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# Iron-Catalyzed Suzuki–Miyaura Cross-Coupling Reactions between Alkyl Halides and Unactivated Arylboronic Esters

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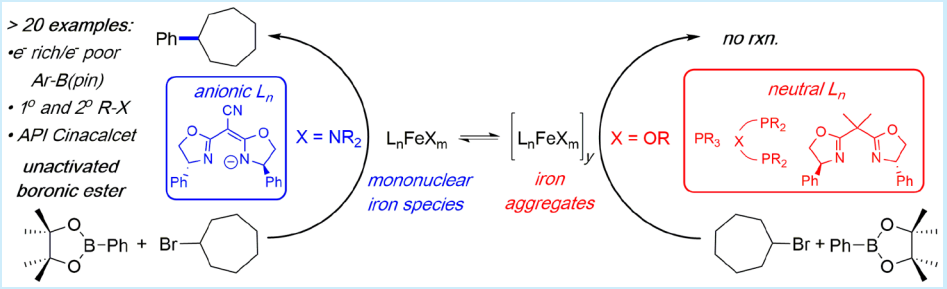
Supporting Information




**ABSTRACT:** An iron-catalyzed cross-coupling reaction between alkyl halides and arylboronic esters was developed that does not involve activation of the boronic ester with alkyllithium reagents nor requires magnesium additives. A combination of experimental and theoretical investigations revealed that lithium amide bases coupled with iron complexes containing deprotonated cyanobis(oxazoline) ligands were best to obtain high yields (up to 89%) in catalytic cross-coupling reactions. Mechanistic investigations implicate carbon-centered radical intermediates and highlight the critical importance of avoiding conditions that lead to iron aggregates. The new iron-catalyzed Suzuki–Miyaura reaction was applied toward the shortest reported synthesis of the pharmaceutical Cinacalcet.



Transition-metal-catalyzed cross-coupling reactions have emerged as robust methods for the efficient construction of carbon–carbon bonds in organic synthesis.[1] Of particular industrial importance are cross-coupling reactions that use boronic esters or acids as transmetalating reagents (i.e., Suzuki–Miyaura reaction).[2] This reaction is typically carried out using palladium-based catalysts,[3] which have demonstrated tremendous utility, but are toxic[4] and costly. Moreover, despite significant advances in ligand design,[5] palladium-based catalysts also demonstrate some substrate scope limitations, most notably for reactions involving secondary or tertiary alkyl halides.[5f] Pioneering work from Fu and co-workers has expanded the substrate scope limitations of palladium-based catalysts with the development of many useful nickel-based catalysts.[6,7] In parallel, potentially less toxic iron-based catalysts have also been developed for similar cross-coupling reactions. However, most of these methods have been primarily limited to reactions involving Grignard (i.e., Kumada-type) or alkyl zinc (i.e., Negishi-type) transmetalating reagents.[8] Iron-catalyzed Suzuki–Miyaura cross-coupling reactions are limited to three examples, all requiring the addition of alkyllithium reagents and magnesium additives.[8c,9] Herein, a new iron-based catalyst system is disclosed for the cross-coupling of alkyl halides with arylboronic esters that avoids activating the boronic ester with pyrophoric alkyllithium reagents and does not require the addition of magnesium salts to aid with transmetalation (Figure 1).

Considering the efficiency of iron-catalyzed Kumada reactions[8e] and the sluggishness of the corresponding Suzuki–Miyaura reactions, we reasoned that transmetalation was the key step. Extensive studies have been carried out to understand how base additives aid transmetalation in palladium-catalyzed systems.[10] Two viable pathways have emerged: either the base forms a nucleophilic organoborate species *in situ* or it converts the palladium(II) aryl-halide species formed after oxidative addition to a palladium(II) aryl-hydroxide intermediate that is better suited for transmetalation with boronic acids.[11] Hartwig[10a] and Denmark[10b,c] have recently demonstrated that conditions which lead to the formation of palladium hydroxides are crucial for successful transmetalation. We hypothesized that application of analogous conditions to iron-based catalyst systems would lead to iron-hydroxide or alkoxide intermediates that would be prone to irreversible aggregation[12] and subsequent deactivation for cross-coupling reactions.

