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Photogenerated Quinone Methides as Useful Intermediates in the Synthesis of Chiral BINOL Ligands

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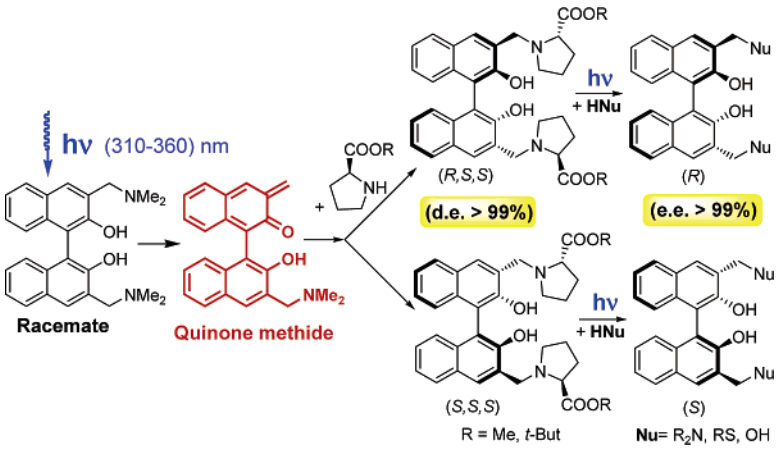
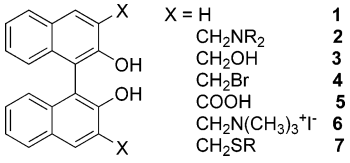


The photoinduced synthesis of chiral 3,3′-CH_2X-disubstituted BINOL ligands (X = NR_2, SR, OH) has been achieved with excellent ee by UV−visible activation of BINOLAMs bearing L-proline ester arms. Quinone methides, detected by laser flash photolysis, are the key intermediates involved in such a synthetic protocol, which undergo reversible nucleophilic conjugate additions by a great variety of nitrogen nucleophiles (amines and α-amino acid derivatives) with complete configuration retention of the BINOL moiety.

Introduction

Optically active binaphthol (BINOL, **1**) and its 3,3′-disubstituted derivatives (**2**−**5**, Chart 1) have been extensively used as chiral auxiliary ligands in asymmetric synthesis.[1] Among them, the 3,3′-substituted derivatives such as the 3,3′-bis(aminomethyl)-2,2′-dihydroxy-1,1′-binaphthalenes (BINOLAMs, **2**) have been applied to asymmetric cyanophosphorylation,[2] cyanosilylation,[3,4] cyanobenzylation, and cyanoformylation[5] of aldehydes, enantioselective C-alkylation of Schiff bases,[6] and asymmetric Michael addition.[7] The tetradentate alcohol ligand (**3**) and its dibromide (**4**)[8] have been used as starting material in the synthesis of (i) chiral pseudorotaxanes[9] and catenanes[10]

CHART 1. Binaphthol 1 and Its 3,3′-Substituted Derivatives



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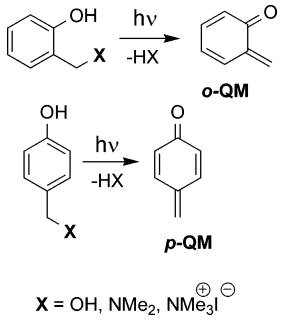
SCHEME 1

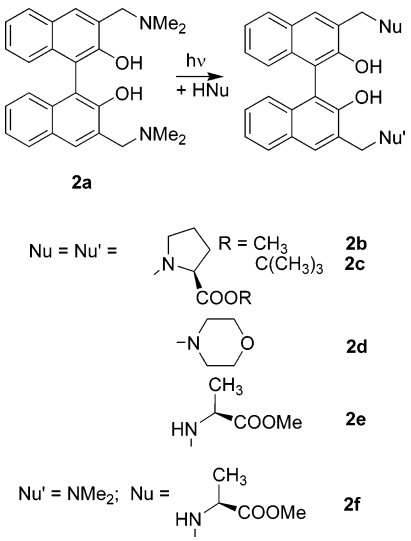


and (ii) bifunctional phosphine oxide catalysts.[11] All the above applications came years after the pioneering work by Cram in the synthesis of chiral crown ethers, which achieved exploiting the chemistry of the chiral derivatives **3**−**5**.[12]

More recently, chiral quaternary ammonium salts of BINOLAMs (such as **6**) have been used as catalysts to promote asymmetric Michael addition with fairly good enantioselectivity.[13] Furthermore, methylthiol derivatives such as **7** (R = Me) have been used as chiral ligands in stereoselective conjugate addition of diethylzinc to enones and nitroalkenes.[14] The importance of such molecules has fueled the development of efficient methodologies to prepare them. Although the asymmetric synthesis of functionalized chiral 3,3′-substituted binaphthols has been achieved by oxidative coupling (catalyzed by Cu^{2+}) of 2-naphthols with chirals amines,[15] classical resolutions of racemic binaphthol (**1**)[16] and its 3,3′-dicarboxylic acid (**5**)[8] (through the separation of diastereomeric salts) are the only published protocols extensively employed for large-scale synthesis of optically pure BINOL derivatives. To our knowledge, no direct resolutions of BINOLAMs **2** nor tetradentate alcohol **3** or thioeter **7** have been published thus far. A fairly different approach for the synthesis of chiral 3,3′-disubstituted BINOL derivatives is presented here, and it is based on the generation of quinone methides (QMs) as bis-alkylating intermediates using BINOLAMs **2a**−**2c** as precursors.

In the past decades, it has been shown that QMs, both the ortho (*o*-QM) and para (*p*-QM) isomers (Scheme 1), are mildly generated by photolysis of several precursors such as benzyl alcohols (X = OH),[17,18] Mannich bases[19] (X = NMe_2), and their quaternary ammonium salts[20] (X = $NMe_3^+I^-$) in water. They are electrophilic transients undergoing Michael addition with a great variety of nucleophiles including amines, amino acids, peptides, and DNA.[20,21]

SCHEME 2. Photolysis of 2a in the Presence of L-α-Amino Acid Methyl Esters and Morpholine



The current interest of our group in the synthesis of new chiral BINOLAM derivatives as precursors of chiral bis-alkylating agents by photoactivation using UV−visible light (at 360−400 nm)[20−22] prompted us to develop the original synthetic protocol described in this article.

