Acid-Catalyzed Highly Enantioselective Synthesis of α-Amino Acid Derivatives from Sulfinamides and Alkynes

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Abstract: an acid-catalyzed enantioselective difunctionalization of activated alkynes using chiral sulfinamide reagents is developed. It is an atom-economic functional groups and chirality transfer process that allows modular synthesis of optically active α-amino acid derivatives under mild conditions. The reaction proceeds through a [2,3]-sigmatropic rearrangement mechanism with predictable stereochemistry and broad scope.

Functional molecules and materials based on optically active α-amino acids are indispensable on earth,[1, 2] among which the unnatural analogues play important roles (Figure 1a).[3, 4] For example, modification of native peptides by unnatural α-amino acids can alter the molecular conformation that offers improved metabolic stability for disease treatment.[5, 6] Reported asymmetric synthesis of enantioenriched unnatural α-amino acids includes the Strecker-type cyanide addition reaction,[7, 8] transition-metal-catalyzed hydrogenation reaction,[9, 10] PTC (phase transfer catalyst)-promoted substitution reaction,[11, 12] and imine-addition reaction.[13-16] The construction of two stereocenters by synergistic catalysis has also been reported.[17-22] Asymmetric C–N bond coupling provides an alternative approach to enantioenriched α-amino acid derivatives, but has been less studied until recently.[23-29]

A chirality and functional groups transfer strategy for the synthesis of α-amino acids from commercial substrates at low cost is attractive. Because it might not need elaborate reaction conditions and deliver the stereochemistry in a straightforward, specific, and predictable manner. Optically pure *tert*-butanesulfinamide is an ideal reagent for this purpose, as both enantiomers are commercially available and affordable. *tert*-Butanesulfinamide and its derivatives have been widely used for chirality transfer events as auxiliary or ligand in organic synthesis since the pioneering work of Ellman.[30] It is also known as sacrificial reagent for the preparation of enantioenriched α-hydroxyl ketones or amides via intramolecular [2,3]-sigmatropic rearrangements.[31-35] Recently, Maulide group found that acid-promoted reaction of *tert*-butanesulfinamide with oxazolidine- or thioether-functionalized alkynes proceeded through a new [2,3]-rearrangement that afforded α-amino acid derivatives (Figure 1b, bottom left).[36] However, the substrate scope and enantioselectivity were unsatisfactory, which limited its synthetic utility. In a complementary approach by the same group, chiral sulfinamides were treated with similar reaction intermediates generated in situ from amide activation, yielding α-amino acid derivatives with inverted configuration and improved enantioselectivity.[37] During the preparation of this manuscript, an intramolecular rearrangement reaction of chiral iminosulfinamide substrates has also been reported to afford similar products.[38]

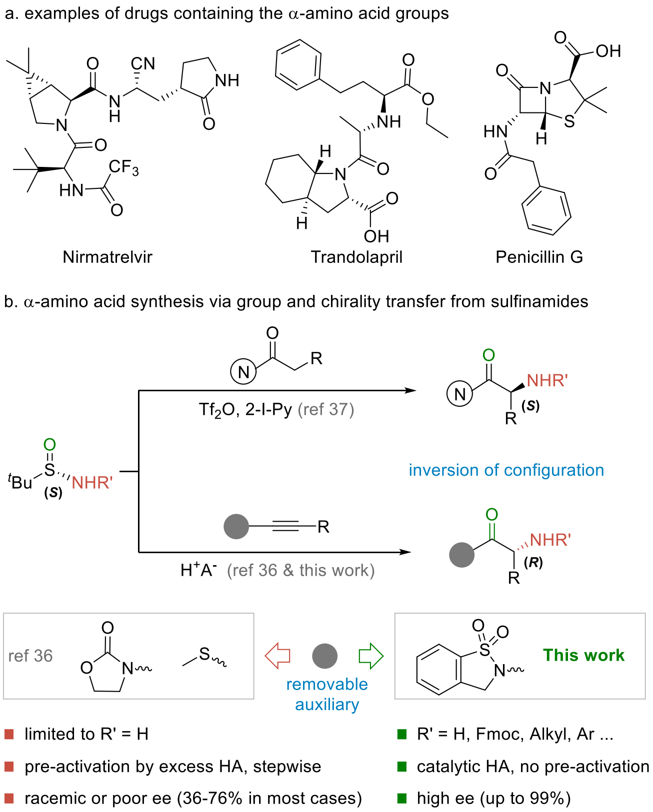
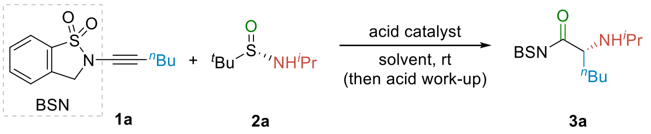


