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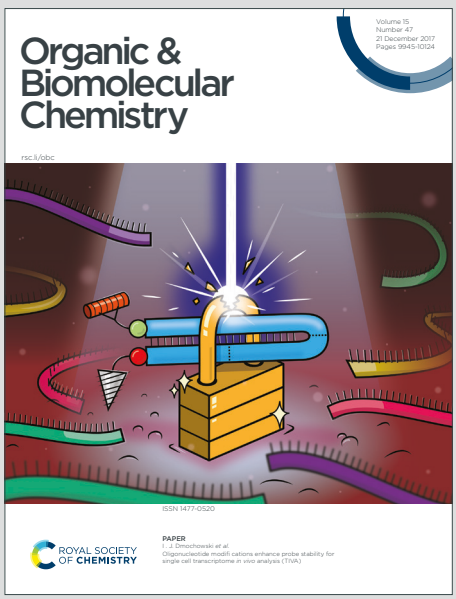

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ARTICLE

Stereoselective deconjugation of macrocyclic α,β-unsaturated esters by sequential amidation and olefin transposition: application to enantioselective phase-transfer catalysis

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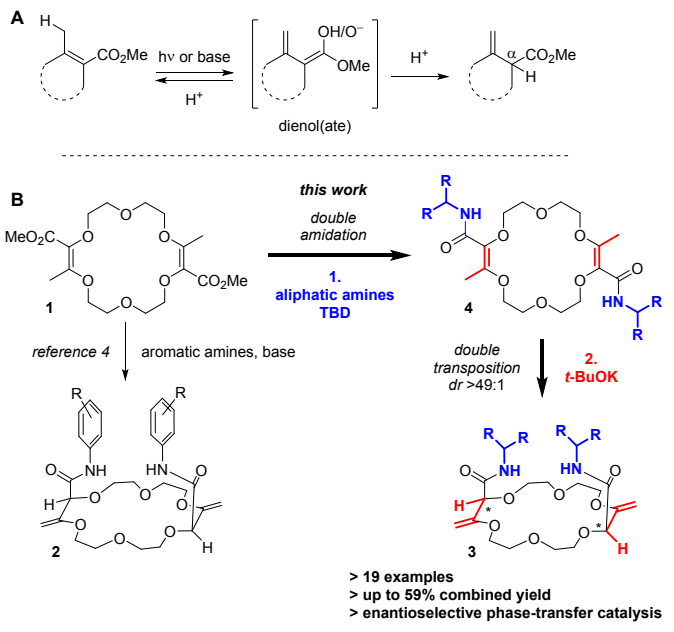
The stereoselective synthesis of chiral macrocycles bearing two aliphatic amide functional groups is reported. After the amidation mediated by TBD, a guanidine derivative, the olefin transposition step is performed with a slight excess of *t*-BuOK. The products are afforded in moderate to good combined yields (up to 59%) and with an excellent *syn* diastereoselectivity (*dr* > 49:1). Introducing enantiopure α-branched substituents was possible and it resulted in mixtures of diastereomers, which could be tested as phase-transfer catalysts using the formation of a phenylalanine analog as a test reaction (up to 43% *ee*). A clear matched-mismatched situation was observed in the two diastereomeric series.