Results and Discussion

Photoreactivity of BINOLAMs. On the basis of the photoreactivity of the BINOLAM **2a** and its quaternary ammonium salts (**6**), we have designed a general protocol for the resolution of chiral BINOLAMs (**2**), tetradentate alcohol ligand (**3**), and 3,3′-disubstituted BINOL thioethers (**7**). Here we present the preliminary results of this strategy. First, we synthesized **2a** as racemic mixture starting from racemic **1** and *i*-butoxymethyldimethylamine in *i*-butanol according to a published procedure.[8] Second, we investigated the photoreactivity of the racemic BINOLAM **2a** in CH_2Cl_2 in the presence of a few L-α-amino esters and morpholine. In more detail, the photolysis of **2a** (at both 310 and 360 nm) in CH_2Cl_2 with methyl and *t*-butyl esters of L-proline and morpholine gave the corresponding adducts **2b** and **2c** as diastereomeric mixtures, and racemic **2d** in good yields (Scheme 2, Table 1).

The preparative irradiation of **2a** in the presence of L-alanine methyl ester afforded a sluggish mixture containing the bis-substituted adduct **2e** (10% yield) together with the monosubstituted derivatives **2f** (22%), unreacted starting material **2a**

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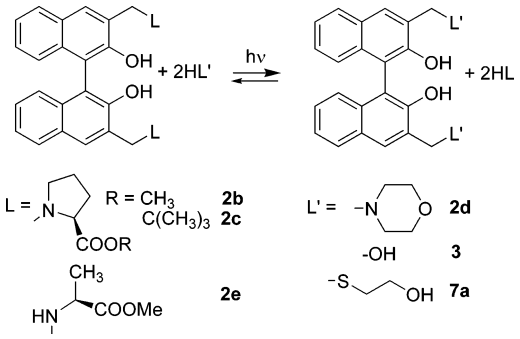
TABLE 1. Photolysis of 2a in the Presence of Amino Esters and Morpholine

nucleophile, HNu[a]	irradiation time (min)[b]	consumption (%)	adduct yield (%)[c]
L-proline-OCH_3	10	90	**2b**, 85[d]
L-proline-*O*-*t*Bu	10	96	**2c**, 99[e]
morpholine	15	90	**2d**, 100
L-alanine-OCH_3	40	55	**2e**, 10[f]

[a] Binolams **2a** (2×10^{-3} M), amino esters, and morpholine (2×10^{-2} M) in CH_2Cl_2. [b] Merry-go-round photoreactor; four lamps 15 W each, 310 nm; ca. 25 °C, under O_2 purged solution. [c] By HPLC analysis (ref 23). [d] (*S*,*S*,*S*)-**2b**/(*R*,*S*,*S*)-**2b** = 1:1. [e] (*S*,*S*,*S*)-**2c**/(*R*,*S*,*S*)-**2c** = 53:47 from preparative column chromatography. [f] 22% monosubstituted adducts **2f**.

SCHEME 3. Photolysis of the BINOLAMs 2b, 2c, and 2e in the Presence of Morpholine, Water, and 2-Mercaptoethanol

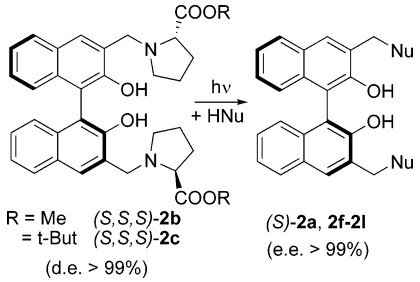


(45%), and an oligomeric residue structurally not well-defined (~20%). The photoreactivity of **2a** in the presence also of L-valine and L-leucine methyl esters was very similar, displaying the formation of both bis- and monosubstituted adducts with low yield. The product distribution analysis, in Table 1, clearly shows that the mild photochemical-induced displacement of the dimethylamino group by an α-amino ester moiety is highly efficient only with L-proline esters and morpholine.

In addition, among the 3,3′-disubstituted adducts **2b**, **2c**, and **2e**, only the diastereomeric L-methyl [(*S*,*S*,*S*)-**2b** and (*R*,*S*,*S*)-**2b**] and L-*t*-butyl esters of proline [(*S*,*S*,*S*)-**2c** and (*R*,*S*,*S*)-**2c**] were easily separated and purified either by crystallization from benzene or ethyl acetate and by column chromatography. The (*S*,*S*,*S*)-**2b** and (*S*,*S*,*S*)-**2c** adducts were the first, among the two diastereoisomers, to be eluted from preparative column chromatography (cyclohexane/ethyl acetate = 7:3), with very good de ≥ 99%. Crystallization of the diastereomeric mixture from benzene and ethyl acetate afforded the (*S*,*S*,*S*) and (*R*,*S*,*S*) pure isomers, respectively, with a slightly lower purity (de ≥ 95%). The absolute configurations of (*R*,*S*,*S*)-**2b**, (*S*,*S*,*S*)-**2b**, (*R*,*S*,*S*)-**2c**, and (*S*,*S*,*S*)-**2c** were assigned by comparison with authentic samples synthesized quantitatively starting from chiral (*R*)- and (*S*)-dibromide **4**[8] and proline methyl and *t*-butyl esters, respectively (see Experimental Section).

Reversibility of the Photoalkylation Process. The photoactivation of BINOLAMs as bis-alkylating agents is a general reactivity feature of such substrates, which can be triggered under very mild photochemical conditions (λ = 310 nm for 10−15 min, or 360 nm for 30−60 min), and most importantly, the alkylation process is photoreversible. In more detail, ligand exchange (L → L′, see Scheme 3) also took place upon irradiation of **2b**, **2c**, and **2e** in CH_2Cl_2 solution in the presence of morpholine and 2-mercaptoethanol in excess or in an aqueous acetonitrile solutions, to yield **2d**, **7a**,[21] and **3**, respectively, in good yields (≥94%).