Figure 1, previous access to α-amino acid derivatives and our method.

During our recent study of the sulfur(IV)-alkenylation and arylation reactions of chiral sulfinamides using activated alkynes and arynes,[39] we independently discovered this unconventional [2,3]-rearrangement reaction between *tert*-butanesulfinamide and ynamides (Figure 1b, bottom right). We found that the 2,3-dihydrobenzo[*d*]isothiazole-1,1-dioxide (BSN)-based ynamides were superior to other analogues in delivering enantioselective chirality transfer from the stereogenic sulfur(IV) of sulfinamide to the tetrahedral carbon of products. In addition, this reaction could be made catalytic with a significantly expanded substrate scope. Here, we disclose the development, scope, and synthetic utility of this method.

Table 1, Reaction optimization.



entry[a]	acid (x equiv)	solvent	yield (**3a**, %)[b]	ee (**3a**, %)[c]
1	HOTf (0.2)	Toluene	67	82
2	HOTf (0.2)	DCE	66	89
3	HOTf (0.2)	THF	47	92
4	HOTf (0.2)	CPME	65	92
5	Tf$_2$NH (0.2)	CPME	67	94
6	TsOH (0.2)	CPME	trace	--
7	BF$_3$-Et$_2$O (0.2)	CPME	64	88
8	AgOTf (0.2)	CPME	32	88
9	Tf$_2$NH (1.0)	CPME	29	96
10[d]	Tf$_2$NH (0.2)	CPME	72 (63[e])	96 (93[e])

[a] conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), acid (20 mol%), solvent (2.0 mL), room temperature (rt), 6 h, N$_2$ atmosphere. For acid work-up: 6M HCl (0.1 mL, 6.0 equiv), rt, 2~3 h. [b] yield determined by ^{1}H NMR spectra using 0.1 mmol of benzyl benzoate as an internal standard. [c] enantiomeric excess (ee) determined by chiral high-performance liquid chromatography (HPLC) analysis. [d] -10 °C, 4 h. [e] 0.2 mmol scale, isolated.