Introduction

In unsaturated esters, olefin transposition from α,β to β,γ-positions is thermodynamically disfavored. To promote this deconjugation, various protocols are usually employed which utilize photochemical[1] or strongly basic[2] conditions to generate dienol(ate) intermediates (Scheme **1A**). Subsequent (enantioselective) protonation in α position leads to the β,γ-unsaturated esters.[3] In that context, our group recently reported the remote stereoselective deconjugations of bis-α,β-unsaturated macrocycle **1** in presence of an excess of aromatic amines and *t*-BuOK.[4] In a single step, chiral polyether macrocycles of type **2** are formed by a double tandem [amidation + olefin transposition] process (Scheme **1B**, left). Mechanistically, it is believed that the ester functions are first transformed into amide groups. Then, irreversible olefin transpositions occur to yield macrocycles **2** as single stereoisomers (racemic, *dr* > 49:1). Various applications have been developed for compounds **2**. In fact, such bis(aromatic) derivatives have been used as pH-independent nanosensor,[5] heteroditopic receptors for salts,[6] ratiometric luminescent or reversible chiroptical switches[7] and as circularly-polarized electrochemiluminescent emmiters.[8] Herein, the stereoselective synthesis of macrocycles of type **3** bearing two aliphatic amide functional groups is reported (Scheme **2B**, right). A two-step process is this time necessary. Amine additions are mediated by TBD (1,5,7-triaza bicyclo[4.4.0]dec-5-ene), a guanidine derivative that helps the formation of the α,β-unsaturated amide derivatives **4**. Then, olefin transpositions under basic conditions (*t*-BuOK) afford the corresponding chiral macrocycles **3** with high *syn* diastereoselectivity (*dr* > 49:1, yields up to 59%). Chiral enantiopure amines can be utilized and, after preparation of the resulting diastereomers, the macrocycles were used as phase-transfer catalysts. In the enantioselective alkylation of a protected glycine (*ee* up to 43%), a clear matched-mismatched situation is observed in the two diastereomeric series.



Scheme 1 Typical conditions for the deconjugation of α,β-unsaturated esters (**A**). Remote stereoselective synthesis of chiral polyether macrocycles (**B**, *syn* transposition, *dr* > 49:1).

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[c] *Electronic Supplementary Information (ESI) available: Experimental conditions, full characterizations, ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra of all new compounds (PDF); CSP-HPLC traces; CCDC 1923025, 1923026 and 1923027. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/x0xx00000x. In addition, the dataset for this article can be found at the following DOI: 10.26037/yareta:fp326563trgt3gp3l3ofsyfiem. It will be preserved for 10 years.*

Results and discussion

Initial attempts

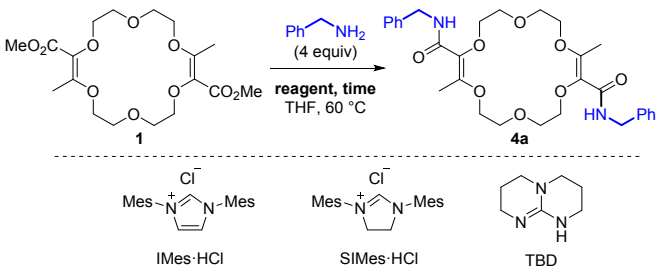
Previously, it was shown that methyl α-diazo-β-ketoester reacts with 1,4-dioxane under dirhodium catalysis in a formal [3+6+3+6] multi-component condensation. The process is mild and affords the resulting unsaturated macrocycle **1** on multi-gram scale (up to 20 grams) while using a low catalyst loading (0.01-0.001 mol%).[9,10] As mentioned earlier, compound **1** reacts with excesses of $ArNH_2$ and *t*-BuOK (> 3 equiv each) to yield unsaturated bis(aromatic) derivatives **2**. This reaction tolerates a large variety of aromatic amines.[4-8, 11] However, despite major efforts in the group, it was never possible to achieve the analogous **1** → **3** transformation with aliphatic amines instead of anilines. Of the two consecutive steps, it was clearly the first one that was problematic under the previous conditions. Care was thus taken to decouple the two steps of the process and perform the amide formation first, prior to the olefin transposition.