TABLE 2. Synthesis of Chiral Ligands by Photolysis of Diastereomeric Pure BINOLAMs (*S*,*S*,*S*)-2b, (*R*,*S*,*S*)-2b, (*S*,*S*,*S*)-2c, and (*R*,*S*,*S*)-2c in the Presence of Achiral Nucleophiles



BINOLAMs	HNu[a]	irradiation time (min)[b]	consumption (%)	adduct yield (%)[c]
(*S*,*S*,*S*)-**2b**	$HNMe_2$[d]	10	100	(*S*)-**2a**, 100
(*S*,*S*,*S*)-**2c**	$HNMe_2$	10	100	(*S*)-**2a**, 100
(*S*,*S*,*S*)-**2b**	$HNEt_2$	30	88	(*S*)-**2g**, 75
(*S*,*S*,*S*)-**2c**	$HNEt_2$	10	100	(*S*)-**2g**, 100
(*R*,*S*,*S*)-**2c**	$HNEt_2$	10	100	(*R*)-**2g**, 100
(*S*,*S*,*S*)-**2c**	$HN(n\text{-}Pr)_2$	10	100	(*S*)-**2h**, 97
(*S*,*S*,*S*)-**2c**	$HNPh_2$	120[e]	96	(*S*)-**2i**, 54[f]
(*S*,*S*,*S*)-**2b**	$HNPh_2$	120[e]	81	(*S*)-**2i**, 22[f]
(*S*,*S*,*S*)-**2b**	morpholine	30	83	(*S*)-**2d**, 78
(*R*,*S*,*S*)-**2c**	morpholine	30	100	(*R*)-**2d**, 100
(*S*,*S*,*S*)-**2c**	morpholine	10	100	(*S*)-**2d**, 100
(*S*,*S*,*S*)-**2b**	$HS(CH_2)_2OH$	30	95	(*S*)-**7a**, 74
(*R*,*S*,*S*)-**2b**	$HS(CH_2)_2OH$	30	95	(*R*)-**7a**, 74
(*S*,*S*,*S*)-**2c**	$HS(CH_2)_2OH$	10	100	(*S*)-**7a**, 98
(*S*,*S*,*S*)-**2b**	H_2O[g]	10	81	(*S*)-**3**, 97
(*R*,*S*,*S*)-**2b**	H_2O[g]	10	80	(*R*)-**3**, 98
(*S*,*S*,*S*)-**2c**	H_2O[g]	10	100	(*S*)-**3**, 100
(*R*,*S*,*S*)-**2c**	H_2O[g]	10	100	(*R*)-**3**, 99

[a] Diastereomeric pure BINOLAMs **2b** and **2c** (2×10^{-3} M) in the presence of several nucleophiles (2×10^{-2} M) in CH_2Cl_2. [b] Merry-go-round photoreactor; four lamps 15 W each, 310 nm; ca. 25 °C. [c] By HPLC analysis of the crude reaction mixture. [d] $HNMe_2$-saturated solution. [e] Four lamps 15 W, 360 nm. [f] 40% monoalkylated adduct. [g] H_2O/acetonitrile = 1:1 mixture.

Such a reversibility of the photoalkylation process could be exploited to achieve (i) the synthesis of chiral 3,3′-CH_2L-disubstituted BINOL ligands (Table 2) and (ii) photoinduced alkylation and cross-linking of DNA using a wide variety of structures capable of molecular recognition.[24]

Photoactivation of Diastereomeric BINOLAMs (2b and 2c) as Chiral Alkylating Agents. To explore the feasibility of the first application, mentioned in the previous chapter, we decided to investigate the photochemistry of the purified chiral proline esters (*S*,*S*,*S*)-**2b**, (*S*,*S*,*S*)-**2c** and their diastereoisomeric counterparts (*R*,*S*,*S*)-**2b** and (*R*,*S*,*S*)-**2c** to assess the possibility of using such substrates as chiral sources in the synthesis of substituted BINOL ligands. We irradiated the adducts (*S*,*S*,*S*)-**2b** and (*S*,*S*,*S*)-**2c** at 310 nm (or at 360 nm) in the presence of several achiral secondary amines (such as dimethyl-, diethyl-, di-*n*-propyl, diphenylamines, and morpholine), mercaptoethanol in CH_2Cl_2, and in a 1:1 mixture acetonitrile/water, affording the chiral adducts (*S*)-**2a**, **2g**−**2i**, **2d**, **7a**, and **3**, respectively, in good yields, *with complete retention of the BINOL moiety configuration* (see data in Table 2).[23]

Similarly, the photolysis of the adducts (*R*,*S*,*S*)-**2b** and (*R*,*S*,*S*)-**2c** at 310 nm in the presence of morpholine, diethylamine, and

(23) The ee values were measured by HPLC analysis on a Daicel Chiracel OD-R 0.46 cm × 25 cm column, with CH_3CN/0.5N $NaClO_4$ eluent.

(24) Work on several water-soluble L-α-amino acid derivatives as photoreactive DNA cross-linking agents is in progress.

