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# Orthoacylimines: A New Class of Chiral Auxiliaries for Nucleophilic Addition of Organolithium Reagents to Imines

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A new class of orthoacylimine-derived chiral auxiliaries has been synthesized and tested in the nucleophilic addition of organolithium reagents to imines. The precursors can be prepared by an aza-Wittig reaction between the corresponding orthoacyl azide and a variety of aldehydes in the presence of trialkylphosphines. The nucleophilic addition of organolithium reagents led to the addition products in good yields and with good to excellent diastereoselectivities (from 85:15 to 99:1). The chiral, nonracemic secondary amines could be readily obtained under mild hydrolytic condition. Furthermore, the chiral auxiliary can be recovered in quantitative yield and reconverted to the starting orthoacyl azide precursor. This method was applied to the synthesis of (*S*)-*t*-leucine.

Chiral amines are among the most important functionality in organic chemistry. This class of compounds are found in numerous natural[1] and unnatural bioactive products,[2] and they are the key component of several chiral ligands[3] and auxiliaries.[4] It is therefore not surprising to see that several synthetic methodologies relying on the stereoselective nucleophilic addition to imines have been developed for their preparation.[5] Recently, many effective catalytic systems have been developed for the preparation of α-chiral amines involving the nucleophilic addition of dialkylzinc reagents.[6] Although several chiral auxiliaries are available for synthesizing chiral amines (Figure 1), the most effective ones (**1**, **2**)[7] usually cannot be recovered upon cleavage or require several steps to regenerate a suitable auxiliary precursor.[8] Others (**3**, **4**)[9] require some additional steps for the regeneration of a suitable precursor.

One aspect of our program involving the development of new routes to chiral, nonracemic secondary amines led us to investigate whether we could develop a new method that would allow the generation of chiral, nonracemic amines as well as the complete recovery of the chiral auxiliary or one of its precursors that could be easily reconverted into the required starting substrate. In light of this, we were intrigued by the possibility of using orthoacylimines **5** as precursors to chiral amines (Scheme 1). The substrate may show an increased electrophilicity

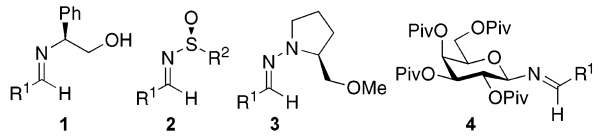


**FIGURE 1.** Some examples of the most effective chiral auxiliaries for nucleophilic addition to imines.

(1) In addition to well-known amino acids and chiral amines, several natural products can be derived from simple chiral amines. For a recent example, see: Davis, F. A.; Mohanty, P. K. *J. Org. Chem.* **2002**, *67*, 1290−1296.

(2) For recent examples, see: (a) Krishnamurthy, D.; Han, Z.; Wald, S. A.; Senanayake, C. H. *Tetrahedron Lett.* **2002**, *43*, 2331−2333. (b) Kobayashi, S.; Matsubara, R.; Kitagawa, H. *Org. Lett.* **2002**, *4*, 143−145. (c) Hett, R.; Fang, Q. K.; Gao, Y.; Wald, S. A.; Senanayake, C. H. *Org. Process Res. Dev.* **1998**, *2*, 96−99. (d) Fang, Q. K.; Senanayake, C. H.; Han, Z.; Morency, C.; Grover, P.; Malone, R. E.; Butler, H.; Wald, S. A.; Cameron, T. S. *Tetrahedron: Asymmetry* **1999**, *10*, 4477−4480. (e) Spencer, C. M.; Foulds, D.; Peters, D. H. *Drugs* **1993**, *46*, 1055.

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(5) For excellent reviews, see: (a) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407−1438. (b) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895−1946. (c) Johansson, A. *Contemp. Org. Synth.* **1995**, *2*, 393−408.

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(8) Davis, F. A.; Reddy, R. E.; Szewczyk, J. M. *J. Org. Chem.* **1995**, *60*, 7037−7039.