Optimization of the two-step process

For the transformation of macrocycle **1** into the corresponding α,β-unsaturated bis(aliphatic) macrocycles **4**, mild conditions of amidation were looked for. With regular non-activated esters,[12] it is required to use additives to promote the reaction such as (*Lewis*) acids,[13] bases,[14] metal salts and complexes,[15] enzymes[16] or organocatalysts.[17] Many such conditions were tested using macrocycle **1** and benzyl amine as model substrate and reagent respectively (Table **1**). Heating the macrocycle and the amine in THF at 60 °C did not provoke a conversion (entry 1). Strongly basic conditions, *t*-BuOK or *n*-BuLi, led either to a total degradation or a partial 30% conversion of macrocycle **1** respectively (entries 2-3). Lewis acids ($Yb(OTf)_3$, $BF_3{\cdot}OEt_2$) and N-heterocyclic carbenes were also tested (entries 4-10). In many instances, a lack of reactivity was observed. Otherwise, it was a full degradation of **1**. Previously, for the transformation of esters into amides, Mioskowski and collaborators used 1,5,7-triazabicyclo [4.4.0]dec-5-ene (TBD) as catalyst.[17g, 18, 19, 20] Using 20 mol% of this cyclic guanidine base, an amidation could not be observed (entry 11).[21] However, with a stoichiometric amount of it (2 equiv), macrocycle **4a** was obtained in a satisfactory yield (47%) after 4 hours of reaction and a simple filtration (entry 12). Increasing the reaction time to 15 hours afforded **4a** in 75% yield (entry 10). The structure of **4a** was confirmed by NMR spectroscopy and X-ray diffraction analysis (see Figure 1A).

Next, the olefin transposition of compound **4a** was considered under basic conditions.[4] After optimization (Table S1), it was found that the combination of *t*-BuOK (2.2 equiv) and 1,4-dioxane as solvent afforded the best conditions.[22] Macrocycle **3a** was isolated in good yield (65%, Scheme 2) as a single diastereoisomer (*dr* >49:1, ^1H NMR monitoring). Once, again, an effective remote stereoselectivity is noticed in this type of process.[4] The relative configuration of **3a** was determined by the solid state structure of the sodium BAr_F (tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) adduct (Figure 1B). Only the chiral *cis*-diastereoisomer (racemic) is formed during the reaction and traces of the achiral (*meso, trans*) stereoisomer could not be detected. This result indicates that the mechanism for the olefin transposition(s) is similar to that previously reported;[4] the potassium ion acts as a template and helps relay the second reprotonation on the same prochiral face than the first one.

Table 1 Amidation of **1**: optimization



Entry	Reagent (equiv)	Time (h)	Isolated yield
1	-	15	no conv.
2[a]	*t*-BuOK (4)	3	degradation
3[a]	*n*-BuLi (4)	3	< 30% conv.[b]
4	$Yb(OTf)_3$ (0.1)	15	no conv.
5	$Yb(OTf)_3$ (2)	15	no conv.
6	$BF_3{\cdot}OEt_2$ (0.2)	15	no conv.
7	$BF_3{\cdot}OEt_2$ (2)	15	no conv.
8	IMes·HCl/ *t*-BuOK (0.05)	15	no conv.
9	IMes·HCl/ *t*-BuOK (2)	15	degradation
10	SIMes·HCl/ *t*-BuOK (2)	15	degradation
11	TBD (0.2)	15	no conv.
12	TBD (2)	4	47%
13	TBD (2)	15	75%

[a] -100 °C (1 min), then 25 °C instead of 60 °C; [b] the isolation of **4a** was attempted but failed; Abbreviations: Mes = mesityl.

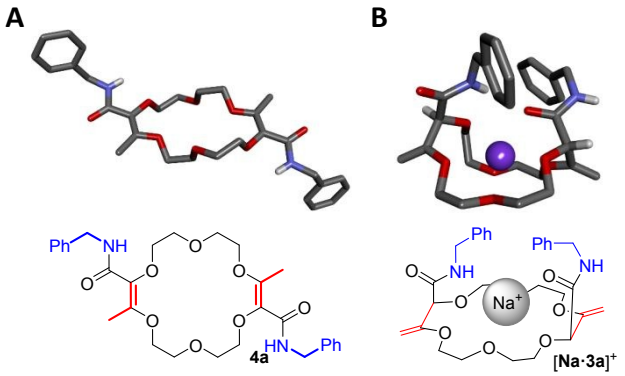
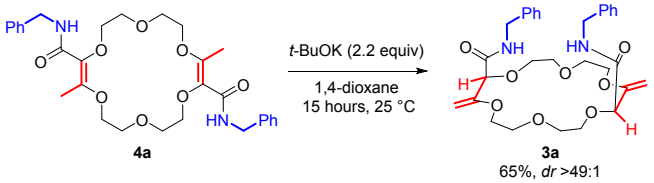


