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The inverted ketene synthon: a double umpolung approach to enantioselective $\beta^{2,3}$-amino amide synthesis†

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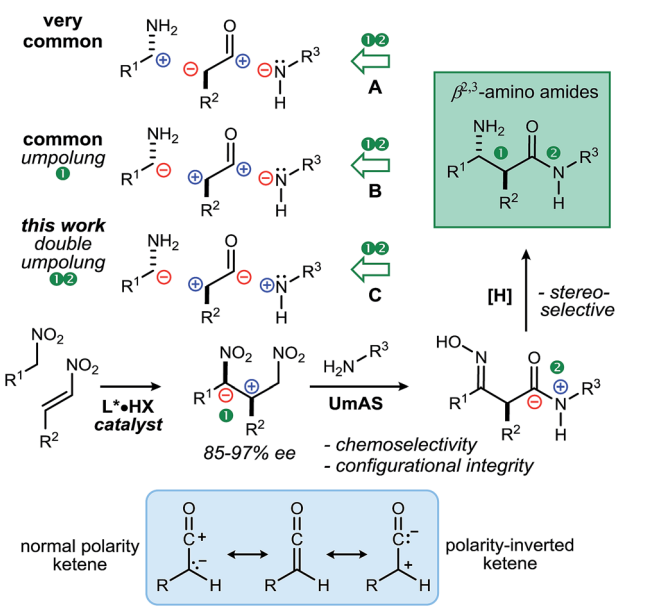
A stereocontrolled synthesis of $\beta^{2,3}$-amino amides is reported. Innovation is encapsulated by the first use of nitroalkenes to achieve double umpolung in enantioselective β-amino amide synthesis. Step economy is also fulfilled by the use of Umpolung Amide Synthesis (UmAS) in the second step, delivering the amide product without intermediacy of a carboxylic acid or activated derivative. Molybdenum oxide-mediated hydride reduction provides the *anti*-$\beta^{2,3}$-amino amide with high selectivity.

Introduction

The β-amino amide motif is featured in a wide range of natural products and marketed drugs. β-Peptides with repeating β-amino amide residues can exhibit helix and sheet secondary structures with a predictable range of stability.[1,2] Structurally, these homologues of α-amino amides provide an additional point of side chain attachment and both α/(C2) and β/(C3) positions have been evaluated for their ability to affect secondary structure in β-peptides.[1,3] In order to increase proteolytic stability, α-amino amide leads in therapeutic development are strategically modified to their β-congener.[4] β-Amino amides are further classified by substitution: β^3 (*e.g.* 3-alkyl: sitagliptin[5]), $\beta^{2,3}$ (2-oxy, 3-alkyl: bestatin,[6] amastatin). Approaches to β-amino amides often focus on β-amino acid preparation and subsequent conversion to an amide,[7] including Arndt–Eistert homologation from the α-amino acid chiral pool,[8] enantioselective Mannich additions (**A**, Scheme 1),[9] and the enantioselective conjugate addition of carbon nucleophiles to vinylogous carbamates[10] or unsaturated amides.[11] Functionalization reactions include reduction of vinylogous carbamates[12,13] and allylic amines,[14] reduction of imines,[15] and stereospecific aziridine ring-opening.[16] Less common are methods that reverse the polarity (umpolung)[17,18] of the C–C bond formed, but use the typical polarity of amide formation (**B**, Scheme 1).[19,20]

Despite this attention paid to β-amino amide synthesis and its importance,[21] no approaches currently reverse both polarities of the bonds formed to the central acyl fragment (**C**, Scheme 1), which is an 'inverted ketene'. We hypothesized that Umpolung Amide Synthesis (UmAS) could enable a new stereocontrolled synthesis of $\beta^{2,3}$-amino amides when preceded by nitroalkane addition to a β-substituted nitroalkene (Scheme 1). Owing to the polarity with which the carbon–carbon bond is formed, the strategy constitutes a double umpolung: both C–C and C–N bonds are formed umpolung relative to the most common approaches to construction of the acyl component.[22] Importantly, this umpoled C–N bond formation could allow enantioenriched β-amino amides with acidic α-chiral carbons to be prepared, endowing polarity-inverted ketene equivalence to nitroalkenes.[23]

Several reports of nitroalkane additions to nitroalkenes have appeared since Du's 2006 Zn(II)/Ti(IV) catalyzed additions of



Scheme 1 $\beta^{2,3}$-Amino amides: retrosynthesis through carbon–carbon bond-forming approaches, mapped by polarity, highlighting an unusual 'double umpolung' and its realization through enantioselective catalysis and Umpolung Amide Synthesis (UmAS) (this work).