(9) (a) Enders, D.; Schubert, H.; Nübling, C. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1109−1110. (b) Enders, D.; Nübling, C.; Schubert, H. *Liebigs Ann./Recl* **1997**, 1089−1100. (c) Laschat, S.; Kunz, H. *J. Org. Chem.* **1991**, *56*, 5883−5889.

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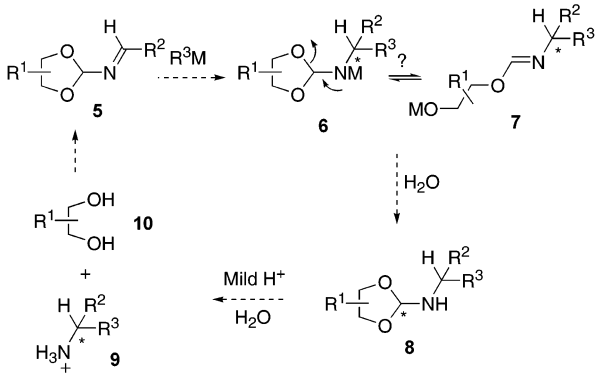
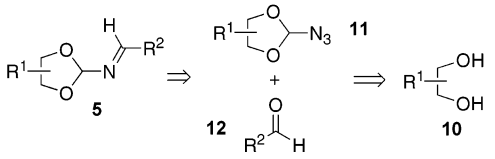
**SCHEME 1**



**SCHEME 2**



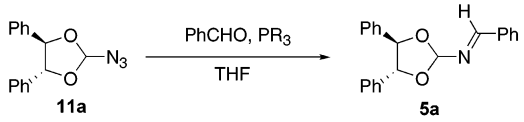
compared to that of simple alkylimines since the amide anion **6** obtained upon nucleophilic addition may undergo ring opening to the more stable alkoxide **7** (p$K_a$ of ~29 for the alcohol vs ~35 for the amine).[10] Furthermore, this ring opening would lead to an *O*-alkylimidate **7** that should be quite unsusceptible to further nucleophilic attack. Protonation and mild acid hydrolysis would lead to the secondary amine. In this paper, we report a method for the preparation of novel chiral orthoacylimines **5** and study their reactivity in the presence of nucleophiles. The optimization of the chiral auxiliary structure to maximize the diastereoselectivities of the addition was also carried out. Finally, an application to the synthesis of *t*-leucine is also presented.

## Results and Discussion

Our strategy for generating orthoacylimines **5** is outlined in Scheme 2. We envisioned that the title compounds could be obtained from the known orthoacyl azides **11** and aldehydes **12** through a Staudinger process.[11] Since orthoacyl azides have been prepared from the corresponding ortho esters, albeit in relatively low yields (30−40%),[12] our first goal was to optimize the conversion of diols **10** to orthoacyl azide **11** and to develop the Staudinger chemistry of the iminophosphorane reagent derived from **11**.

The synthesis of orthoacyl azide has been accomplished by taking an ortho ester and treating it with a large excess of trimethylsilyl azide (10 equiv) without solvent.[12] These conditions were not appropriate for our system, and after optimization of the reaction conditions, we found that the synthesis of orthoacyl azides could be readily accomplished by treating a stoichiometric amount of the diol with trimethyl- or triisopropylorthoformate in the presence of *p*-toluenesulfonic acid in THF. The ortho ester is typically formed in quantitative yield but we found that it was preferable to carry the introduction of the azide group reaction directly by submitting the reaction mixture to trimethylsilyl azide without the need to isolate the ortho ester.

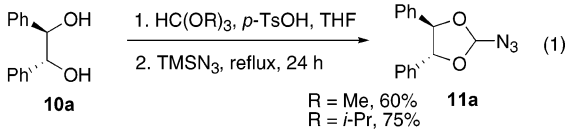
**TABLE 1. Optimization of the Aza-Wittig[a]**



| entry | R | time (h) | conversion (%)[b] |
|---|---|---|---|
| 1 | Ph | 4 | 9 |
| 2 | Ph | 20 | 21 |
| 3 | Ph | 48[c] | >95 |
| 4 | Me | 4 | >95 (89)[d] |
| 5 | Bu | 4 | 69 |
| 6 | Bu | 20 | >95 |

[a] All reactions were carried out at room temperature using a stoichiometric amount of phosphine. [b] Conversions were determined by $^1$H NMR on the crude reaction mixture. [c] Reaction was carried out under refluxing toluene. [d] Isolated yield.