Fig. 1 Stick view of the crystal structure of **4a** and [Na·**3a**][BAr_F] (BAr_F anion and hydrogens atoms are hidden for clarity).



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Scheme 2 Base-induced olefin transposition of **4a** to form **3a**.

In solution, compounds **3** differ from the bis-anilide derivatives **2**. In fact, in terms of simple host-guest chemistry, it had been previously observed that a water molecule is usually complexed inside the cavity of macrocycles **2**.[4] Herein, in chloroform-*d*, there is little of interaction of **3a** with water as monitored by ^{1}H NMR spectroscopy at different concentrations (8-116 mM, see ESI). In comparison with the aniline series (compounds **2**), the proton signals of the amide groups or of the water molecule are only weakly perturbed.

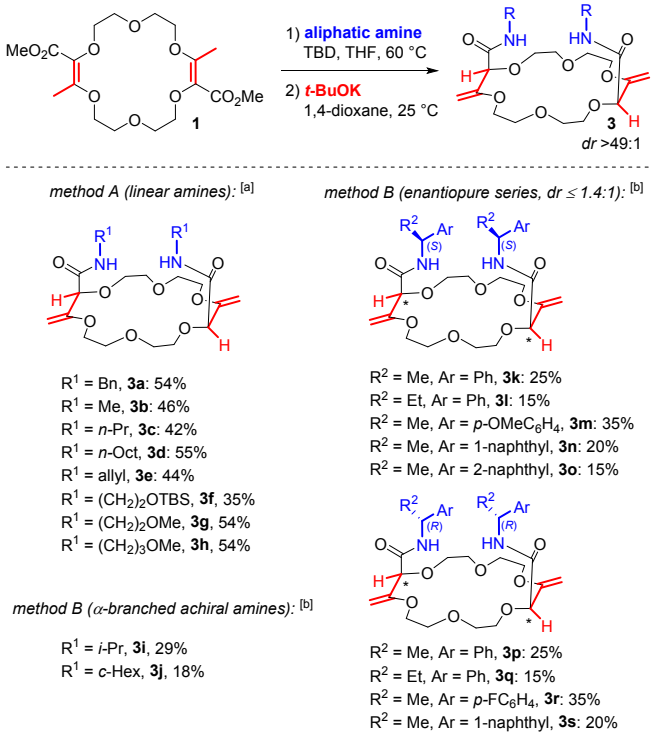
2-Step process: Scope and (lack of) asymmetric induction with enantiopure amines

With the optimal conditions for the amidation and the olefin transposition in hand, various linear and α-branched amines were introduced. In Table 2, the yields are reported for the two steps. In general, with linear primary amines, moderate to good combined yields were obtained (35-55%); the nature of the side chains has little influence on the outcome. For the standard reaction, macrocycle **3a** was obtained in 54% overall yield. Methyl, propyl, octyl and allyl substituted derivatives **3b** to **3e** were obtained in similar yields (42%-55%). Silyl or methyl protected amino alcohols were used and afforded macrocycles **3f** to **3h** in 35% to 54% yield.[23]