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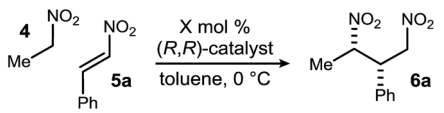
† Electronic supplementary information (ESI) available: Complete experimental details and analytical data for all new compounds. See DOI: 10.1039/c8sc04330b

nitroethane,[24] including organocatalyzed[25] and metal-mediated transformations.[23,26,27] The reaction's development has been driven mostly by interest in simple 1,3-diamines,[28] and focused applications are all but absent.[23,29] We reasoned that the use of β-functionalized terminal nitroalkanes in UmAS would not only extend their impact by connecting directly with amides, but also provide a rare double umpolung[22] at the strategy-level, culminating in a concise and modular enantioselective β-amino amide synthesis.

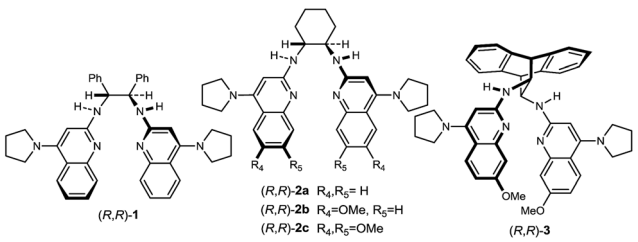
Results and discussion

Reports of enantioselective nitroalkane–nitroalkene conjugate additions use catalysts derived from the chiral pool, or diamine backbones that similarly limit utility, and they have noted pronounced concentration effects on reactivity and selectivity.[25b] Moreover, some require the use of neat conditions that restrict the use of some solid nitroalkanes such as derivatives of phenyl nitromethane (*i.e.* *p*-Cl, *p*-NO_2).[25a] This state of the art was anticipated to limit the impact of the approach outlined in Scheme 1. Bis(AMidine) [BAM] catalysis might remedy these shortcomings, but is unproven with electrophiles other than azomethines[30] and nucleophilic alkenes.[31,32] Initial investigations probed the suitability of electron-deficient alkene **5a** using the leading BAM ligands. Nitroethane (**4**) and nitrostyrene (**5a**) were combined with StilbPBAM (**1**) (10 mol%), and the desired addition product was obtained in low dr and low ee (Table 1, entry 1). Its triflimidic acid salt (**1**·$HNTf_2$) salt positively impacted the outcome, resulting in higher dr and ee (Table 1, entry 2). This correlation between protonation state, reactivity, and selectivity normally indicates that bifunctional catalysis is operative.[33] PBAM (**2a**)[34] and its salt (Table 1, entries 3–4) behaved similarly. Further attempts to manipulate the chiral ligand through substituents at the periphery of the presumed amidine binding pocket did not improve reactivity and selectivity (Table 1, entries 5–6). Lowering the temperature to −20 °C improved dr and ee to near-useful levels (Table 1, entry 7), but still impractical for broad utility. We reasoned that the substrate binding pocket may not adequately accommodate the nitroalkene electrophile. Derivatives of the conformationally rigid diamine derived from anthracene were therefore sought (*i.e.* **3**),[35] as this diamine is reported to have an N–C–C–N dihedral angle of 114–117°, compared to *trans*-stilbene and *trans*-cyclohexane diamines (52° and 69°, respectively).[36] The selectivity of the free base (**3**) trended with the analogous free base–salt pairs (Table 1, entry 8) when considering ee, but not dr (Table 1, entry 9). However, its improved reactivity allowed for lower temperature and time to completion while enhancing dr (Table 1, entry 10). The catalyst loading could be further lowered to 5 mol% provided that nitroethane is used at higher

Table 1 Development of a chiral proton-catalyzed Michael addition of nitroethane to β-nitrostyrene

