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# Enzymatic Desymmetrization of Prochiral 2-Substituted-1,3-Diamines: Preparation of Valuable Nitrogenated Compounds

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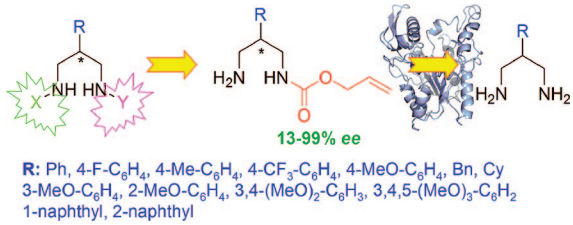


A wide range of prochiral 1,3-diamines were first efficiently synthesized and subsequently desymmetrized by using lipase from *Pseudomonas cepacia* as catalyst and diallyl carbonate as alkoxycarbonylating agent. In all cases, the amino carbamates of *R*-configuration were recovered. Final selective cleavage of the *N*-allyloxycarbonyl moiety was carried out under mild reaction conditions, which demonstrates the high versatility and potential of this chemoenzymatic route as a source of intermediates in the synthesis of related optically active nitrogenated derivatives.

Optically active diamines are central to chemistry. They are bidentate ligands able to form chiral complexes and supramolecular entities and confer them with enantioselectivity in the different asymmetric transformations in which they participate.[1] Moreover, they can be used as linkers in solid phase synthesis, surface and bioconjugate chemistries, as monomers for the preparation of chiral polymers,[2] and as building blocks in the synthesis of pharmaceuticals and agrochemicals.[3] Among all the classes of diamines described in the literature, $C_2$-symmetrical 1,2-diamines have received, by far, most of the attention.[4] The reason is the excellent asymmetric induction properties they show, usually, when complexed with transition metals.[5] However, increasing efforts in the development of new classes of diamine ligands are being reported in the literature.[1b] Easy and versatile routes to new optically active diamine cores are required since new ligands would lead to significant different catalytic activities.

Enzymes are now recognized as efficient catalysts in the preparation of chiral compounds.[6] The mild reaction conditions under which they operate, their selectivity and substrate promiscuity, and the recent advances in protein, medium, and substrate engineering have accounted for this fact.[7] For those cases in which the substrate is prochiral or *meso*, it can be enantioselectively desymmetrized with a maximum theoretical yield of 100%, thus avoiding the typical substrate "waste" of kinetic resolutions. Enantioselective enzymatic desymmetrizations have been successfully applied to the synthesis of many valuable compounds.[8] However, little attention has been paid to prochiral or *meso* diamines.[9] We have recently reported the first enantioselective methodology to prepare optically active 2-monosubstituted propane-1,3-diamine derivatives by using lipase from *Pseudomonas cepacia* (PCL) as catalyst and prochiral 2-substituted propane-1,3-diamines as substrates,[10] compounds for which even the regioselective monofunctionalization is a challenging task.[11] Here we report on the synthesis and subsequent PCL-catalyzed desymmetrization of a wide set of 2-substituted propan-1,3-diamines using readily available commercial compounds as starting materials. The analysis of the resulting structure−enantioselectivity profile shows the type of compounds that can be successfully obtained by means of this methodology.

First, substitution at the 4-position of the phenyl ring was explored by adding to the previously described series of amines (**8a**−**d**)[10] bulkier substituents such as the trifluoromethyl (**8e**) or the phenyl (**8f**) moieties. Next, the methoxy group was selected as the probe to examine the preferred position of the phenyl ring for monosubstitution (**8g**,**h**) and polysubstitution (**8i**,**j**). The synthetic route described for the enzymatic desym-