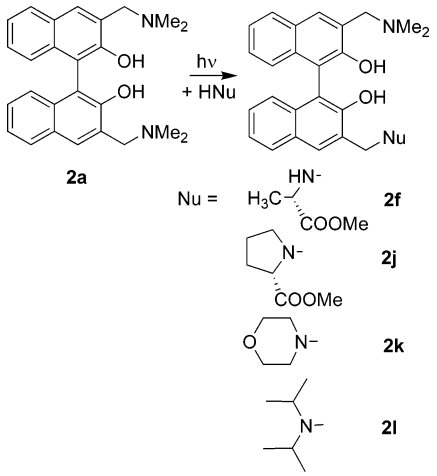
2-mercaptoethanol in CH_2Cl_2 and in a 1:1 mixture acetonitrile/water afforded the chiral adducts (*R*)-**2d**, **2g**, **7a**, and **3**. The structural and configurational assignment of the above adducts has been done by comparing their properties, including retention time on chiral column,[23] to those of authentic samples already published.[4,6a,7,8]

General Features of the Photosynthetic Protocol. The above data show that various 3,3′-BINOLAMs including a few amino acid derivatives are suitable starting materials in a new and quite general protocol for the synthesis of BINOL derivatives with high enantiomeric purity, on a 0.4−5.0 mmol preparative scale (see Experimental Section). The key aspects of the synthetic protocol described in this article are (i) the complete retention of the BINOL configuration in the photoactivation process, (ii) the facile separation of the diastereomeric BINOLAM derivatives bearing proline L-*t*-butyl ester arms, (iii) the synthesis of the latter with excellent yields starting from racemic amine **2a**, and (iv) the quantitative conversion of the BINOLAMs containing L-proline moieties into final chiral adducts, using secondary amines, mercaptoethanol, and water. In addition to these advantages, our photosynthetic protocol also exhibits a couple of limited drawbacks. The photosubstitutions of the CH_2 ligand by primary amines (including L-alanine, valine, and leucine methyl esters) display much lower yields. This probably is due to the higher nucleophilicity of the resulting adducts (due to their lower steric hindering in comparison to the adducts resulting from secondary amines), which allow them to compete with the free primary amines for the photogenerated transient electrophile. Such a hypothesis is suggested by the presence of not well-characterized oligomeric byproducts in the crude. The protocol works also with aromatic amines, but with a longer wavelength (360 nm) and with longer irradiation time. This is caused by the red-shifted absorbance of the aniline derivatives (in comparison to alkylamines), which suggests to shift the activation wavelength to 360 nm, where the aromatic amines do not absorb the radiation. Unfortunately, the BINOL derivatives exhibit a lower absorbance at the new wavelength.

Mechanistic Insights. The photoactivation of BINOLAMs **2a**−**2f** as bifunctional alkylating agents and the complete retention of the BINOL moiety configuration are the key aspects of our synthetic protocol. Therefore, considering worthwhile the investigation of its mechanism, we run two sets of clarifying experiments: (i) a product distribution analysis of the photochemical reaction under low conversion of the substrate **2a** and (ii) laser flash photolysis (LFP) investigations, flashing diluted CH_2Cl_2 solutions of **2a**−**2c**. Running the photochemical reaction under low conversion conditions (achievable at higher concentration of the precursor **2a** [10^{-2} M]), in the presence of L-alanine, L-proline methyl esters, and morpholine, we have been able to separate the monoalkylated adducts **2f** (21% yield), **2j** (22%), and **2k** (18%), respectively. **2f** and **2j** have been isolated as diastereomeric mixtures, from unreacted starting material **2a** (≥57%) (Scheme 4). Using highly hindered nucleophiles such as di-*i*-propylamine, we have been able to isolate from the reaction mixture only the monoalkylated adduct **2l** (34% yields); even running the photoreaction under lower concentration of the precursors (2×10^{-3} M), no bis-alkylated adduct was detected in the crude.

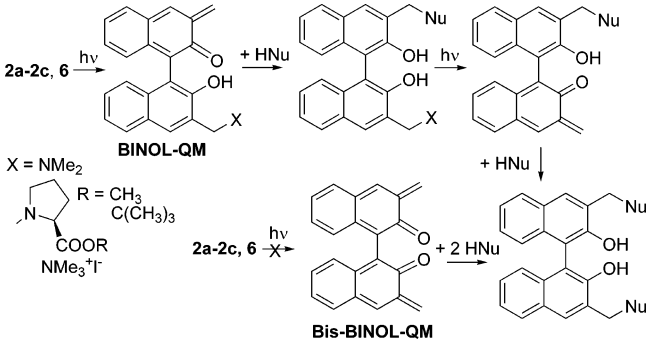
QM Detection by LFP. We have shown, in the recent past, that LFP provides an effective method for direct detection of electrophilic QMs,[20−22,25] starting from Mannich bases and their quaternary ammonium salts. More recently, we had demonstrated that LFP of the quaternary ammonium salt **6** (λ_{ecc} = 266 nm, Nd:YAG laser, <10 mJ/pulse) in an aqueous solution yielded a transient species with λ_{max} = 380 nm, which was confidently assigned to the electrophilic structures BINOL-QM (Scheme 5, X = NMe_3^+).[21] LFP of **2a**, under the very same laser conditions, in a CH_2Cl_2 solution, yielded a transient species displaying a UV−visible absorbance spectra (see Figure 1) very similar to that obtained from flashing **6** in water solution, but with a longer lifetime. Since the profile of such a transient absorbance is not fitted by a single-exponential decay, the quenching of such an intermediate is complex, and it could follow multiple reaction pathways in absence of added nucleophiles (Figure 1, inset a).[26] The decay trace becomes a single exponential only with the addition of L-methyl proline ester and morpholine (Figure 1, insets b and c). In this case, the decay traces do not return to baseline, and the residual absorbance is stable in the time scale of the laser experiments. Nucleophile addition does not affect the intensity of the transient signal

SCHEME 4. Photochemical Reaction under Low Conversion Experimental Conditions[a]



[a] **2a** (10^{-2} M), merry-go-round photoreactor, 310 nm; 10−60 min (four lamps 15 W), in the presence of L-alanine and proline methyl esters, morpholine, and di-*i*-propylamine (10^{-2} M) in CH_2Cl_2.

SCHEME 5. Photoactivation Mechanism of the BINOLAMs 2a−2c as Bis-alkylating Agents



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(26) LFP investigation is still in progress, with the aim of searching for other transient species generated from the BINOL-QM in the absence of nucleophiles.