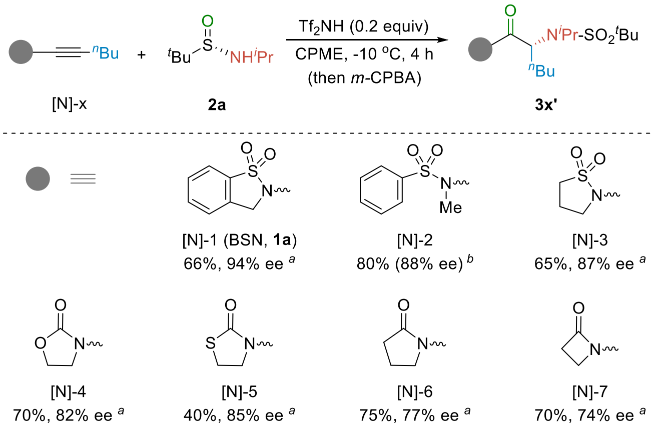


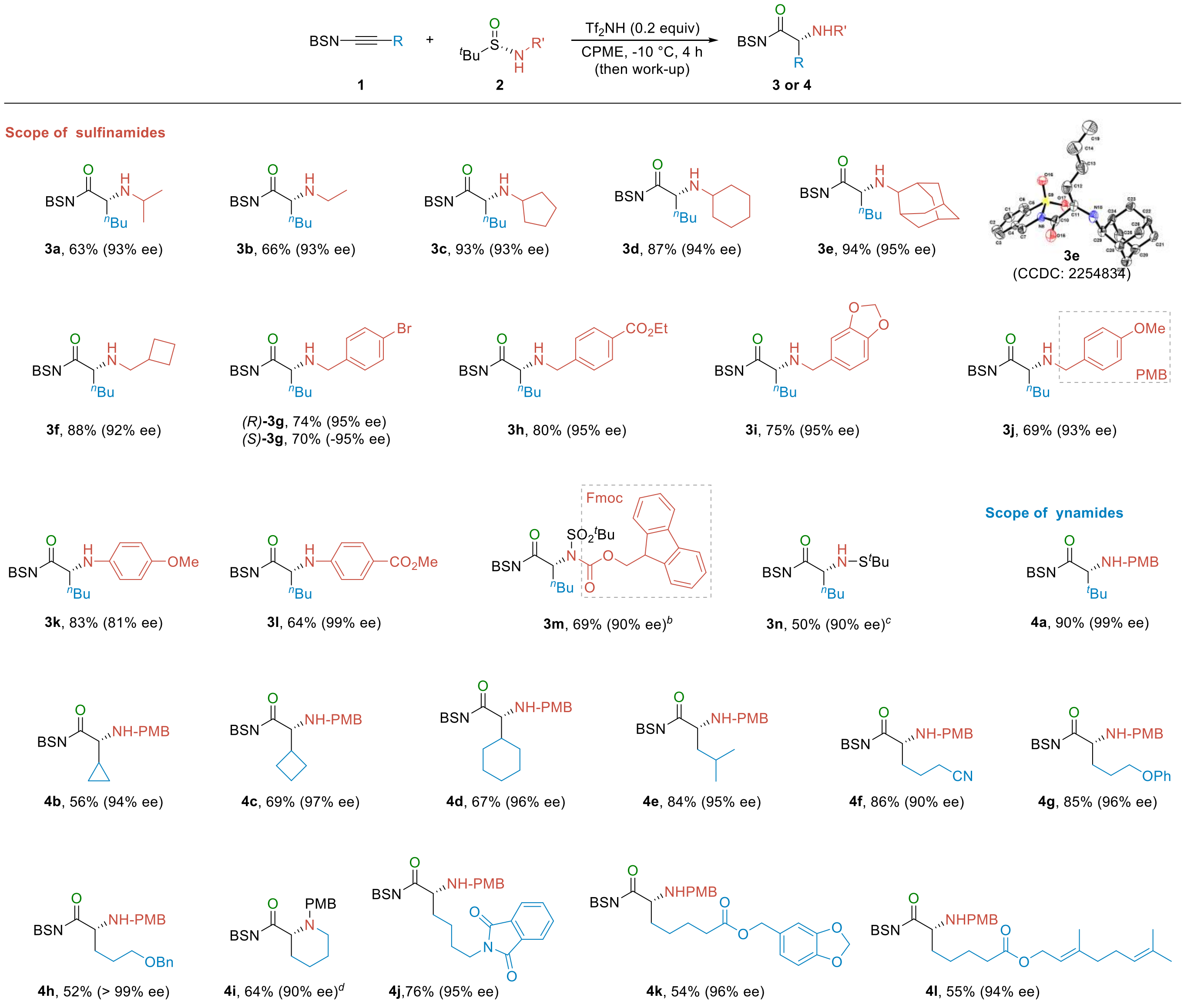
Figure 2, Effects of ynamide auxiliaries. [a] alkyne (0.2 mmol), **2a** (0.3 mmol), Tf$_2$NH (20 mol%), CPME (2.0 mL), -10 °C, 4 h, N$_2$ atmosphere, then *m*-CPBA (1.0 mmol), rt, overnight. [b] standard acid work-up due to quick hydrolysis of its N-S^{t}Bu intermediate, and it was 'H' instead of 'SO$_2$^{t}Bu' in the corresponding product.