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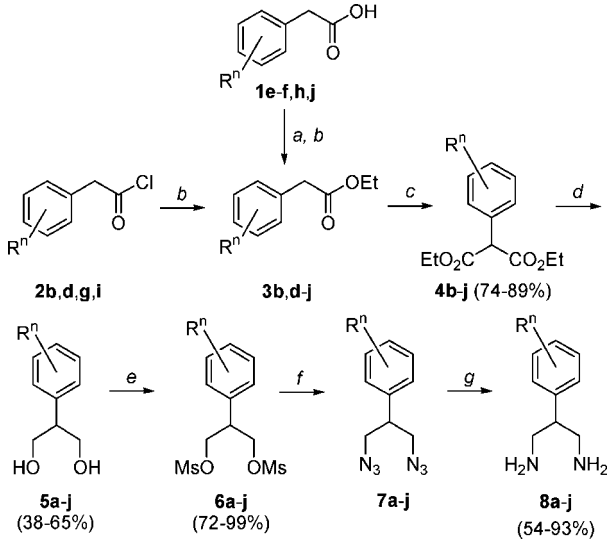
**SCHEME 1. Chemical Synthesis of Diamines 8a−j**[a]



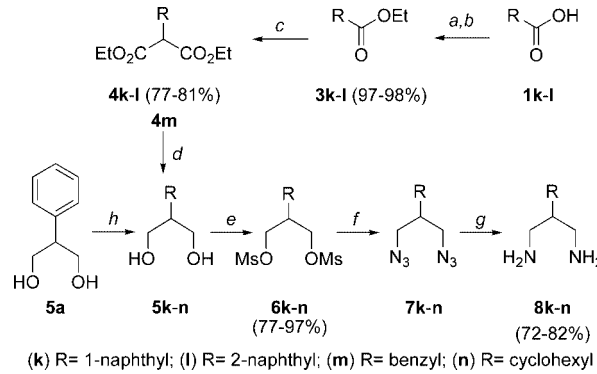

[a] Reaction conditions: (a) ClCOCOCl, DMF, THF, 0 °C; (b) EtOH, rt; (c) 1. $(Me_3Si)_2NLi$, THF, −78 °C; 2. EtOCOCN, rt; (d) $LiAlH_4$, $Et_2O$, 0 °C to rt; (e) MsCl, pyridine, $CH_2Cl_2$ or THF, 0 °C to rt; (f) $NaN_3$, DMF, 55 °C; (g) $H_2$, Pd−C, MeOH, rt.

metrization of prochiral propane-1,3-diamines **8a**−**d**[10] was also applied to the preparation of substrates **8e**−**j** (Scheme 1). Suitable commercially available compounds (carboxylic acids or acid chlorides) were used as starting materials to obtain prochiral 2-arylpropane-1,3-diazides (**7a**−**j**) via preparation of the corresponding diols (**5a**−**j**) and subsequent transformation into the corresponding mesylates (**6a**−**j**), which are suitable substrates for the $S_N2$ substitution with sodium azide.[12] The diazides were finally transformed into the desired diamines by means of a catalytic hydrogenation. Such a clean step with an easy workup before the enzymatic processes is mandatory due to the inherent instability of 1,3-diamines under atmospheric conditions.

Acid chlorides (**2b**,**d**−**j**) were subjected to esterification with ethanol at room temperature and led to the corresponding esters (**3b**,**d**−**j**), which were further transformed into malonates **4b**,**d**−**j** using lithium bis(trimethylsilyl)amide and ethyl cyanoformate, prior to the reduction of the diester groups with lithium aluminum hydride. The so-obtained diols (**5b**−**j**)[13] were next protected with mesyl chloride and pyridine using dichloromethane as solvent. However, for **5f**, THF was employed as solvent due to the poor solubility of this diol in dichloromethane. Nucleophilic substitution of the resulting mesylated diols (**6a**−**j**) with sodium azide at 55 °C in dry DMF led to diazides **7a**−**j**,[14] which were hydrogenated in the presence of Pd−C in MeOH to obtain after just a filtration through Celite the prochiral diamines **8a**−**j** in good overall yields.

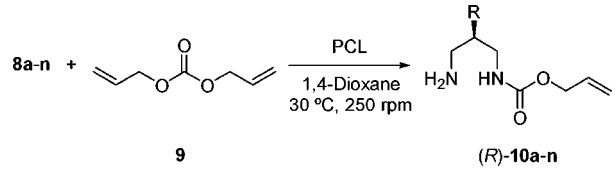
Other structurally more different diamines were also prepared (Scheme 2). Thus, the effect of the presence of fused aromatic rings (a special case of polysubstitution) was explored by introduction of the 1- and 2-naphthyl groups (**8k**,**l**). Finally, the

**SCHEME 2. Chemical Synthesis of Diamines 8k−n**[a]




[a] Reaction conditions: (a) ClCOCOCl, DMF, THF, 0 °C; (b) EtOH, rt; (c) 1. $(Me_3Si)_2NLi$, THF, −78 °C; 2. EtOCOCN, rt; (d) $LiAlH_4$, $Et_2O$, 0 °C to rt; (e) MsCl, pyridine, $CH_2Cl_2$ or THF, 0 °C to rt; (f) $NaN_3$, DMF, 55 °C; (g) $H_2$, Pd−C, MeOH, rt; (h) $H_2$, $PtO_2$, AcOH, rt (55%).