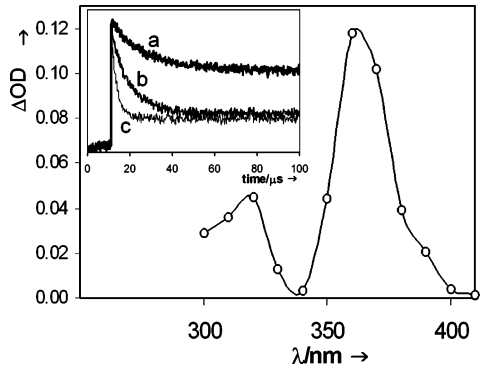

FIGURE 1. Absorption spectra recorded by LFP (λ_{max} = 266 nm) flashing BINOLAMs **2a**−**2c** CH_2Cl_2 solution. Inset: decay traces monitored at 370 nm, in the absence (a) and in the presence of morpholine [(b) 3.5×10^{-4} M, (c) 1.7×10^{-3} M].

immediately after the laser pulse, and therefore the nucleophile does not quench the photoexcited state of the BINOLAM precursors, but only the QM generated from it.

After 10−15 laser shots (λ_{max} = 266 nm, 8 mJ power), **2j** and **2k** were detected in the flashed CH_2Cl_2 solutions, together with unreacted **2a**. Very similar transient absorbance has been also detected flashing **2b** and **2c** in diluted (2×10^{-4} M) CH_2Cl_2 solutions.

The above combined laser flash photolysis data and product distribution analysis clarified the mechanism of the BINOLAM photoactivation, suggesting that they act as electrophilic agents through a sequential and stepwise QM generation (Scheme 5). Moreover, these data ruled out the possibility of a photochemical generation in a single step of a bis-alkylating bis-BINOL-QM as a reaction intermediate. This mechanistic observation also provides a logical basis for retention of the BINOL's configuration after substitution. In fact, monoalkylating BINOL-QM displays all the structural features that, similarly to BINOL derivatives, prevent racemization by conformational equilibration through C_1-C_1' bond rotation.

Conclusion

We have described a new mild and general protocol for the synthesis of chiral BINOLAMs (**2**), tetradentate alcohol ligand (**3**), and 3,3′-disubstituted BINOL thioethers (**7**) with very high ee, taking advantage of (i) the facile separation of the diastereomeric BINOLAMs **2b** and **2c** mixtures containing L-proline ester moieties (with de ≥ 99%) and (ii) their mild photoactivation as bis-alkylating agents through the generation of LFP detectable chiral quinone methide, with complete retention of the BINOL moiety configuration.

Experimental Section

Photochemical Reactions. Small-Scale Irradiations. The typical procedure for the photochemical synthesis of BINOLAMs is as follows. A solution of BINOLAMs (**2a**−**2c**, 2×10^{-3} M) and a nucleophile (amines, thiols, or amino esters, 2×10^{-2} M) in 200 mL of CH_2Cl_2 (or in CH_3CN/H_2O) was poured into 20 Pyrex tubes, flushed with argon for 5 min, and externally irradiated by means of four 15 W phosphor-coated lamps (center of emission 310 nm) for 10−40 min or by means of four 15 W phosphor-coated lamps (center of emission 360 nm) for 25−100 min in a merry-go-round apparatus. The irradiated solution was evaporated under reduced pressure, and the residue was purified by chromatography on silica gel 60 HR, eluting with cyclohexane/ethyl acetate mixtures. The products were obtained as solids or oils from the fractions (by repeating the chromatography in the case of unsatisfactory separation) or by crystallization from benzene or ethyl acetate.

The preparative irradiation of **2a** in the presence of L-alanine methyl esters (and similarly in the presence of L-valine and L-leucine) has been performed under very similar conditions.

Photochemical Reactions. Preparative Irradiations. To scale-up the photochemical synthesis, a solution of **2a** (2×10^{-3} M) in 2.5 L of a CH_2Cl_2 solution of L-proline *t*-butyl esters (2×10^{-2} M) was flushed with argon for 15 min and then internally irradiated in an immersion well apparatus by means of a Pyrex-filtered 500 W medium-pressure mercury arc. The course of the reaction was monitored by HPLC, and the irradiation continued, for 18 min, until ca. 90% conversion was reached. Workup and purification of the resulting (*S*,*S*,*S*)-**2c** and (*R*,*S*,*S*)-**2c** adducts were achieved following the above procedure.

3,3′-Bis-(2-methoxycarbonylpyrrolidin-1-ylmethyl)-1,1′-binaphthyl-2,2′-diol (2b).[21] **2b** was formed as a diastereomeric mixture (1:1), which was separated by silica gel column chromatography and eluted with cyclohexane/ethyl acetate = 7:3 in the following order: (*S*,*S*,*S*)-**2b** and after (*R*,*S*,*S*)-**2b**.

(*S*,*S*,*S*)-**2b** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.87−2.07 (m, 4H), 2.16−2.28 (m, 2H), 2.57−2.65 (m, 2H), 3.14−3.21 (m, 2H), 3.49−3.54 (dd, J = 8.7, 4.8 Hz, 2H), 3.67 (s, 6H), 3.71−3.73 (m, 2H), 3.98 (d, J = 13.3 Hz, 2H), 4.37 (d, J = 13.3 Hz, 2H), 7.18−7.37 (m, 6H), 7.55 (s, 2H), 7.9 (d, J = 7.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.1, 29.4, 51.9, 52.5, 57.5, 64.7, 116.5, 122.7, 124.8, 125.1, 125.7, 127.3, 127.4, 128.0, 134.0, 153.2, 173.5. Anal. Calcd for $C_{34}H_{36}N_2O_6$: C, 71.81; H, 6.38; N, 4.93; O, 16.88. Found: C, 71.69; H, 6.43; N, 4.91.

(*R*,*S*,*S*)-**2b** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.83−2.01 (m, 4H), 2.19−2.26 (m, 2H), 2.54−2.62 (m, 2H), 3.08−3.15 (m, 2H), 3.41−3.46 (dd, J = 9.12, 6.2 Hz, 2H), 3.67 (s, 6H), 3.70−3.73 (m, 8H), 3.81 (d, 2H, J = 13.1 Hz), 4.51 (d, J = 13.1 Hz, 2H), 7.14−7.28 (m, 6H), 7.66 (s, 2H), 7.70 (d, J = 7.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.1, 29.4, 52.0, 52.7, 57.7, 65.2, 116.4, 122.7, 124.6, 125.0, 125.8, 127.4, 127.5, 128.1, 134.0, 153.2, 173.5. Anal. Calcd for $C_{34}H_{36}N_2O_6$: C, 71.81; H, 6.38; N, 4.93; O, 16.88. Found: C, 71.49; H, 6.40; N, 4.88.