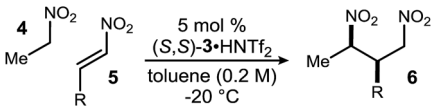


Entry[a]	Catalyst	4 (equiv.)	X mol%	Yield[b] (%)	dr	ee[c] (%)
1	**1**	5	10	70	3 : 1	30/34
2	**1**·$HNTf_2$	5	10	80	14 : 1	80
3	**2a**	5	10	75	1.6 : 1	25/25
4	**2a**·$HNTf_2$	5	10	80	6 : 1	85/77
5	**2b**·$HNTf_2$	5	10	65	5.5 : 1	80/73
6	**2c**·$HNTf_2$	5	10	65	3.3 : 1	79/70
7	**2a**·$HNTf_2$[d]	5	10	60	7 : 1	89
8	**3**	5	10	65	2 : 1	25/30
9	**3**·$HNTf_2$	5	10	73	3.5 : 1	92/90
10	**3**·$HNTf_2$[e]	5	10	55	5 : 1	95/95
11	**3**·$HNTf_2$[e]	20	5	85	20 : 1	94



[a] All reactions were performed on a 0.10 mmol scale (0.2 M) using nitroethane (5 equiv.) and a standard 24 h reaction time at 0 °C. [b] Isolated yield. [c] Enantiomeric ratios were measured by HPLC using a chiral stationary phase. See ESI for details. [d] Reaction conditions: −20 °C for 4 d. [e] Reaction conditions: −20 °C for 45 h.

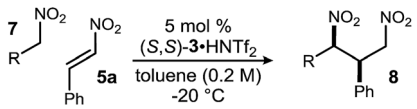
Table 2 Chiral proton-catalyzed Michael addition of nitroethane to β-nitrostyrenes



Entry[a]	R	6	dr[b]	Yield[c] (%)	ee[d] (%)
1	Ph	**a**	20 : 1	85	94
2	2-MeO-C_6H_4	**b**	20 : 1	94	92
3	3-MeO-C_6H_4	**c**	20 : 1	85	93
4	4-MeO-C_6H_4	**d**	20 : 1	81	95
5	3,4-$(MeO)_2$-C_6H_3	**e**	20 : 1	83	93
6	4-Me-C_6H_4	**f**	20 : 1	88	95
7	2-F-C_6H_4	**g**	20 : 1	85	94
8	4-F-C_6H_4	**h**	20 : 1	88	95
9	2-Cl-C_6H_4	**i**	20 : 1	88	95
10	3-Cl-C_6H_4	**j**	18 : 1	80	97
11	4-Cl-C_6H_4	**k**	20 : 1	80	96
12	3-Br-C_6H_4	**l**	15 : 1	78	97
13	4-CF_3O-C_6H_4	**m**	20 : 1	81	94
14	1-Naphthyl	**n**	20 : 1	93	95
15	2-Naphthyl	**o**	20 : 1	88	95
16	2-Furanyl	**p**	9 : 1	82	85
17	$PhCH_2CH_2$	**q**	10 : 1	80	90
18	^{i}Pr	**r**	11 : 1	25	91

[a] All reactions were performed on a 0.30 mmol scale (0.2 M) using nitroethane (20 equiv.) and a standard 45 h reaction time at −20 °C. [b] Measured by ^{1}H NMR. [c] Isolated yield. [d] Enantiomeric ratios were measured by HPLC using a chiral stationary phase. See ESI for details.

Table 3 Chiral proton-catalyzed Michael addition of aryl nitromethanes to β-nitrostyrene



Entry[a]	R	8	dr[b]	Yield[c] (%)	ee[d] (%)
1	C_6H_5	**a**	15 : 1	95	92
2	4-F-C_6H_4	**b**	8 : 1	98	92
3	4-Cl-C_6H_4	**c**	7 : 1	96	91
4	4-Me-C_6H_4	**d**	16 : 1	98	93
5	4-NO_2-C_6H_4	**e**	3 : 1	97	75/70

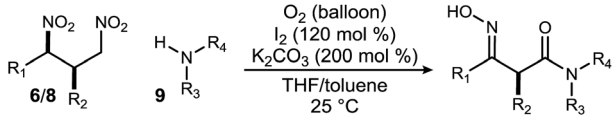
[a] All reactions were performed on a 0.10 mmol scale (0.05 M) using the aryl nitromethane (1 equiv.) and a standard 24 h reaction time. [b] dr after purification on silica gel column chromatography. [c] Isolated yield. [d] Enantiomeric ratios were measured by HPLC using a chiral stationary phase. See ESI for details.