**SCHEME 3. Enzymatic Desymmetrization of Diamines 8a−n**




role played by the aromaticity and the effect of the distance between the chiral center and the phenyl ring in enantiorecognition were studied by means of the desymmetrization of amines **8m** and **8n**, respectively. For the synthesis of diamines **8k**−**n**, carboxylic acids **1k**,**l**, malonate **4m**, and diol **5a** were used as starting materials (Scheme 2). The diol intermediates **5k**−**n** were obtained through either reduction of the ester groups of the malonates **4k**−**m** using lithium aluminum hydride or by catalytic hydrogenation of the phenyl ring of diol **5a** to yield the cyclohexyl moiety (**5n**). The subsequent steps leading to diamines **8k**−**n** are identical to those described in Scheme 1 for diamines **8a**−**j**. In this way, substrates **8k**−**n** were prepared in good overall yields and excellent purities.

The PCL-catalyzed alkoxycarbonylation of prochiral diamines **8a**−**n** afforded, in all cases, the amino carbamates **10a**−**n** of *R*-configuration as unique compounds (Scheme 3). Reaction in absence of enzyme did not occur in any extension, and for the majority of cases, good overall yields (ca. 70%) and high enantiomeric excesses (close to or higher than 90%) were attained in the enzymatic process after 72 h (Table 1). A more detailed inspection of these results affords interesting relationships between the observed enantioselectivities and reactivities and the structure of the 2-substituent present in the propane-1,3-diamino core. Considering 2-phenylpropane-1,3-diamine (entry 1, **8a**) as the reference substrate, one of the most striking features of the series summarized in Table 1 is the key role played by aromaticity in the enzymatic enantiorecognition mechanism of diamines bearing cyclic 2-substituents. Thus, the exchange of the 2-phenyl group (**8a**) by a cyclohexyl one (**8n**) has a dramatic effect on enantioselectivity (compare entries 1 and 14). On the other hand, it is also worth noticing that the two least reactive diamines (entries 8 and 11; **8h**,**k**) are also the aromatic ones that show the lowest enantiomeric excesses. Then, it seems logical to hypothesize that the observed differences in reaction rate and enantioselectivity of these diamines

(12) Katz, C. E.; Aube, J. *J. Am. Chem. Soc.* **2003**, *125*, 13948–13949.
(13) Diol **5a** was commercially available.
(14) In all cases, diamines **8e**−**j** were isolated with yields up to 75% except for compound **8e** (54%). In this case, elimination byproducts were detected in the reaction crude of the nucleophilic substitution with sodium azide.

**TABLE 1. Enzymatic Desymmetrization of Prochiral Diamines 8a−n**

| entry | substrate | R | yield (%)[a] | ee (%)[b] |
|---|---|---|---|---|
| 1 | **8a** | phenyl | 73 | >99 |
| 2 | **8b** | 4-fluorophenyl | 70 | 88 |
| 3 | **8c** | 4-methylphenyl | 72 | 96 |
| 4 | **8d** | 4-methoxyphenyl | 68 | 86 |
| 5 | **8e** | 4-trifluoromethylphenyl | 65 | 91 |
| 6 | **8f** | 4-biphenyl | 62 | 64 |
| 7 | **8g** | 3-methoxyphenyl | 62 | 91 |
| 8 | **8h** | 2-methoxyphenyl | 39 | 60 |
| 9 | **8i** | 3,4-dimethoxyphenyl | 65 | 79 |
| 10 | **8j** | 3,4,5-trimethoxyphenyl | 64 | 70 |
| 11 | **8k** | 1-naphthyl | 35 | 13 |
| 12 | **8l** | 2-naphthyl | 61 | 87 |
| 13 | **8m** | benzyl | 70 | 69 |
| 14 | **8n** | cyclohexyl | 72 | 58 |

[a] Isolated yields after flash chromatography. [b] Determined by HPLC after adequate derivatization (see Supporting Information).