Chiral HPLC analysis (Daicel Chiralcel OD-R250 × 4.6 mm, eluent CH_3CN/0.5 M $NaClO_4$ = 3:2, flow rate 0.5 mL/min) was also used to assign the absolute configuration of the diastereomeric adducts (*S*,*S*,*S*)-**2b**,**2c** and (*R*,*S*,*S*)-**2b**,**2c** by time retention (t_R) comparison of the enantiomeric adducts arising from the irradiation in the presence of morpholine [(*R*)-**2d**, t_R = 29.1min; (*S*)-**2d**, t_R = 32.3 min], water [(*R*)-**3**, t_R = 10.5 min; (*R*)-**3**, t_R = 12.6 min], and mercaptoethanol [(*R*)-**7a**, t_R = 19.6 min; (*S*)-**7a**, t_R = 21.7 min] with authentic chiral samples prepared from the chiral (*S*)-**3** and (*R*)-**3** alcohols following published procedure.[8]

3,3′-Bis-(2-*t*-Butoxycarbonylpyrrolidin-1-ylmethyl)-1,1′-binaphthyl-2,2′-diol (2c). (*S*,*S*,*S*)-**2c** as white crystals: Mp 87.5−89.0 °C (from benzene); ^{1}H NMR (300 MHz, DMSO) δ 1.35−1.45 (s, 18H), 1.60−1.95 (m, 6H), 2.10−2.28 (m, 2H), 2.85−3.00 (m, 2H), 3.30−3.45 (m, 4H), 3.77 (d, J = 13.2 Hz, 2H), 4.32 (d, J = 13.2 Hz, 2H), 6.87−6.95 (d, 2H), 7.10−7.30 (m, 6H), 7.80−7.85 (m, 2H). ^{13}C NMR (75 MHz, DMSO) δ 23.1, 27.6, 29.3, 52.3, 56.9, 67.7, 81.0, 115.9, 122.5, 124.0, 125.7, 126.9, 127.6, 133.3, 153.2, 179.9. Anal. Calcd for $C_{40}H_{48}N_2O_6$: C, 73.59; H, 7.41; N, 4.29; O, 14.70. Found: C, 73.48; H, 7.42; N, 4.24.

(*R*,*S*,*S*)-**2c** as white crystals: Mp 99.5−101 °C (from ethyl acetate). ^{1}H NMR (300 MHz, DMSO) δ 1.30−1.51 (s, 18H), 1.60−1.90 (m, 6H), 2.10−2.25 (m, 2H), 2.90−3.00 (m, 2H), 3.30−3.45 (m, 4H), 3.81 (d, J = 13.4 Hz, 2H), 4.28 (d, J = 13.4 Hz, 2H), 6.90−7.00 (d, 2H), 7.10−7.25 (m, 6H), 7.80−7.95 (m, 2H). ^{13}C NMR (75 MHz, DMSO) δ 22.9, 27.6, 29.2, 52.5, 56.9, 65.9, 80.8, 115.8, 122.4, 124.3, 125.5, 127.0, 127.7, 133.5, 153.1, 179.8. Anal. Calcd for $C_{40}H_{48}N_2O_6$: C, 73.59; H, 7.41; N, 4.29; O, 14.70. Found: C, 73.51; H, 7.40; N, 4.21.

Thermal Synthesis of Enantiopure (*S*,*S*,*S*)-2c and (*R*,*S*,*S*)-2c. A solution of L-proline-*t*-butyl ester (423 mg, 2.5 mmol) and the racemic 3,3′-dibromo-1,1′-binaphthyl-2,2′-diol (500 mg, 1.16 mmol) was added slowly, at room temperature, to a stirred suspension of potassium carbonate (325 mg, 2.35 mmol) in CH_2Cl_2 (25 mL). Then the stirring mixture was refluxed for 5 h, and after this period, the carbonate was filtered off from the solution, which was concentrated to give a yellow oil. This oil was crystallized from diethyl ether to give a 1:1 (*S*,*S*,*S*)-**2c** and (*R*,*S*,*S*)-**2c** mixture as solid white crystals.

The diastereoisomers have been separated and purified by column chromatography (cyclohexane/ethyl acetate = 7:3) eluting them in the following order: first (*S*,*S*,*S*)-**2c** and then (*R*,*S*,*S*)-**2c**.

General Thermal Synthesis of 2b and 2e. The very same protocol described above was also followed for the synthesis of **2b** and **2e**.

2-({2,2′-Dihydroxy-3′-[(1-methoxycarbonylethylamino)-methyl]-[1,1′]binaphthalenyl-3-ylmethyl}-amino)-propionic Acid Methyl Ester (2e). (*S*,*S*,*S*)-**2e** as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (d, J = 7.1 Hz, 6H), 3.56 (q, J = 7.1 Hz, 2H), 3.79 (s, 6H), 4.18 (d, J = 14.0 Hz, 2H), 4.30 (d, J = 14.0 Hz, 2H), 7.10−7.35 (m, 6H), 7.70−7.90 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.8, 51.3, 52.2, 55.3, 117.4, 123.7, 124.5, 124.8, 126.1, 127.7, 127.8, 128.2, 133.8, 153.4, 174.6. Anal. Calcd for $C_{30}H_{32}N_2O_6$: C, 69.75; H, 6.24; N, 5.42; O, 18.58. Found: C, 69.63; H, 6.28; N, 5.40.