An alternative hypothesis is that unfavorable thermodynamics hinder transmetalation. To investigate this possibility, a computational model was developed to evaluate transmetalation from phenylboronic acid pinacol ester [PhB(pin)] to diphenylphosphinoethane (dppe) iron(II) complexes (Figure S1). This study revealed that the thermodynamics for transmetalation from iron alkoxides are uphill but accessible at room temperature ($\Delta G$ = +5 kcal/mol). Given this finding, the possibility for a boron-to-

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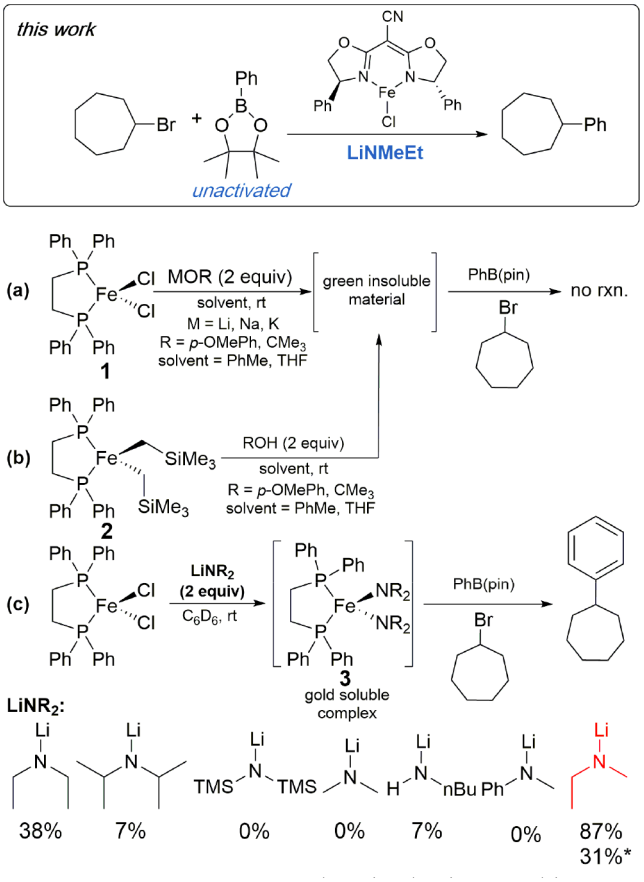


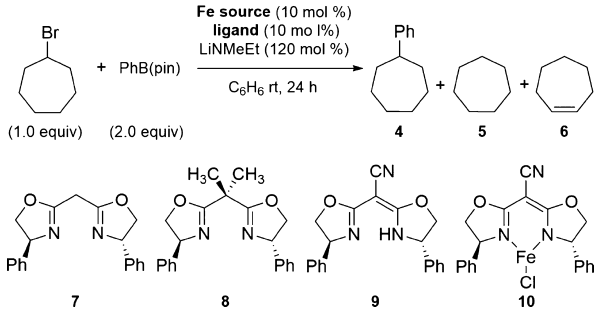

**Figure 1.** Attempted synthesis of (dppe)Fe(OR)$_2$ using (a) salt metathesis and (b) protonolysis. (c) Stoichiometric reactions between (dppe)FeCl$_2$ and LiNR$_2$ and activity for alkyl-aryl Suzuki−Miyaura cross-coupling; *10 mol % (dppe)FeCl$_2$.