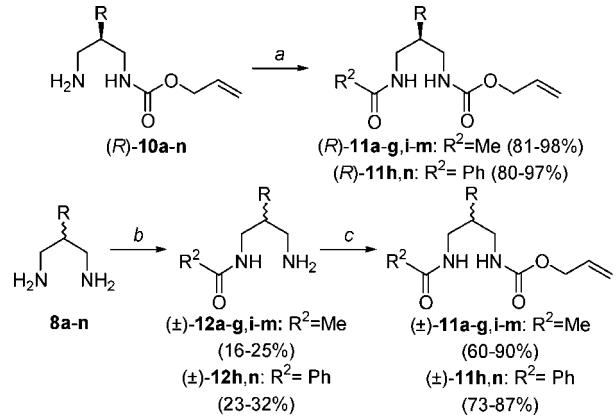
as compared to **8a** are mainly due to differences in the reactivity of the fast-reacting orientation of these diamines (pro *R*) in the active site of PCL.

Structural comparison of the substituents of amines **8h** and **8k** reveals that, interestingly, the common feature between them is that the phenyl group is substituted at the *ortho* position. Due to the different electronic properties of the two *ortho*-substituents considered (methoxy and a fused aromatic ring), it can be concluded that either the active site of the enzyme has no space to accommodate any substituent in that position or the *ortho*-substitution of a phenyl group disrupts the conformation adopted by the pro-*R* orientation of these substrates in the active site of the enzyme due to intramolecular instability.

Diamines **8f**, **8j**, and **8m** (entries 6, 10, and 13) also show no synthetically useful enantioselectivities, but, conversely to the case of substrates **8h**,**k** (entries 8 and 11), here the reaction rate is of similar magnitude to the one displayed by the reference compound (entry 1, **8a**). Accordingly, we argued that, in this case, the reactivity of the slow-reacting orientation (pro-*S*) increases considerably upon substitution.

As it can be seen in Table 1, **8a** (entry 1) is the best substrate for PCL as no other diamine can match the enantiomeric excess of (*R*)-**10a**. Nevertheless, the biotransformation also affords synthetically useful enantioselectivities in many other cases. In particular, substitution of the phenyl ring in the *para* position always leads to a good enantiodiscrimination (entries 2−5, **8b**−**e**) with the sole exception of **8f** (entry 6). The consideration of electronic effects in terms of electron-donor or electron-withdrawing characters did not afford any plausible explanation for the different enantioselectivity displayed by **8f** as compared to **8b**−**e**. That is why we believe that this difference is more likely due to differences in the size of the substituents attached to the phenyl ring of these compounds. Thus, big substituents at the *para* position (i.e., phenyl, **8f**) would abolish enantioselectivity while small to medium-sized ones would be tolerated by the enzyme. This could in turn mean, from a molecular point of view, again a pocket of limited size in the active site of the enzyme or simply solvation effects which would affect enantioselectivity the more, the bigger the substituent were. It is also worth mentioning that substitution at the *meta* position seems to have the same effect as substitution at the *para* position, as the enantioselectivities obtained for substrates **8d** and **8g** (entries 4 and 7) are very similar. Moreover, the effect of the "tolerated" substitution on the enantioselectivity displayed by the enzyme

**SCHEME 4. Preparation of Optically Active and Racemic Amido Carbamates 11a−n for Enantiomeric Excess Analysis[a]**




[a] Reaction conditions: (a) AcCl, $Ac_2O$ or PhCOCl, $Et_3N$, $CH_2Cl_2$, rt; (b) $Ac_2O$ or $Bz_2O$, $CH_2Cl_2$, rt; (c) allyl chloroformate, pyridine, $CH_2Cl_2$, rt.