We commenced the study using BSN-derived alkyne **1a** and (*S*)-*N*-isopropyl-*tert*-butanesulfinamide **2a** as model substrates. The reaction could be promoted by 20 mol% of TfOH acid in various solvents to yield a *N*-S^{t}Bu rearrangement product, which was partially hydrolyzed on silica gel during column purification. Therefore, it was converted to **3a** by acid work-up (Table 1, entries 1-4). The enantiomeric excess (ee) of **3a** was up to 94% using Tf$_2$NH as acid in cyclopentyl methyl ether (CPME, entry 5). However, only the hydrolysis of **1a** was observed using TsOH catalyst. Decreased yields and ee were obtained with catalysts BF$_3$•Et$_2$O and AgOTf (entries 6-8). Stoichiometric amounts of Tf$_2$NH resulted in early hydrolysis of the corresponding *N*-S^{t}Bu product, which reacted with **1a** through undesired pathways. Therefore, only a 29% yield of **3a** was obtained (entry 9). All reagents were added in one portion under the catalytic reaction conditions without pre-activation of the ynamide that was advantageous over the previous report of stepwise reaction promoted by excess acid.[36] In addition, the reaction yield and ee of **3a** could be further improved at -10 °C (entry 10).

The effects of different ynamide auxiliaries to this reaction was also investigated (Figure 1, [N]-1 to [N]-7). Removal of the -S^{t}Bu group of corresponding rearrangement products by acid work-up had different reaction rates and also resulted in partial hydrolysis of some auxiliaries. Therefore, the corresponding *N*-S^{t}Bu rearrangement products were converted to sulfonamides **3x'** by treatment with *m*-chloroperbenzoic acid (*m*-CPBA) in this study. As depicted in Figure 2, the other ynamides generally afforded less satisfactory ee than **1a**. BSN was advantageous in delivering high reaction enantioselectivity probably for two reasons, namely the appropriate electronic property and steric effects of the bulky sulfonamide skeleton.

Substrate scope of the (*S*)-*tert*-butanesulfinamide derivatives was studied under optimal reaction conditions (Table 2). The enantioselectivity of this reaction seemed not sensitive to steric effects of the *N*-substituents on sulfinamides. While the model substrate bearing a *N*-isopropyl motif afforded product **3a** in 93% ee, a linear and less bulky *N*-ethyl sulfinamide gave **3b** in the comparable ee. Other sulfinamides with cyclic or acyclic *N*-substituents also gave satisfactory results (**3c**-**3f**). The absolute configuration of **3e** was confirmed as *R* by X-ray analysis (CCDC 2254834). Both stereoisomers of the desired products could be obtained from different stereoisomers of the corresponding sulfinamide substrates (eg. **3g**). The *N*-benzylic derivatives were also good substrates for this reaction, regardless of electronic and steric profiles of arenes (**3g**-**3j**). Among them, *para*-methoxyl benzyl group (PMB, **3j**) was particularly valuable as a protecting group, which was removable to yield free amines under mild oxidation conditions. However, functional groups on the *N*-aryl substituents had significant impact on the enantioselectivity of corresponding reactions. Substrate bearing an electron-rich arene gave 81% ee (**3k**), whereas the electron-deficient one afforded 99% ee (**3l**). The Fmoc (9-fluorenylmethyloxycarbonyl) functionalized α-amino acid derivatives could also be obtained with this method (**3m**), which was particularly useful in peptide synthesis. In addition, unfunctionalized *tert*-butanesulfinamide was also tolerated and afforded desired product in moderate yield but excellent ee (**3n**). The N-S^{t}Bu group was oxidized to N-SO$_2$^{t}Bu in **3m** and left untouched in **3n** only because that the related compounds were easy for chiral HPLC analysis. As mentioned early, the N-S^{t}Bu was also cleavable in these cases to give free amines.

Table 2, substrate scope.