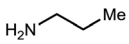
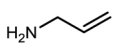
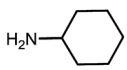
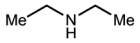
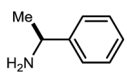
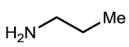
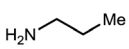
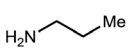
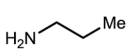
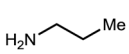
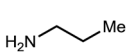
equivalents, delivering the addition product in 20 : 1 dr and 94% ee in 85% yield (Table 1, entry 11). Given the improved, but still similar selectivity of **3** relative to **1** and **2** might suggest that the latter diamines use their conformational mobility to expand the binding pocket while **3** is locked into the more productive and selective diamine conformation.

These conditions, optimized for **6a**, were then applied to additional β-nitro styrenes (Table 2). β-Nitrostyrenes bearing electron-donating substituents at different positions gave products in uniformly high yield and selectivity (Table 2, entries 2–5). 4-Me-substituted nitrostyrene converted to product with high yield (88%), dr (20 : 1), and 95% ee (Table 2, entry 6), as did halogen substituents (Table 2, entries 7–12), trifluoromethoxy (Table 2, entry 13), and large naphthyl substituents (Table 2, entries 14–15). The 2-furanyl derivative gave lower dr (9 : 1) and ee (85%) (Table 2, entry 16), similar to an aliphatic substituent (Table 2, entries 17–18).

As noted above, a limited number of nitroalkanes have been evaluated in additions of this type. Only fluorinated phenyl

Table 4 Umpolung amide synthesis using β-nitro nitroalkanes



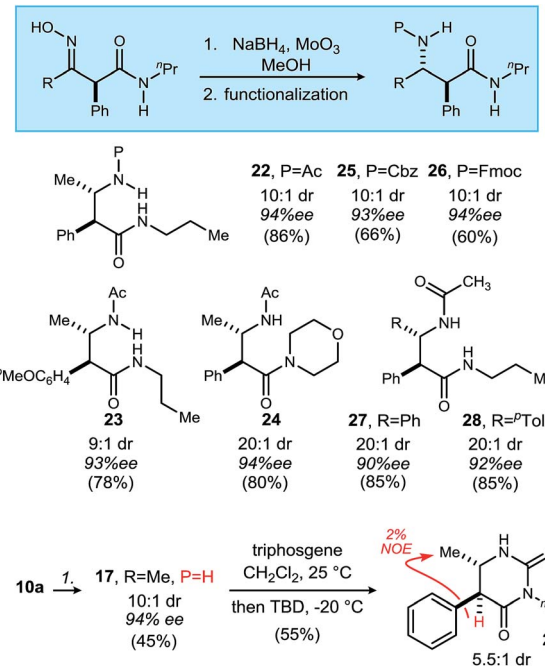
Entry[a]	R_1/R_2	6/8	ee (6/8)[b]	ee (amide)[b]	Amine	Amide	Yield[c] (%)
1	Me/Ph	**a**	94	94		**10a**	70
2	Me/Ph	**a**	94	94		**10b**	71
3	Me/Ph	**a**	94	94		**10c**	75
4	Me/Ph	**a**	94	94		**10d**	74
5	Me/Ph	**a**	94	94		**10e**	70
6	Me/Ph	**a**	94	94		**10f**	83
7	Me/Ph	**a**	94	94		**10g**	81
8	Me/Ph	**a**	94	94[d]		**10h**	67
9	Me/$BnCH_2$	**q**	90	90		**11**	82
10	Me/4-$MeOC_6H_4$	**d**	95	93		**12**	73
11	Me/3-Cl-C_6H_4	**j**	96	95		**13**	75
12	Ph/Ph	**a**[e]	92	90		**14**	75
13	4-Cl-C_6H_4/Ph	**c**[e]	91	89		**15**	78
14	4-Me-C_6H_4/Ph	**d**[e]	93	92		**16**	76

[a] All reactions were performed on a 0.1 mmol scale (0.1 M) using amine (2 equiv.) and standard 24 h reaction time at 25 °C. [b] Enantiomeric ratios were measured by HPLC using a chiral stationary phase. See ESI for details. [c] Isolated yield. [d] Diastereomeric excess, determined by ^{1}H NMR. [e] Reaction conditions: 0 °C for 2.5 d.