For example, (*R*,*R*)-1,2-diphenylethylene-1,2-diol (**10a**) is converted into orthoacyl azide **11a** in 60% overall yield when trimethylorthoformate is used and in 75% overall yield with triisopropylorthoformate (eq 1). A small amount of the unreacted ortho ester accounts for the rest of the mass and always remains present even if an excess of the reagent is used. All our attempts to push the reaction to completion were unsuccessful. Typically, the yield for the orthoacyl azide formation is slightly higher with triisopropylorthoformate, but it was more convenient and practical to use trimethylorthoformate since the residual ortho ester byproduct was more easily separated from the orthoacyl azide on a larger scale.

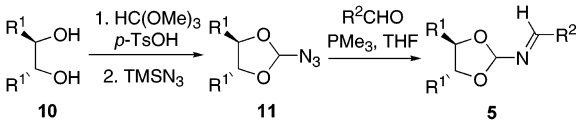


The subsequent conversion of azide **11a** into the orthoacylimine derived from benzaldehyde using the aza-Wittig reaction was then investigated. Attempts to carry the aza-Wittig reaction with triphenylphosphine led to a low yield of the desired imine even if the reaction mixture was stirred for 20 h at room temperature (Table 1, entries 1 and 2). However, quantitative conversion could be achieved with triphenylphosphine, but high temperatures and long reaction times were necessary (Table 1, entry 3). It was clear that under these conditions, the iminophosphorane was formed but was not sufficiently reactive to react with benzaldehyde. Conversely, the use of trialkylphosphines led to the rapid quantitative conversion to the orthoacylimine (entries 4 and 6). The reaction with trimethylphosphine led to quantitative formation of the imine within 4 h, whereas that with tributylphosphine was complete after 20 h. The orthoacylimine **5a** was chromatographically stable (buffered with $Et_3N$) and could be isolated in high yield (89%). In all cases, only one isomer of the imine was observed.

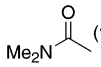
These reaction conditions were then applied to a wide range of different diols and aldehydes, and the results are shown in Table 2. Diols **10a**−**f** were converted to their corresponding orthoacyl azide **11** in yields ranging from

(10) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456−463.
(11) Staüdinger, H.; Meyer, J. *Helv. Chem. Acta* **1919**, *2*, 635−646.
(12) Hartmann, W.; Heine, H.-G. *Tetrahedron Lett.* **1979**, *20*, 513−516.

**TABLE 2. Synthesis of Orthoacylimine 5**




**10** **11** **5**

| Entry | $R^1$ | Yield (**11**) | $R^2$ | Yield (**1**) |
|---|---|---|---|---|
| 1 | Ph (**10a**) | 60[a] (**11a**) | Ph (**5a**) | 89 |
| 2 | | | $PhCH{=}CH_2$ (**5b**) | 86 |
| 3 | | | *t*-Bu (**5c**) | 93 |
| 4 | | | 1-furyl (**5d**) | 76 |
| 5 | | | *i*-Pr (**5e**) | 36[b] |
| 6 | 1-Naphthyl (**10b**) | 65 (**11b**) | Ph (**5f**) | 84 |
| 7 |  (**10c**) | 65 (**11c**) | Ph (**5g**) | 76 |
| 8 | $BnOCH_2$ (**10d**) | 68 (**11d**) | Ph (**5h**) | 85 |
| 9 |  (**10e**) | 62 (**11e**) | Ph (**5i**) | 87 |
| 10 | **10f**[c] | 57 (**11f**) | Ph (**5j**) | 74 |

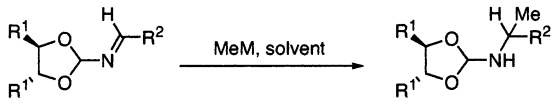
[a] Yield increases to 75% when $HC(Oi\text{-}Pr)_3$ is used instead of $HC(OMe)_3$. [b] Conversion is >90%, but the product decomposed upon purification. [c] **10f** = 1,3-Diphenylpropane-1,3-diol.