However, when the introduction of α-branched amines was investigated under the above conditions, only poor conversions were observed for the first amidation step; the sterically-hindered amines being much less reactive. It was necessary to increase both the amount of TBD (from 2 to 4 equiv) and the reaction time (15 hours to 10 days) to reach full conversion of **1**. Then, upon transposition with *t*-BuOK, macrocycles **3i** (*i*-Pr) and **3j** (*c*-Hex) were obtained in moderate combined yields (29% and 18% respectively). Similarly, with enantiopure α-alkyl substituted benzyl or methylnaphthyl amines, we could isolate the corresponding macrocycles **3k** to **3s** (15-35%). In all these reactions, the critical step in terms of yield is not the transposition but the amidation. In fact, a slow competitive degradation of starting macrocycle **1** occurs during the amidation that disfavors the overall process.[24]

Finally, care was taken to study the stereochemical outcome of the reaction in the presence of enantiopure α-branched amines.[25] Satisfactorily, the double transposition still occurs with a *syn* stereoselectivity but it leads, this time, to two different products. Indeed, the enantiopure amine residues exert little influence on the newly created stereogenic centers inside the macrocyclic skeleton and two diastereoisomers are formed. For instance, with (*S*)-phenylethylamine, product **3k** exists in two different (*S*,*S*,*S*,*S*) and (*S*,*R*,*R*,*S*) configurations with a low overall stereoselectivity (*dr* 1.3:1).[26] Several other amines were tested and the selectivity has remained low in all cases (*dr* ≤ 1.4:1). In Table 2, the yields are given for the two steps and both diastereoisomers together; the stereoisomers were separated in only in one instance (see next paragraph).

Table 2 Combined yields (two steps) of macrocycles **3a**-**3s**



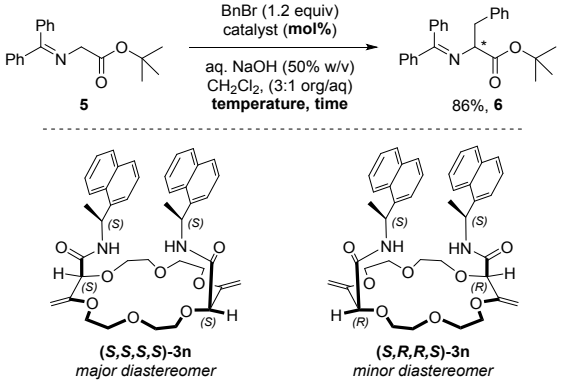
[a] Method A: **1** (0.25 mmol), linear amine (4.0 equiv), TBD (2.0 equiv), THF, 60 °C, 15 hours; then *t*-BuOK (2.2 equiv), dioxane, 25 °C, 15 hours. [b] Method B: **1** (0.25 mmol), α-branched amine (4.0 equiv), TBD (4.0 equiv), THF, 60 °C, 10 days; then *t*-BuOK (2.2 equiv), dioxane, 25 °C, 15 hours. Macrocycles **3k** to **3s** are obtained as mixtures of diastereoisomers (1:1 ≤ *dr* ≤ 1.4:1, see ESI).

Application: Enantioselective phase-transfer catalysis

Crown ethers, thanks to their ability to complex alkali metal salts and render them soluble in both polar and apolar solutions, are efficient phase-transfer catalysts (PTCs). Several chiral non-racemic versions of these derivatives have been developed and applied in various enantioselective reactions such as alkylations, 1,4-additions or oxidations.[27] It was then logical to test compounds **3k** to **3s** bearing α-branched enantiopure substituents as PTCs. We selected the alkylation of protected glycine **5** with benzyl bromide which affords chiral phenylalanine derivative **6** as product as benchmark; this reaction occurring only in the presence of catalysts (Table 3, entry 1).[28] The different macrocycles were reacted under conditions that are standard for phase-transfer catalysis with chiral crown ethers (Tables S2-S5). Overall and not surprisingly, it was found that sodium and potassium salts afforded the best conversions (Tables S3). A rather large screening of solvents was also performed and CH_2Cl_2 was most favorable followed by 1,1-dichloroethane and 1,1,1-trichloroethane; similar *ee* values being however observed (Tables S5). With derivative **3k** as catalyst (5 mol%, Table 3, entry 2), amino acid (+)-**6** was obtained in good yield (86%) and low enantioselectivity (17% *ee*). The increase of catalyst loading to 10 mol% improved slightly the enantiomeric excess to 21% (entry 3). With toluene as solvent, longer reaction time, lower enantioselectivity and a reversal of the stereoinduction in favor of the antipodal

