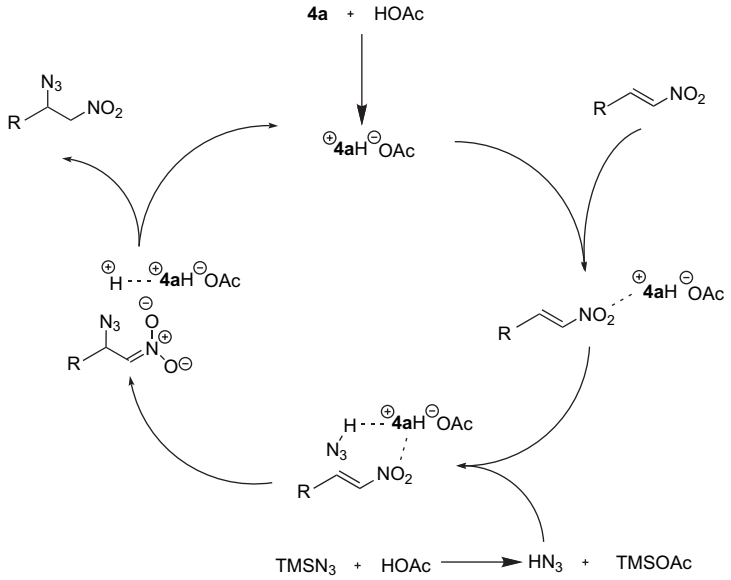


Figure 1. Proposed catalytic cycle.

the enantioselective azide addition to the nitro alkene. Thus, one of the two basic sites present in the dimeric alkaloid is probably coordinated to the acid. This partially charged moiety then coordinates to the nitro group. The second basic site in the catalyst then coordinates to the in situ generated hydrazoic acid, which then undergoes the nucleophilic attack on the activated α,β-unsaturated nitro compound. Finally, a protonation of the anionic intermediate forms the product and leaving the protonated catalyst ready for a new catalytic cycle. This proposal may also explain why large excess of acid relative to $TMSN_3$ diminishes the stereoselectivity. When too much acid is used, both the basic sites might be protonated leaving no coordination site left for hydrazoic acid.

In summary, we have presented the formation of optically active β-azido-α-nitro compounds through a stereoselective addition of azide to vinylic nitro compounds catalyzed by dimeric quinidines. The addition of additive proved to have tremendous effect on the facial selectivity. Reduction of the azido nitro moiety forms the attractive 1,2-diamino scaffold.

3. Experimental section

3.1. General

The ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. The chemical shifts are reported in parts per million relative to $CHCl_3$ (δ=7.26) for ^{1}H NMR and relative to the central $CDCl_3$ resonance (δ=77.0) for ^{13}C NMR. Flash chromatography (FC) was carried out using Iatrobeads 6RS-8060 (Spherical silica gel). Optical rotation was measured on a Perkin–Elmer 241 polarimeter. Trimethylsilyl azide **1**, 1-nitrocyclohex-1-ene **2g**, catalysts **4a**–**d**, and acids **5a**–**b** are commercially available and used as received. Substrates **2a**–**f** were synthesized according to the literature procedures.[25] All solvents were of p.a. quality and used without further purification.

3.2. General procedure for the addition of azide to vinylic nitro compounds forming 3

$TMSN_3$ **1** (164 μL, 1.25 mmol) and the acid **5** (1.25 mmol) were mixed in 2 mL toluene in a Schlenk tube and stirred for 20 min at rt. Then the mixture was cooled to −78 °C and the catalyst **4** (0.05 mmol) was added. Immediately after that the vinylic nitro compound **2** (0.25 mmol) was added. The mixture was stirred at −78 °C for 16–30 h and the reaction mixture was plugged using Et_2O in pentane as eluent. If the TMS-protected additive was present, the resulting mixture was then stirred in MeOH at 50 °C for 5 h.[26] After evaporation of MeOH, the pure product was obtained after column chromatography.

3.2.1. 2-Azido-1-nitro-heptane (3a). ^{1}H NMR: δ 4.37 (dd, 1H, J=22.8, 13.6 Hz), 4.36 (dd, 1H, J=22.0, 13.2 Hz), 4.12 (m, 1H), 1.62–1.31 (m, 10H), 0.90 (m, 3H). ^{13}C NMR; δ 77.7, 59.4, 31.7, 21.2, 25.2, 22.3, 13.9. The ee was determined by GC on an Astec G-TA column. Temperature program from 70 to 130 °C at a rate of 10 °C/min, isotherm for 23 min. t_R (min): 24.1 (minor enantiomer), 26.4 (major enantiomer). $[\alpha]_D^{25}$ −8.7 (c 2.0, $CHCl_3$).

3.2.2. 2-Azido-3,3-dimethyl-1-nitro-butane (3b). ^{1}H NMR: δ 4.51 (dd, 1H, J=13.6, 2.4 Hz), 4.29 (dd, 1H, J=13.6, 10.8 Hz), 3.90 (dd, 1H, J=11.2, 2.4 Hz), 1.02 (s, 9H). ^{13}C NMR: δ 75.7, 69.3, 35.5, 26.2 (2C). The ee was determined by GC on a Chrompak CP-Chirasil Dex CB-column. Temperature program from 70 to 140 °C at a rate of 10 °C/min, isotherm for 3 min. t_R (min): 8.17 (major enantiomer), 8.36 (minor enantiomer). $[\alpha]_D^{25}$ −2.4 (c 1.3, $CHCl_3$).