iron transmetalation proceeding through the intermediacy of an iron alkoxide complex was tested experimentally. However, attempts to synthesize a mononuclear iron alkoxide complex either through a salt metathesis route from (dppe)FeCl$_2$ (i.e., **1**, Figure 1a) or a protonolysis route from (dppe)Fe(CH$_2$SiMe$_3$)$_2$ (i.e., **2**, Figure 1b)[12c] led to a green insoluble material that was completely inactive for cross-coupling reactions.[13]

Iron amides were explored next as possible intermediates for transmetalation. The computational model predicted that these intermediates would have favorable thermodynamics for transmetalation (−6 kcal/mol), and the steric and electronic environment about iron amides are more readily tunable compared to iron alkoxides. When **1** was treated with lithium diethylamide, a golden homogeneous reaction mixture resulted, and its $^1$H NMR spectrum suggested the formation of predominately one new species (Figure 1c and Figure S2). The instability of this complex has precluded further characterization, but we hypothesize that the expected (dppe)Fe(NEt$_2$)$_2$ complex **3** was formed because the desired cross-coupled product **4** was produced in 38% yield when PhB(pin) and cycloheptyl bromide were added to the reaction mixture. The only other products formed were cycloheptane (**5**) and cycloheptene (**6**). As expected, the yield of **4** was strongly dependent on the identity of the lithium amide used (Figure 1c). Sterically demanding and/or electron deficient amides gave little to no product (e.g., LDA, LiHMDS, or LiNMePh). Small amides, such as LiNMe$_2$ and LiHNBu, were also ineffective. The sensitivity of the reaction to the steric environment of the amide was highlighted by LiNMeEt, which was superior to all other amides evaluated. Furthermore, catalytic cross coupling could be achieved when LiNMeEt was used in conjunction with catalytic amounts of **1** (Figure 1c).[14]

An extensive ligand evaluation (Table S2) revealed that bisoxazoline (BOX) ligands were exceptionally effective for the catalytic transformation. Yields were particularly sensitive to substitution on the bridging carbon of the BOX ligand (Table 1).

**Table 1. Reaction Optimization**




| entry | Fe source | ligand | **4** (%) | **5** (%) | **6** (%) |
|---|---|---|---|---|---|
| 1 | FeCl$_2$ | none | 25 | 15 | 48 |
| 2 | FeCl$_2$ | **7** | 36 | 14 | 16 |
| 3 | FeCl$_2$ | **8** | 25 | 16 | 26 |
| 4 | FeCl$_2$ | **9** | 58 | 14 | 10 |
| 5[a] | FeCl$_2$ | **9** | 72 | 6 | 6 |
| 6 | **10** | none | 74 | 0 | 10 |
| 7[b] | **10** | **9** | 82 | 1 | 7 |
| 8[c] | **10** | **9** | 89 | 2 | 6 |
| 9[bd] | **10** | **9** | 75 | 2 | 13 |
| 10[be] | **10** | **9** | 69 | 1 | 19 |

[a]20% of **9**. [b]48 h. [c]48 h; 10% of **10** and 60% of LiNMeEt added after 24 h. [d]5% of **10** and **9**. [e]1% of **10** and **9**.

Significantly higher yields were obtained when using the commercially available cyanoBOX ligand **9** as opposed to unsubstituted ligand **7** or isopropylidene ligand **8** (entries 2−4). Yields were further improved to 72% when an additional equivalent of **9** relative to iron was added (entry 5). The higher yields observed under these reaction conditions coincided with reduced amounts of cycloheptane and cycloheptene side products. We hypothesized that **9** was superior to the other BOX ligands due to its increased acidity, which led to ligand deprotonation under the basic reaction conditions. To test this hypothesis, iron complex **10** containing a monoanionic cyanoBOX ligand **9** was synthesized and evaluated. This complex was found to be more effective than the *in situ* formed catalyst (cf. entry 6 to entry 4). Yields were once again improved by adding exogenous ligand to **10** (entry 7), although prolonged reaction times were required. Alternatively, full conversion of the alkyl halide and nearly 90% yield was obtained if an additional 10 mol % of **10** and 0.6 equiv of LiNMeEt were introduced to the reaction after 24 h (entry 8). Catalyst loadings as low as 1% led to useful yields of **4**, although cycloheptene became more prevalent at lower catalyst loadings (entries 9−10).