enantiomer (–)-**6** were observed (entry 4). Using macrocycle **3p** (with an inverted configuration on the amide side chain), analogous results to **3k** were obtained in favor of the levorotatory enantiomer. It was then shown that 1-naphthyl derivative **3n** is the most efficient of the series (see ESI). Using **3n** as PTC (10 mol%, *dr* 1.4:1) at 25 °C, amino acid (+)-**6** was obtained in good yield (86%) and moderate enantioselectivity (32% *ee*) (Table 3, entry 6). Decreasing the temperature to 10 °C improved slightly the enantiomeric excess (39% *ee*, entry 7). The two diastereoisomers of **3n**, namely (*S*,*S*,*S*,*S*)-**3n** (major) and (*S*,*R*,*R*,*S*)-**3n** (minor), could be separated by column chromatography (SiO_2, CH_2Cl_2/MeOH gradient) and used independently in the phase-transfer reaction. The configuration of (*S*,*S*,*S*,*S*)-**3n** was ascertained by the X-ray structural analysis of the $NaBAr_F$ salt. With (*S*,*S*,*S*,*S*)-**3n**, the dextrorotatory enantiomer of **6** was again favored with a slightly improved enantiomeric excess (43% *ee*, entry 8). Higher catalyst loading (20 mol%) or temperature decrease (0 °C) did not lead to a larger enantioinduction (entries 9 and 10). Interestingly, using minor diastereoisomer (*S*,*R*,*R*,*S*)-**3n** and after a longer reaction time (48 hours), the antipodal enantiomer (–)-**6** was obtained in 86% yield and only a 13% *ee* value (entry 11). The difference of reactivity and selectivity between the two diastereoisomers of **3n** illustrates thus a clear matched-mismatched situation in the enantioselective alkylation of glycine **5**.

Table 3 Asymmetric phase-transfer catalysis with **3n** [a]



Entry	Catalyst (mol%)	Temp (°C)	Time (h)	*ee* (%)
1	- (blank)	25	15	-[b]
2	**3k** (5)	25	15	17
3	**3k** (10)	25	15	21
4[c]	**3k** (5)	25	96	-12
5	**3p** (5)	25	15	-17
6	**3n** (10)	25	15	32
7	**3n** (10)	10	15	39
8	(*S*,*S*,*S*,*S*)-**3n** (10)	10	15	43
9	(*S*,*S*,*S*,*S*)-**3n** (20)	10	15	42
10	(*S*,*S*,*S*,*S*)-**3n** (10)	0	15	42
11	(*S*,*R*,*R*,*S*)-**3n** (10)	10	48	-13

[a] For all catalyzed reactions, yields are consistent in the range of 85-87%. [b] No conversion of **5**. [c] In toluene instead of CH_2Cl_2.

Conclusion

Starting from readily prepared unsaturated macrocyclic precursor **1**, chiral crown ethers bearing two aliphatic amide functional groups were synthetized. It was necessary to separate the amidation (mediated by TBD) and the olefin transposition step (induced by a slight excess of *t*-BuOK). The products were afforded in moderate to good combined yields (up to 59%) and with an excellent *syn* diastereoselectivity (*dr* > 49:1). Introducing enantiopure α-branched substituents was possible and resulted in mixtures of diastereomers, which could be tested as phase-transfer catalysts using the formation of enantioenriched phenylalanine analogs as a benchmark (up to 43% *ee*). In this reaction, a clear matched-mismatched situation was observed in the two diastereomeric series.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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23 The isomerization does not proceed with unprotected alcohol functional groups. See ESI.
24 Full conversion of **1** is always reached. The degradation products could unfortunately neither be isolated nor identified.
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