57 to 68% when trimethylorthoformate was used. The reactions were very clean in all cases, and the intermediate ortho ester was the only byproduct. All the reaction products were chromatographically stable and could be separated from the residual ortho ester by chromatography. The orthoacyl azides (**11a**−**f**) thus obtained were then treated with several aldehydes in the presence of trimethylphosphine to give the corresponding orthoacylimines in high yields. The only exception was with the imine derived from isobutyraldehyde for which a quantitative conversion was observed, but our attempts to isolate it by chromatography on silica gel were not successful due to the instability of the product (entry 5).[13]

Although the acyl azide **11a** reacted with aliphatic, unbranched aldehydes in quantitative yields, the lability of the corresponding imine also prevented its isolation in pure form.

With the orthoacylimines in hand, the next step was to estimate their electrophilicity when submitted to organometallic reagents and to optimize the structure of the chiral auxiliary to maximize the diastereoselectivities. Some selected reaction conditions are shown in Table 3. Among the wide range of nucleophiles that were tested (organolithium, Grignard, organocerium, organozinc, and organocopper reagents), only the organolithium reagents produced the desired addition products in high yields (Table 3). This is somewhat surprising on the basis of our mechanistic picture for this reaction. It appears that orthoacylimines **5** are not significantly more electrophilic than other alkylimines. Allylmagnesium bromide was the only Grignard reagent to react cleanly but with a poor level of diastereocontrol. The unique reactivity of allyl Grignard reagents with imines compared to other Grignard reagents has been observed before.[14] The diastereoselectivities in this system were then optimized using the orthoacylimine **5a** derived from 1,2-diphenylethane-1,2-diol (entries 1−4). It was noticed that the solvent played a profound role, causing a high level of diastereocontrol. The use of strong complexing solvents led to higher diastereoselectivities, and DME was identified as the optimal and most practical solvent among the most complexing ones.[15,16] With these conditions established, several orthoacylimines derived from structurally similar diols were tested (entries 7−11). Replacement of the phenyl substituent by several other groups such as naphthyl or benzyloxymethyl led to lower diastereoselectivities (entries 7 and 9). The only slight improvement could be observed when 1,3-diphenylpropane-1,3-diol was used as the chiral auxiliary precursor. Although the selectivities were similar, we opted to use the simpler auxiliary derived from 1,2-diphenylethane-1,2-diol to define the synthetic scope of the reaction.

**TABLE 3. Optimization of the Nucleophilic Addition**




**5a, f-j** **8a, f-j**

| entry | **5** | MeM, solvent[a] | dr[b] |
|---|---|---|---|
| 1 | **a** | MeLi, toluene | 52:48 |
| 2 | **a** | MeLi, ether | 75:25 |
| 3 | **a** | MeLi, THF | 79:21 |
| 4 | **a** | MeLi, DME | 91:9 |
| 5 | **a** | MeMgBr, THF | nr[c] |
| 6 | **a** | $Me_2CuLi$, ether | nr |
| 7 | **f** | MeLi, DME | 74:26 |
| 8 | **g** | MeLi, DME | 60:40 |
| 9 | **h** | MeLi, DME | 81:19 |
| 10 | **i** | MeLi, DME | dec |
| 11 | **j** | MeLi, DME | 92:8 |

[a] Unless otherwise noted, the conversions were >90%. [b] Diastereoselectivities were estimated by measuring the ee of the amine obtained after cleavage (HCl, MeOH). [c] nr= no reaction. dec = decomposition. [d] **5f** = imine derived from 1,3-diphenylpropane-1,3-diol.