The reaction scope was explored next (Scheme 1). Primary and secondary alkyl bromides were tolerated (**4b**, **11b**−**12b**) and even the tertiary alkyl chlorides **19a** and **20a** led to some of the desired cross-coupled product. A marked difference in reactivity was observed for benzylic substrates with respect to the identity



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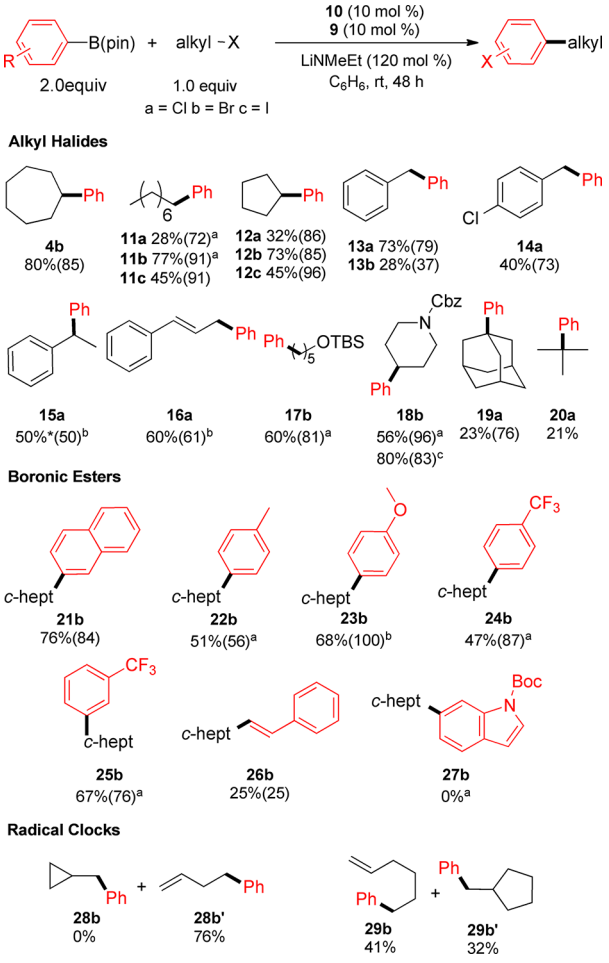
**Scheme 1. Substrate Scope [Isolated Yield (brsm)]**




[a]50 °C. [b]**10** (0.1 mmol) and LiNMeEt (0.6 mmol) added after 24 h. [c]48 h; **10** (0.1 mmol), PhB(pin) (1 mmol), and LiNMeEt (0.6 mmol) added after 24 h.

of the halide. Typically, alkyl bromides were superior to alkyl iodides, which were superior to alkyl chlorides (cf. **11a**–**11c**). In contrast, higher yields were obtained for benzyl chloride (**13a**) compared to benzyl bromide (**13b**). This difference was attributed to the propensity for benzylic substrates to undergo homocoupling as a result of radical recombination; similar homocoupling was not observed for unactivated alkyl halide substrates. Competitive homocoupling of the secondary benzyl chloride **15a** and allylic chloride **16a** led to depressed but still synthetically useful yields for these substrates. Functionalized alkyl halides, including a protected alcohol (**17b**) and a protected amine (**18b**), were tolerated, leading to clean reactions with high yields based on recovered starting materials. The reaction also tolerated different boronic esters (Scheme 1). Cross-coupling involving naphthylboronic ester **21** proceeded similarly as PhB(pin). Electron-rich arylboronic esters **22** and **23** demonstrated reduced efficiency, which is likely due to slower transmetalation rates.[15] Electron-deficient substrates **24** and **25** were competent if the reaction mixture was heated. Alkenylboronic esters (e.g., **26**) produced the desired cross coupling product, albeit in lower yields compared to arylboronic esters. Unfortunately, heteroaromatic substrates (e.g., **27**) were not tolerated under these conditions nor were substrates with enolizable functional groups (e.g., alkyl halides containing esters or nitrile functional groups). Most reactions proceeded without formation of side products, leading to high yields based on recovered starting material; low yields were often a consequence of catalyst deactivation. Filtration and resubjecting such reaction mixtures to the reaction conditions led to further 10–25% improvement in yield as demonstrated for **18** (Scheme 1).