3.2.3. (3-Azido-4-nitro-butyl)-benzene (3c). ^{1}H NMR: δ 7.25 (td, 2H, J=7.6, 1.2 Hz), 7.17 (td, 1H, J=7.6, 1.2 Hz), 7.13 (d, 2H, J=8.0 Hz), 4.30 (d, 2H, J=6.8 Hz), 4.02 (m, 1H), 2.80 (m, 1H), 2.68 (m, 1H), 1.81 (m, 2H). ^{13}C NMR: δ 139.5, 128.8 (2C), 128.3, 128.2, 126.6, 77.6, 58.6, 33.4, 31.7. The ee was determined by HPLC on Daicel Chiralpak AD column with hexane/i-PrOH (99:1) as the eluent: t_R (min): 15.1 (major enantiomer), 16.7 (minor enantiomer). $[\alpha]_D^{25}$ −3.8 (c 2.2, $CHCl_3$).

3.2.4. 6-Azido-7-nitro-heptanoic acid methyl ester (3d). ^{1}H NMR: δ 4.38 (m, 2H), 4.13 (m, 1H), 3.68 (s, 3H), 2.35 (m, 2H), 1.72–1.43 (m, 6H). ^{13}C NMR: δ 173.6, 77.6, 59.2, 51.6, 33.5, 31.5, 25.1, 24.3. The ee was determined by GC on an Astec G-TA column. Temperature program from 70 to 160 °C at a rate of 10 °C/min, isotherm for 15 min, then to 180 °C at a rate of 10 °C/min, isotherm for 8 min. t_R (min): 29.6 (minor enantiomer), 30.0 (major enantiomer). $[\alpha]_D^{25}$ −5.2 (c 1.1, $CHCl_3$).

3.2.5. (1-Azido-2-nitro-ethyl)-cyclohexane (3e). ^{1}H NMR: δ 4.46 (ddd, 1H, J=13.6, 4.0, 0.8 Hz), 4.34 (ddd, 1H, J=13.2, 9.6, 0.8 Hz), 3.99 (m, 1H), 1.83–1.53 (m, 6H), 1.31–1.09 (m, 5H). ^{13}C NMR: δ 77.3, 64.7, 40.7, 29.5, 28.4, 25.8, 25.8, 25.6. The ee was determined by GC on an Astec G-TA column. Temperature program from 70 to 165 °C at a rate of 5 °C/min, isotherm for 10 min. t_R (min): 24.7 (major enantiomer), 25.0 (minor enantiomer). $[\alpha]_D^{25}$ +9.2 (c 2.3, $CHCl_3$).

3.2.6. 1-Azido-2-nitro-cyclohexane (3f). ^{1}H NMR: δ 4.52 (br, 1H), 4.29 (m, 1H), 2.20–2.01 (m, 4H), 1.93–1.88 (m, 1H), 1.72–1.62 (m, 1H), 1.59–1.54 (m, 1H), 1.35–1.25 (m, 1H). ^{13}C NMR: δ 84.0, 59.2, 29.2, 24.1, 23.3, 19.2. The ee was determined by GC on an Astec G-TA column. Temperature program from 70 to 160 °C at a rate of 5 °C/min, isotherm for 8 min. t_R minor diastereoisomer (min): 21.6 (major enantiomer), 21.8 (minor enantiomer); t_R major diastereoisomer (min): 22.1 (major enantiomer), 23.2 (minor enantiomer). $[\alpha]_D^{25}$ 0 (c 1.0, $CHCl_3$).

3.3. General procedure for the reduction of 2-azido-1-nitro compounds and subsequent amidation forming 5

The 2-azido-1-nitro compound **3** (0.350 mmol) is dissolved in Et_2O. Then 140 mg of Pd/C is added. After 30 min in 10 barH_2 the mixture is filtered and mixed with 4 equiv Et_3N and 3 equiv 4-chlorobenzoyl chloride in dichloromethane at 0 °C.[27] After 3 h the mixture is columned using Et_2O in CH_2Cl_2 providing pure product **5**.

3.3.1. *N*,*N*′-(Heptane-1,2-diyl)bis(4-chlorobenzamide) (5a). The title compound was prepared according to the general procedure described above. ^{1}H NMR: δ 7.71 (t, 4H,

J=7.8 Hz), 7.42–7.34 (m, 5H), 6.86 (d, 1H, J=8 Hz), 4.29–4.24 (m, 1H), 3.74–3.66 (m, 1H), 3.50–3.41 (m, 1H), 1.63–1.57 (m, 4H), 1.43–1.19 (m, 6H), 0.86 (t, 3H, J=7). ^{13}C NMR: δ 167.6 (2C), 137.9 (2C), 132.3 (2C), 128.8 (2C), 128.8 (2C), 128.4 (2C), 128.4 (2C), 51.2, 45.5, 32.8, 31.6, 25.8, 22.5, 14.0. HRMS calcd $C_{21}H_{24}Cl_2N_2NaO_2^+$: 429.1107, found: 429.1100.

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