Several imines were prepared and tested with MeLi, BuLi, and PhLi in DME (Table 4). Four classes of imines were suitable for nucleophilic addition chemistry: the arylimines, the α,β-unsaturated imines, heteroarylimines, and alkylimines without enolizable protons. In most cases, the yields were quite good and the selectivities ranged from 85:15 to 99:1. The yields were also quite good even with the imine derived from pivaldehyde (entries 6−9). In one case, the diastereoselectivities were outstanding (entry 8), but the yield decreased to 54%. All our attempts to improve the yield by increasing the reaction temperature led to a slightly lower diastereoselectivities (entry 9). It should also be pointed out that in all cases, the chiral diol could be recovered in high yield (>95%) after mild acid hydrolysis.

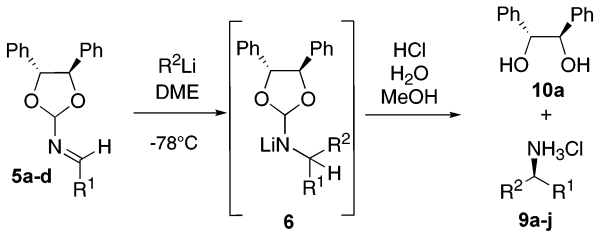
(13) Although we could directly submit the crude imine to the nucleophilic addition conditions, only decomposition occurred upon treatment with alkyllithium reagents. This is presumably due to the competitive enolization reaction of the alkylimine.

(14) Kleinman, E. F.; Volkman, R. A. In *Comprehensive Organic Synthesis: Additions to C−X π-Bonds*; Heathcock, C. H., Ed.; Pergamon: Oxford 1991; Vol. 2, Part 2, pp 975−1006.

(15) Additives such as DMPU, TMEDA, and HMPA were also tested, but no increase in the diastereocontrol could be observed. The addition of Lewis acids was also not effective in improving the selectivities.

(16) Although the role of DME is not clear, it certainly decreases the aggregation state of methyllithium. See for example: Deacon, G. B.; Forsyth, C. M.; Scott, N. M. *J. Chem. Soc., Dalton Trans.* **2001**, 2494−2501.

**TABLE 4. Scope of the Addition of Organolithium Reagents**




| Entry | $R^1$ | $R^2$ | Yield (**9**) | *er (ee)* **9**[a,b] |
|---|---|---|---|---|
| 1 | Ph (**5a**) | Me | >98 (**9a**) | 91:9 (83) |
| 2 | Ph (**5a**) | Bu | 95 (**9b**) | 86:14 (72) |
| 3 | PhCH=CH- (**5b**) | Me | >98 (**9c**) | 88:12 (74) |
| 4 | PhCH=CH- (**5b**) | Bu | >98 (**9d**) | 85:15 (70) |
| 5 | PhCH=CH- (**5b**) | Ph | 90 (**9e**) | 88:12 (74) |
| 6 | *t*-Bu (**5c**) | Me | 62 (**9f**) | 93:7 (86) |
| 7 | *t*-Bu (**5c**) | Bu | 70 (**9g**) | 96:4 (92) |
| 8 | *t*-Bu (**5c**) | Ph | 54 (**9h**) | 99:1 (98) |
| 9[c] | *t*-Bu (**5c**) | Ph | 70 (**9h**) | 96:4 (92) |
| 10 |  (**5d**) | Me | 70 (**9i**) | 89:11 (78) |
| 11 |  (**5d**) | Bu | 33 (**9j**) | 85:15 (70) |

[a] The enantiomeric ratios were determined by SFC on chiral phase (chiralsel OD or OJ). [b] The stereochemistry (shown) was established by comparison with authentic material. [c] Reaction was run at −50 °C.

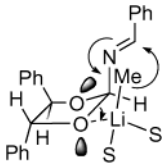
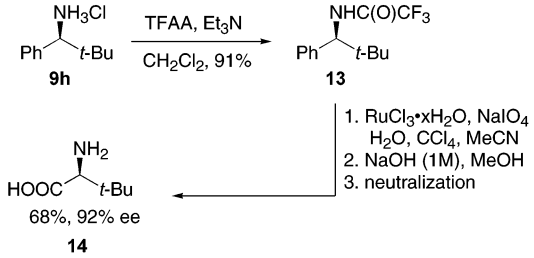