3a, 63% (93% ee)
3b, 66% (93% ee)
3c, 93% (93% ee)
3d, 87% (94% ee)
3e, 94% (95% ee)
3f, 88% (92% ee)
(R)-**3g**, 74% (95% ee)
(S)-**3g**, 70% (-95% ee)
3h, 80% (95% ee)
3i, 75% (95% ee)
3j, 69% (93% ee)
3k, 83% (81% ee)
3l, 64% (99% ee)
3m, 69% (90% ee)[b]
3n, 50% (90% ee)[c]
4a, 90% (99% ee)
4b, 56% (94% ee)
4c, 69% (97% ee)
4d, 67% (96% ee)
4e, 84% (95% ee)
4f, 86% (90% ee)
4g, 85% (96% ee)
4h, 52% (> 99% ee)
4i, 64% (90% ee)[d]
4j,76% (95% ee)
4k, 54% (96% ee)
4l, 55% (94% ee)

[a] reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), Tf$_2$NH (20 mol%), CPME (2.0 mL), -10 °C, 4 h, N$_2$ atmosphere. Then acid work-up, 6M HCl (6.0 equiv), rt, 2~3 h. [b] oxidation work-up, *m*-CPBA (1.0 mmol, 5.0 equiv), rt, overnight. [c] no acid work-up. [d] in situ cyclization of amine with terminal alkyl chloride (R = [CH$_2$]$_4$Cl in substrate **1i**).

The scope of ynamides was also studied using sulfinamide **2j** as a model substrate. Changing the *n*-butyl group to its *t*-butyl isomer resulted in improved yield with 99% ee (**4a** vs **3a**). Cyclic alkyl derivatives of various sizes also gave satisfactory results (**4b**-**4d**). The *i*-butyl ynamide worked equally well (**4e**). Substrates bearing other linear alkyl groups also afforded excellent ee (**4f**-**4h**). In addition, many functional groups were tolerated, including the cyanide (**4f**), ether (**4g**, **4h**), halide (**4i**), amide (**4j**), carboxylic ester (**4k**), and even alkene (**4l**). It is worth mentioning that an in situ intramolecular substitution of the alkyl chloride by PMB-functionalized amine occurred after the rearrangement step, giving piperidine derivative **4i** in high yield with excellent ee.

Based on previous understanding of ynamide-participated rearrangement reaction and our study,[36,37,40-46] a catalytic reaction cycle was proposed in Figure 3. The ynamide reacted with HNTf$_2$ to give a keteniminium species, which was captured by sulfinamide through *O*-addition. The resulting enolonium intermediate underwent rapid [2,3]-rearrangement to an α-amino acid skeleton and released H$^+$ as catalyst. The *N*-S^{t}Bu product was isolable by chromatography. Alternatively, it could be converted to free amine by excess acid or to sulfonamide by oxidation. The [2,3]-sigmatropic rearrangement of enolonium intermediate was essential in determining enantioselectivity of the overall chirality transfer event.[36] This step was calculated by density functional theory (DFT) calculations using the BSN-modified propyne (R = Me in **1**) and (*S*)-**2j** as model substrates (Figure 3, see supporting information for more details). The formation of (*R*)-product via transition state **TS**-(*R*) was kinetically favored over the formation of (*S*)-product via **TS**-(*S*). Gibbs free energy gap of these two transition states was 3.52 kcal•mol^{-1}, suggesting an estimated 99% ee of corresponding

(R)-product from (S)-sulfinamide. That was in good agreement with our experimental results.[44]