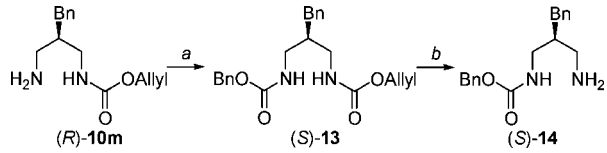
as compared to the reference substrate **8a** appears to be additive. Thus, the *para*-substitution (**8b**−**e**, entries 2−5) slightly lowers the enantioselectivity; this decrease becomes bigger for the disubstituted diamine **8i** (entry 9), but the worst scenario is for the trisubstituted diamine **8j** (entry 10), which lacks synthetic usefulness.

The reference compounds [(±)-**11a**−**n**] were directly prepared from the prochiral diamines **8a**−**n** by a nonenzymatic monoacylation with acetic or benzoic anhydride followed by alkoxycarbonylation with allyl chloroformate in the presence of pyridine (Scheme 4). In the monoacylation processes, portions of the corresponding anhydride were added at intervals of 15 min. This was meant to keep a low concentration of the acylating agent in the reaction medium, thus minimizing the amount of diacylated product. Nevertheless, both mono- and diamides were observed and separated through *flash* chromatography. The racemic monoamides (±)-**12a**−**n** were obtained in low yields (16−32%), but the amounts of products obtained were enough to carry out the subsequent nonenzymatic alkoxycarbonylation, affording the corresponding amido carbamates [(±)-**11a**−**n**] in high yields (66−85%). Adequate chiral HPLC conditions were optimized in order to find a reliable method for the measurement of the enantiomeric excesses of the amino carbamates (*R*)-**10a**−**n** obtained in the enzymatic desymmetrizations. Thus, the free amino groups of products (*R*)-**10a**−**n** were acylated with acetic anhydride, acetyl, or benzoyl chloride in the presence of triethylamine in dichloromethane,[15] yielding the amido carbamates (*R*)-**11a**−**n** (80−98%). The *R*-configuration for the amino carbamate **10c** was demonstrated by X-ray diffraction analysis of the amido carbamate obtained by its reaction with (*S*)-(+)-α-methoxy-α-trifluoromethylphenyl acetic acid chloride.[10] The *R*-configuration was also assigned to amino carbamates **10a**,**b**,**d**−**n** on the basis of their structural similarity to **10c**, the comparison of the retention times of the peaks for the major and minor enantiomers in the HPLC analyses, and the enantiopreference shown by lipases toward isosteric 2-substituted propan-1,3-diols.[16]

For the particular case of (−)-**10m**, the closely related carbamate (−)-**14** had been previously assigned the *S*-config-

(15) Monoacetylation of compound **8h** was also attempted, but we were not able to separate the enantiomers of the final product under any chiral HPLC conditions, so we decided to prepare **12h** using benzoic anhydride instead of acetic anhydride.

**SCHEME 5. Assignment of the Absolute Configuration of (*R*)-10m**[a]




[a] Reaction conditions: (a) CbzCl, pyridine, $CH_2Cl_2$, rt (92%); (b) 1,3-dimethylbarbituric acid, $Pd(OAc)_2$, $PPh_3$, $CH_2Cl_2$, 35 °C (70%).

uration.[17] Thus, we decided to prepare it starting from (−)-**10m** in order to confirm the *R*-configuration assigned to it. Inspection of both compounds reveals that the transformation of (−)-**10m** into (−)-**12m** requires an inversion of the configuration of the chiral center and the exchange of the allyl by a benzyl group in the carbamate moiety. This can be achieved by alkoxycarbonylation of the unreacted amino group with benzyloxycarbonyl chloride followed by selective deprotection of the allyl carbamate (Scheme 5). The first step was carried out as described previously for the preparation of the racemic amino carbamates using benzyl chloroformate to form (*S*)-**13**, and for the deprotection of the allyl carbamate, 1,3-dimethylbarbituric acid and in situ generated $Pd(PPh_3)_4$ were used. The corresponding (*S*)-(−)-**14** was obtained in 65% overall yield, and its optical rotation did confirm the *R*-configuration already assigned to (*R*)-(−)-**10m**. It must be highlighted that migration of the allyl carbonate was not detected in any extension. Moreover, this simple chemical transformation demonstrates the importance of the chemoenzymatic route described herein to prepare optically active nitrogenated compounds: the optically active amino carbamates obtained from the enzymatic reaction can be subsequently protected and deprotected at wish at any of the two nitrogens of the propan-1,3-diamine core, thus leading to both enantiomeric series of interesting chiral building blocks or ligands, not easily accessible through other synthetic routes.