(*R*,*S*,*S*)-**2e** as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (d, J = 7.1 Hz, 6H), 3.56 (q, J = 7.1 Hz, 2H), 3.68 (s, 6H), 4.10 (d, J = 14.1 Hz, 2H), 4.37 (d, J = 14.1 Hz, 2H), 7.10−7.35 (m, 6H), 7.70−7.90 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.0, 51.4, 52.1, 55.4, 117.6, 123.1, 124.4, 124.7, 126.1, 127.8, 127.8, 128.2, 129.9, 154.6, 175.0. Anal. Calcd for $C_{30}H_{32}N_2O_6$: C, 69.75; H, 6.24; N, 5.42; O, 18.58. Found: C, 69.69; H, 6.27; N, 5.44.

2-[(3′-Dimethylaminomethyl-2,2′-dihydroxy-[1,1′]binaphthalenyl-3-ylmethyl)-amino]-propionic Acid Methyl Ester (2f). L-Alanine methyl ester (0.66 g, 6.4 mmol) and **2a** (0.43 g, 1.1 mmol) were dissolved in 100 mL of CH_2Cl_2. The solution was purged with argon, poured into Pyrex tubes, and irradiated for 20 min. After this time, the solution was evaporated and purified by column chromatography (cyclohexane/ethyl acetate = 1:1), giving the reactant **2a** (0.245 g, 0.63 mmol, 57%) and a pale yellow oil, **2f** (0.11 g, 0.24 mmol, 21.5% yield), as a 1:1 diastereomeric mixture.

(*S*,*S*)-**2f** as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (d, J = 7.4 Hz, 3H), 2.39 (s, 6H), 3.50 (q, J = 7.4 Hz, 1H), 3.82 (s, 3H), 3.90 (AB system, 2H), 4.36 (AB system, 2H), 7.3 (m, 6H), 7.7 (s, 2H), 7.79 (d, J = 7.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.0, 44.2, 51.4, 52.1, 55.1, 63.1, 116.1, 117.0, 122.8, 122.9, 124.4, 124.63, 124.65, 124.74, 124.79, 125.5, 125.9, 126.0, 127.49, 127.54, 127.59, 127.8, 128.2, 133.8, 153.2, 153.8, 174.9. Anal. Calcd for $C_{28}H_{30}N_2O_4$: C, 73.34; H, 6.59; N, 6.11; O, 13.96. Found: C, 73.42; H, 6.61; N, 6.16.

(*R*,*S*)-**2f** as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (d, J = 7.4 Hz, 3H), 2.41 (s, 6H), 3.50 (q, J = 7.4 Hz, 1H), 3.84 (s, 3H), 3.95 (AB system, 2H), 4.34 (AB system, 2H), 7.3 (m, 6H), 7.7 (s, 2H), 7.81 (d, J = 7.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.9, 44.2, 51.5, 52.1, 55.5, 63.1, 116.1, 116.9, 122.8, 122.9, 124.4, 124.63, 124.65, 124.74, 124.79, 125.5, 125.9, 126.0, 127.49, 127.54, 127.6, 127.8, 128.2, 133.7, 153.3, 153.8, 174.9. Anal. Calcd for $C_{28}H_{30}N_2O_4$: C, 73.34; H, 6.59; N, 6.11; O, 13.96. Found: C, 73.39; H, 6.58; N, 6.14.

The chiral (*R*) and (*S*) alkylation adducts **2a**, **2g**, **2h**, and **3** have been previously reported[8] and were characterized by comparison with an authentic sample or by comparison of the ^{1}H and ^{13}C NMR spectroscopic data and retention time on chiral column.

3,3′-Bis-(diphenylaminomethyl)-1,1′-binaphthalenyl-2,2′-diol (2i) from a Thermal Synthesis. A solution of 3,3′-dibromomethyl-1,1′-binaphthyl-2,2′-diol (**4**, 0.12 g, 0.28 mmol) and diphenylamine (0.17 g, 1.01 mmol) in 10 mL of CH_2Cl_2 containing a suspension of anhydrous Na_2CO_3 (1.1 g, excess) was heated to reflux for 24 h. After cooling, the solid was filtered off, the solution was evaporated, and the product was purified by column chromatography (cyclohexane/ethyl acetate = 98:2) to give **2i** (36.3 mg, 0.06 mmol yield 20%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.25 (s, 4H), 5.97 (s, 2H acids), 7.01−7.12 (m, 8H), 7.23−7.38 (m, 18H), 7.82 (d, J = 7.9 Hz, 2H), 8.00 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.1, 111.7, 121.1, 121.94, 123.92, 124.0, 126.5, 126.8, 128.2, 128.4, 129.1, 129.3, 132.6, 147.9, 151.1. Anal. Calcd for $C_{46}H_{36}N_2O_2$: C, 85.16; H, 5.59; N, 4.32; O, 4.93. Found: C, 85.07; H, 5.63; N, 4.30.

1-(3′-Dimethylaminomethyl-2,2′-dihydroxy-[1,1′]binaphthalenyl-3-ylmethyl)-pyrrolidine-2-carboxylic Acid Methyl Ester (2j). A solution of **2a** (0.35 g, 0.87 mmol) and L-proline-methyl ester (0.11 g, 0.87 mmol) in 90 mL of CH_2Cl_2 was stripped with argon, poured into Pyrex tubes, and irradiated for 60 min. After this time, the solution was evaporated and purified by column chromatography using ethyl acetate as eluent affording unreacted **2a** (0.210 g, 0.52 mmol, 60%) and **2j** (92.7 mg, 0.19 mmol 22% yield) as a 1:1 (*S*,*S*)+(*R*,*S*) diastereomeric mixture. (*S*,*S*)-**2j**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.86−2.00 (m, 3H), 2.19−2.30 (m, 1H), 2.38 (s, 6H), 2.55−2.70 (m, 1H), 3.14−3.21 (m, 1H), 3.52 (dd, J = 9.1, 5.3 Hz, 1H), 3.67 (s, 3H), 3.77 (AB system, J = 11.6 Hz, 2H), 4.00 (d, J = 13.4 Hz, 1H), 4.13 (d, J = 13.4 Hz, 1H), 7.16−7.28 (m, 6H), 7.64 (s, 1H), 7.66 (s, 1H), 7.79 (d, J = 7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 23.1, 29.4, 44.2, 51.9, 52.6, 57.6, 63.0, 65.0, 116.4, 117.4, 122.68, 122.72, 123.1, 123.5, 124.5, 124.7, 125.1, 125.76, 125.84, 127.31, 127.39, 127.57, 128.7, 129.6, 133.90, 133.94, 153.3, 153.6, 173.5. Anal. Calcd for $C_{30}H_{32}N_2O_4$: C, 74.36; H, 6.66; N, 5.78; O, 13.21. Found: C, 74.48; H, 6.79; N, 5.82.