nitromethane derivatives are precedented in enantioselective conjugate additions to nitroalkenes, perhaps due to the acidity of the phenyl nitromethane adducts.[37] After optimization of the conditions (see ESI† for details), a single equivalent of the nucleophile was sufficient for the reaction at 24 h at −20 °C. Addition of phenyl nitromethane gave 15 : 1 dr and 92% ee of **8a** in high yield (Table 3, entry 1). An assortment of substituted aryl nitromethanes displayed unremarkable behavior (Table 3, entries 2–4). It was noted, however, that the dr observed in the crude reaction mixture (10 : 1) degraded to 8 : 1 after column chromatography for **8b**. The effect of silica gel exposure was similar in the case of **8c** (dr = 12 : 1 in crude reaction mixture), which changed to 7 : 1 after chromatography (96% yield, 91% ee for **8c**, Table 3, entry 3). Only in the case of the strongest electron withdrawing group was selectivity modest (Table 3, entry 5).

In order to complete the vision for a $\beta^{2,3}$-amino amide synthesis, and explore the use of β-functionalized donors in UmAS,[38] the one-pot strategy for conversion of primary nitroalkanes to amide was applied.[39] Use of I_2 as the halogen source was necessary to achieve the desired amide formation, presumably to generate the α-iodo-nitroalkane intermediate necessary for UmAS. Despite the formally oxidative conditions, the β-nitro group was concomitantly reduced to an oxime. Dinitroalkane **6a** converted to **10a** in 70% yield without change in ee (Table 4, entry 1), as expected due to the reversed polarity characteristic of C–N bond formation in UmAS. Nitroalkane **6a** was assayed using a range of primary mono- (Table 4, entries 2–4) and disubstituted amines (Table 4, entries 5–7), each recording unchanged ee. (*S*)-α-Methyl benzyl amine delivered amide **10h** in 67% yield without detectable epimerization (Table 4, entry 8). In these studies, α-aryl amides that might be particularly prone to epimerization under the basic conditions were examined (Table 4, entries 9–14). At room temperature degradation of ee was observed through post-reaction amide epimerization. Lowering the reaction temperature to 0 °C required a longer reaction time (2.5 d) but gave **14** in 90% ee (Table 4, entry 12). Similar was the case with substrates **8c** and **8d** whose products **15** and **16** were obtained in 78% and 76% yield with 89 and 92% ee respectively (Table 4, entries 13–14).

These observations suggest all but complete conservation of configuration during the UmAS step. Consistent with prior mechanistic studies, we hypothesize that the secondary nitro effects redox amidation by oxygen atom transfer to an α-aminomethyl radical (or cation) intermediate.[40,41] This mechanism would also suggest post-reaction epimerization. Both events are consistent with the outcomes detailed in Table 4, and the need to lower the reaction temperature for **8a–8d** to slow base-mediated racemization. The overall strategy for enantioselective β-amino amide synthesis was realized by diastereoselective reduction of the β-oximino-amide using molybdenum-modified borohydride as described Scheme 2.[42] These were later functionalized to their corresponding acyl, Cbz, and Fmoc derivatives (Scheme 2). Compound **10a** was reduced to $\beta^{2,3}$-amino amide **17** which was then converted to a dihydropyrimidinone,[43] which confirmed the relative stereochemical assignment (NOE).[44]



Scheme 2 Diastereoselective reduction of oximes to *anti*-$\beta^{2,3}$-amino amides, and subsequent derivatizations.

Conclusions

In conclusion, the sequencing of nitroalkane–nitroalkene conjugate addition/UmAS/reduction provides an enantioselective synthesis of *anti*-$\beta^{2,3}$-amino amides. Use of a new conformationally restricted BAM Brønsted acid-base catalyst delivered key intermediates with high enantiomeric excess. An unprecedented redox-UmAS delivered secondary and tertiary amides that can be reduced to their corresponding *anti*-β-amino amides. Retrosynthetically, this approach and protocol provides a solution to the unusual double umpolung involving an acyl retron – an inverted ketene – wherein both C–C and C–N bonds are formed with unusual polarities. These findings suggest that other β-chiral amides might be prepared by deploying the double umpolung strategy.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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