In summary, a general and straightforward chemoenzymatic methodology has been described for the synthesis of optically active amino carbamates in high yields and enantiomeric excesses. The key step is the PCL-catalyzed desymmetrization of prochiral 2-substituted propane-1,3-diamines, which were prepared from readily available starting materials, such as carboxylic acids, acid chlorides, malonates, or diols. The enantioselectivity and reactivity displayed by the lipase are highly dependent on the nature of the 2-substituent bonded to the propan-1,3-diamine core. Final selective cleavage of the allyloxycarbonyl moiety has been also carried out, which evidence the versatility and potential of this route as both nitrogen atoms can be functionalized at wish by means of a protection−deprotection strategy.

(16) (a) Guanti, G.; Banfi, L.; Riva, R. *Tetrahedron: Asymmetry* **1994**, *5*, 9–12. (b) Tombo, G. M. R.; Schär, H.-P.; Fernández i Busquets, X.; Ghisalba, O. *Tetrahedron Lett.* **1986**, *27*, 5707–5710.

(17) $[\alpha]_D = -15.78$ (*c* 1.56, $CHCl_3$) described in ref 9b, for enantiomerically pure (*S*)-**12m**, meanwhile $[\alpha]_D = -11.6$ (*c* 1.5, $CHCl_3$) for 70% ee found in our experimental conditions that has been obtained from (*R*)-**10m**.

## Experimental Section

**Typical Experimental Procedure for the Enzymatic Desymmetrizacion of Diamines 8e−n.** To a suspension of the corresponding diamine (**8e−n**) (0.83 mmol) and PCL (250 mg) in dry 1,4-dioxane (8.5 mL) was added diallyl carbonate (120 μL, 0.83 mmol) under nitrogen atmosphere, and the mixture was shaken at 30 °C and 250 rpm, following the progress of the reaction by TLC analysis. The reaction was stopped after 72 h, and the enzyme was filtered off and washed with MeOH (3 × 10 mL). The solvent was evaporated under reduced pressure, and the resulting crude was purified by flash chromatography (MeOH/EtOAc), affording the corresponding monocarbamates (*R*)-**10e−n** as colorless oils.

**(*S*)-Allyl benzyl (2-benzylpropane-1,3-diyl)biscarbamate (13).** To a solution of compound (*R*)-(−)-**10m** (116 mg, 0.47 mmol) in dry $CH_2Cl_2$ (6.0 mL) were successively added pyridine (56 μL, 0.56 mmol) and benzyl chloroformate (79 μL, 0.56 mmol) under nitrogen atmosphere. The mixture was stirred for 4 h at room temperature, and after this time, the solvent was evaporated under reduced pressure, obtaining a reaction crude that was purified by flash chromatography (20% EtOAc/hexane), affording 165 mg of the biscarbamate (*S*)-(−)-**23** as a colorless oil (92%).

**(*S*)-Benzyl (3-amino-2-benzylpropyl)carbamate (14).** To a solution of $Pd(OAc)_2$ (2.5 mg, 0.01 mmol), $PPh_3$ (8 mg, 0.03 mmol), and 1,3-dimethylbarbituric acid (112 mg, 0.72 mmol) in dry $CH_2Cl_2$ (1.2 mL) was added (*S*)-(−)-**13** (100 mg, 0.26 mmol) under nitrogen atmosphere. The mixture was stirred for 4 h at 35 °C, and after this time, the solvent was evaporated under reduced pressure, obtaining a reaction crude which was redisolved in $CH_2Cl_2$ (10 mL) and washed with 1 N NaOH (3 × 10 mL). Then the organic phase was dried over $Na_2SO_4$, and the solvent was removed under reduced pressure, obtaining a crude that was purified by flash chromatography (100% MeOH), affording 54 mg of the monocarbamate (*S*)-(−)-**14** as a colorless oil (70%).

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**Supporting Information Available:** Experimental procedures, full compound characterization data, and copies of $^1H$, $^{13}C$, and DEPT NMR spectra are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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