(*R*,*S*)-**2j**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.86−2.00 (m, 3H), 2.19−2.30 (m, 1H), 2.38 (s, 6H), 2.55−2.70 (m, 1H), 3.14−3.21 (m, 1H), 3.52 (dd, J = 9.1, 5.3 Hz, 1H), 3.67 (s, 3H), 3.79 (d, J = 12.7 Hz, 1H), 4.00 (d, J = 13.4 Hz, 1H), 4.13 (d, J = 13.4 Hz, 1H), 4.38 (d, J = 12.7 Hz, 1H), 7.16−7.28 (m, 6H), 7.64 (s, 1H), 7.66 (s, 1H), 7.79 (d, J = 7.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) 23.1, 29.3, 44.2, 51.9, 52.6, 57.7, 63.1, 65.1, 116.4, 117.4, 122.68, 122.72, 123.5, 124.4, 124.5, 124.7, 124.9, 125.76, 125.84, 127.0, 127.4, 128.1, 128.7, 129.6, 133.90, 133.93, 153.3, 153.6, 173.4. Anal. Calcd for $C_{30}H_{32}N_2O_4$: C, 74.36; H, 6.66; N, 5.78; O, 13.21. Found: C, 74.45; H, 6.77; N, 5.80.

3-Dimethylaminomethyl-3′-morpholin-4-ylmethyl-[1,1′]binaphthalenyl-2,2′-diol (2k). 2a (0.41 g, 1.0 mmol) and morpholine (0.87 mL, 1.0 mmol) were dissolved in 100 mL of CH_2Cl_2. The resulting solution was stripped with argon, poured into Pyrex tubes, and irradiated for 60 min. After this time, the solution was evaporated and purified by column chromatography ($CHCl_3$/*i*-PrOH = 95:5) to give 79.7 mg (0.18 mmol, 18% yield) of a colorless oil (**2k**) and unreacted starting material (0.28 g, 0.68%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.40 (s, 6H), 2.67 (m, 4H), 3.71−3.81 (m, 4H), 3.83 (d, J = 13.6 Hz, 1H), 3.89 (d, J = 13.8 Hz, 1H), 4.10 (d, J = 13.6 Hz, 1H), 4.16 (d, J = 13.8 Hz, 1H), 7.16−7.28 (m, 6H), 7.65 (d, J = 5.6 Hz, 2H), 7.79 (d, J = 8.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 44.2, 52.9, 63.3, 63.1, 66.5, 116.2, 116.7, 122.8, 122.9, 123.1, 124.4, 124.6, 124.7, 125.8, 126.0, 127.5 (2C), 127.6, 128.0, 128.1, 128.2, 133.7, 133.9, 153.1, 153.8. Anal. Calcd for $C_{28}H_{30}N_2O_3$: C, 75.99; H, 6.83; N, 6.33; O, 10.85. Found: C, 76.09; H, 6.88; N, 6.29.

3-[(Di-*i*-propylamino)-methyl]-3′-dimethylaminomethyl-[1,1′]-binaphthalenyl-2,2′-diol (2l). 2a (0.39 g, 0.97 mmol) and di-*i*-propylamine (0.10 g, 0.14 mL, 1.0 mmol) were dissolved in 100 mL of CH_2Cl_2. The obtained solution was purged with argon, poured into Pyrex tubes, and irradiated for 10 min. After this time, the solution was evaporated and the crude was purified by column chromatography ($CHCl_3$/*i*-PrOH = 95:5) to yield **2l** (0.15 mg, 0.33 mmol, 34% yield) as a colorless oil and unreacted starting material **2a** (0.23 g, 58%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (m, 12H), 2.35 (s, 6H), 3.28−3.18 (m, 2H), 3.86 (d, J = 13.6 Hz, 1H), 4.01 (d, J = 13.6 Hz, 1H), 4.05 (d, J = 14.3 Hz, 1H), 4.26 (d, J = 14.3

Hz, 1H), 7.15−7.28 (m, 6H), 7.63 (s, 1H), 7.66 (s, 1H), 7.77 (d, J = 7.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.8, 20.6, 44.3, 47.8, 49.3, 63.2, 116.1, 116.5, 122.5, 122.6, 124.4, 124.5, 124.8, 125.6, 127.3, 127.5, 128.06, 128.11, 133.5, 133.6, 153.7, 154.4. Anal. Calcd for $C_{30}H_{36}N_2O_2$: C, 78.91; H, 7.95; N, 6.13; O, 7.01. Found: C, 78.80; H, 7.89; N, 6.03.

3,3′-Bis-(2-hydroxyethylsulfanylmethyl)-1,1′-binaphthalenyl-2,2′-diol (7a):[21] Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.28 (broad s, 2H acids), 2.71−2.91 (m, 4H), 3.62−3.78 (m, 4H), 4.01 (d, J = 13.0 Hz, 2H), 4.13 (d, J = 13.0 Hz, 2H), 6.20 (broad s, 2H acids), 7.30 (m, 2H), 7.50 (m, 2H), 7.55 (m, 2H), 7.8−8.0 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.6, 33.9, 59.9, 111.8, 123.4, 123.4, 126.3, 126.4, 127.1, 128.2, 129.9, 132.2, 150.3.

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Supporting Information Available: ^{1}H NMR, ^{13}C NMR, and DEPT-135 for the diastereomeric BINOLAMs (*S*,*S*,*S*)-**2b**, (*R*,*S*,*S*)-**2b**, (*S*,*S*,*S*)-**2c**, and (*R*,*S*,*S*)-**2c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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