**FIGURE 2.** Model consistent with the observed relative diastereoselection (S = DME).

The relative diastereoselection can be explained by the transition model shown in Figure 2. We believe that the reaction proceeds via a six-membered transition structure in which the equatorial and more accessible lone pair of the dioxolane oxygen atom is involved in the chelation with the monomeric organolithium·DME complex. The imine nitrogen substituent adopts the pseudoaxial conformation due to the anomeric stabilization (oxygen lone pairs into $\sigma^*_{C-N}$). Transfer of the methyl group to the *Re* face of the most stable conformation of the imine leads to the (*R*)-α-chiral amine. The absolute configuration of all the amines obtained are consistent with this model.

Amine **9h** could be converted into *t*-leucine using a simple three-step process (Scheme 3).[17] Protection as the trifluoroacetamide **13**, followed by Sharpless oxidation[18] and deprotection, afforded *t*-leucine **14** in 68% overall yield and without any racemization.

**SCHEME 3. Synthesis of *t*-Leucine**




In conclusion, we have studied a novel class of chiral auxiliaries for the nucleophilic addition to imines. The main advantage of the method is the ease of recovery of the chiral auxiliary after the addition and the mild cleavage conditions for liberating the amine. Further work is in progress to optimize the auxiliary structure.

## Experimental Section

**General Procedure for the Synthesis of Orthoacyl Azide 11a−f.** To a solution of diol **10a** (20.0 g, 93.4 mmol, 1.00 equiv) and *p*-TsOH·$H_2O$ (888 mg, 4.67 mmol, 0.05 equiv) in THF (950 mL, 0.1M) was added trimethylorthoformate or triisopropylorthoformate (10.7 mL, 98.0 mmol, 1.05 equiv). The reaction mixture was stirred at room temperature for 1 h, and trimethylsily azide (62.0 mL, 466 mmol, 5.00 equiv) was added. The clear solution was heated under reflux for 24 h (CAUTION: Care should be taken when manipulating trimethylsilyl azide due to its explosive nature and toxicity). The reaction mixture was cooled to room temperature, transferred to a separatory funnel, and diluted with $CH_2Cl_2$, and the reaction was quenched with saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was washed with three portions of $CH_2Cl_2$. The organic solution was dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography to afford the pure orthoacyl azide.

**General Procedure for the Synthesis of Orthoacylimine 5a−k.** To a solution of orthoacyl azide **11a** (1.0032 g, 3.75 mmol, 1.00 equiv) and benzaldehyde (419 μL, 4.13 mmol, 1.10 equiv) in THF (38 mL, 0.1 M) was added trimethylphosphine (420 μL, 4.13 mmol, 1.10 equiv). Nitrogen evolution was observed instantly upon the addition of trimethylphosphine. The reaction mixture was stirred at room temperature for at least 10 h and then concentrated under reduced pressure. The crude residue was purified by flash chromatography to give the pure orthoacylimine.

**General Procedure for the Nucleophilic Addition to Orthoacylimines 5a−j.** To a solution of orthoacylimine **5a** (525.9 mg, 1.60 mmol, 1.00 equiv) in DME (16 mL, 0.1 M) at −78 °C was added dropwise MeLi (1.35 M) (salt free) (1.8 mL, 2.39 mmol, 1.50 equiv) at a rate that maintained the internal temperature below −70 °C. The reaction mixture was stirred for 2 h at −78 °C, and then the reaction was quenched by the slow addition of methanol (2 mL). The mixture was then warmed to room temperature, and 10 mL of a 50% (v/v) HCl/MeOH solution was added. The resulting mixture was stirred for at least 10 h or until TLC analysis showed complete consumption of orthoacylamide **6a**. Silica gel (ca. 5 g) was added, and the mixture was concentrated under reduced pressure (dry pack column). The residual silica gel was then introduced on top of a prepacked silica gel flash chromatography colomn and elution (15% MeOH/$CH_2Cl_2$) afforded diol

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**10a** (342.8 mg, 100%) in the first fractions followed by the pure amine hydrochloride **9a** as a white solid (252.2 mg, 100%).

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**Supporting Information Available:** Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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