Our mechanistic understanding of the reaction is contextualized within the framework proposed by Nakamura,[8c] and supported by Neidig[16] for iron-catalyzed Suzuki–Miyaura cross-coupling reactions between alkyl electrophiles and preactivated aryl borates (Figure 2a). While this reaction

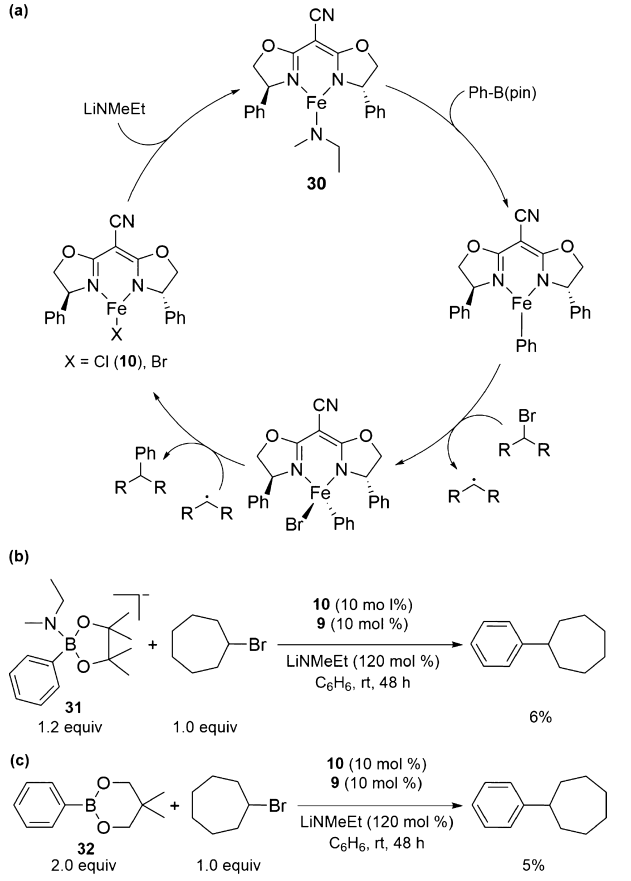



**Figure 2.** (a) Working mechanistic hypothesis. Effect of using (b) $[Ph(NMeEt)B(pin)]^-$ **31** or (c) PhB(neo) **32** in reaction.

mechanism involves the interconversion of iron(II) and iron(III) intermediates, we cannot rule out alternative pathways, such as the iron(I)/iron(II)/iron(III) pathway proposed by Norrby and Bedford.[8k,9a] Regardless of the precise details, carbon-based radical intermediates are likely formed here because ring-opened products are exclusively produced when the radical clock substrate **28** is used (Scheme 1). Likewise, mixtures of direct cross-coupling and cross-coupling that occur after ring closure were also observed when radical clock **29** was used, suggesting radical lifetimes on the order of $10^5$ $s^{-1}$.[17] Similar results were obtained by Nakamura,[8c] which is consistent with our working hypothesis that the cross-coupling mechanism follows a similar route (Figure 2a).