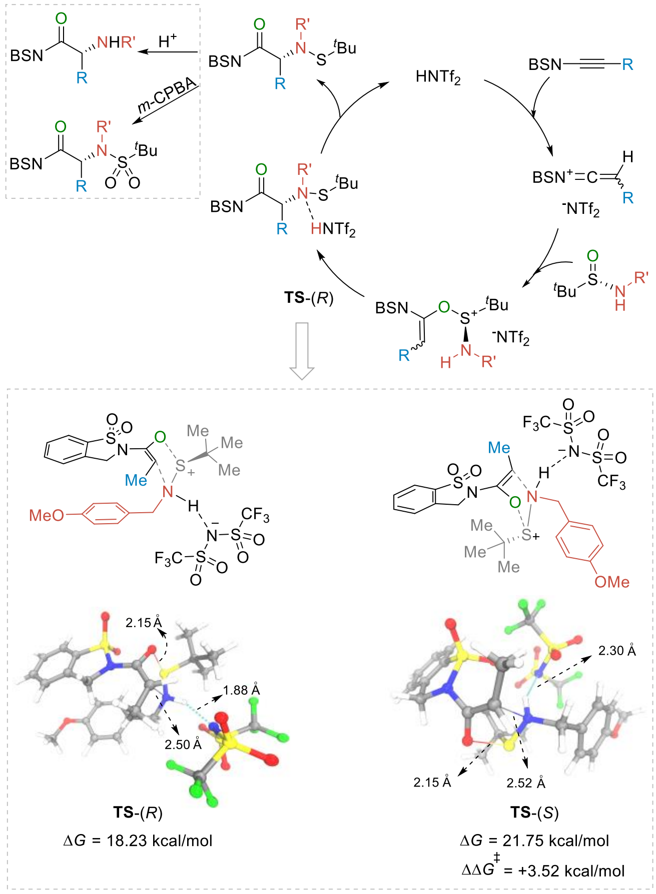


Figure 3, Mechanism discussion and computed Gibbs free energy gap between two transition states leading to (R)- or (S)-products. (calculated at M06-2X-D3/6-31G(d,p)//M06-2X-D3/jul-cc-pVTZ level, BSN functionalized propyne and (S)-**2j** as model substrates).

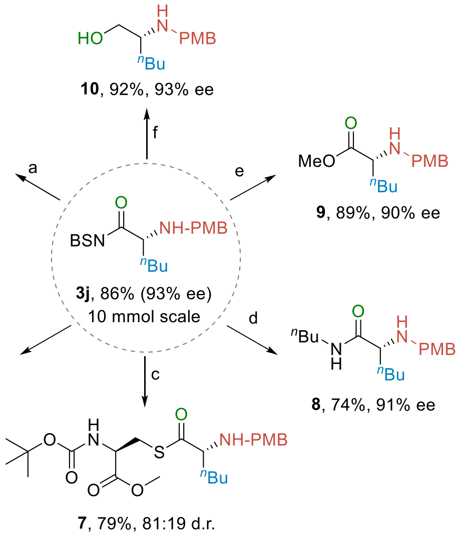


Figure 4. Synthetic transformations. ^{a} PhCOCl, NaH, THF, 0 °C. ^{b} $Ce(NH_4)_2(NO_3)_6$, CH_3CN/H_2O, 0 °C. ^{c} LDA, RSH, THF, -10 °C. ^{d} DBU, RNH_2, DCM. rt. ^{e} ROH, ^{n}BuLi, THF, -78 °C to rt. ^{f} $LiAlH_4$, THF, 0 °C.

In Figure 4, we highlighted that this reaction could be scaled up to 10 mmol in the preparation of compound **3j**. High ee was maintained. Diverse synthetic utility of this compound was also demonstrated. For example, *N*-functionalization of amine could be practiced to afford tertiary amide **5**. The PMB group was removed by treatment with ammonium cerium nitrate (**6**). The BSN auxiliary could be replaced by nucleophilic substitution, allowing the ligation of many functional molecules such as the thiol ester **7**, amide **8**, and ester **9**. Chiral β-amino alcohol could also be derived by amide reduction reaction (**10**).[47]

Conclusions

In summary, a highly enantioselective functional groups and chirality transfer reaction between chiral sulfinamides and ynamides has been achieved. It is atom-economic and efficient that allows the preparation of α-amino acid derivatives under mild conditions. Optically pure *tert*-butanesulfinamide reagent is commercially available and affordable. The stereochemistry of resulting products is predictable and tunable. Therefore, this method is practical to use for medicinal chemists in building α-amino acid-based libraries during drug development.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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