Two key differences between the system reported here and those reported by Nakamura and Bedford are the identity of the ligand and the involvement of the amide base. In addition to forming an anionic cyanoBOX ligand that is less prone to



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dissociation and subsequent iron aggregation compared to neutral bisphosphines, we also posit that the lithium amide base is necessary to convert the putative iron halide **10** into an iron amide species (**30**) that is superior for effecting transmetalation (Figure 2a). Several trends observed during catalyst optimization are more consistent with an iron amide being involved in transmetalation as opposed to transmetalation proceeding through a borate species formed from reaction of the boronic ester with the amide base. PhB(pin) reacts with LiNMeEt to make borate species **31**, which we have detected by $^{11}$B NMR spectroscopy (Figure S4). However, boronic esters that are expected to form borate species more readily result in sluggish reactions (e.g., electron-deficient boronic esters) or nearly no reaction at all (e.g., **32**, Figure 2c). Moreover, when independently synthesized **31** was added to the cross-coupling reaction, greatly diminished yields were obtained (6%) compared to when the lithium amide and boronic ester are added to the reaction separately (82%) (Figure 2b).[18] While these findings do not definitively rule out the intermediacy of a borate species, the inhibitory nature observed when such species predominate makes us favor a pathway that involves iron amide intermediates as a necessary precursor for transmetalation.

Finally, the utility of the new cross-coupling method was demonstrated with the synthesis of the pharmaceutical agent Cinacalcet (a.k.a. Sensipar from Amgen). Cinacalcet is a calcimimetic[19] that is used to treat secondary hyperparathyroidism.[20] Most methods currently used for the synthesis of Cinacalcet rely on noble metal catalysts for its construction and/or involve the alkene intermediate **33** (Figure 3a).[21] We

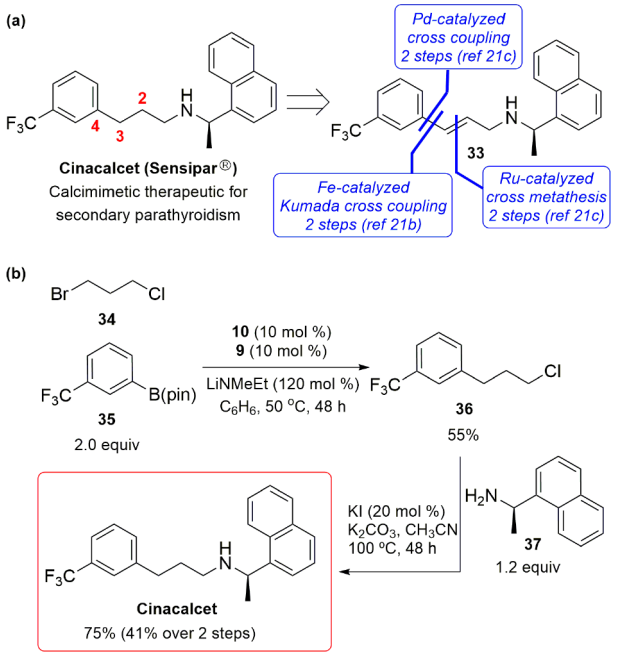


**Figure 3.** Synthesis of cinacalcet: (a) three-step syntheses previously reported and (b) two-step synthesis using iron-catalyzed alkyl-aryl Suzuki−Miyaura cross-coupling reaction.

envisioned that the hydrogenation step involved to convert **33** to Cinacalcet could be avoided if $C_3$−$C_4$ was formed using our newly developed iron-catalyzed Suzuki−Miyaura reaction, providing access to the pharmaceutical agent in two steps. Figure 3b contains the new synthesis, which takes advantage of the difference in reactivity between alkyl chlorides and bromides, leading to an efficient coupling reaction between the commodity chemical 1-bromo-3-chloropropane (**34**) and arylboronic ester **35**. The reaction proceeded in 55% yield with only 10% of bisarylated product being formed. The alkyl halide **36** could then be efficiently elaborated to Cinacalcet by using it to alkylate the commercially available amine **37**. This route constitutes a high yielding synthesis of Cinacalcet (41% overall) in fewer steps than any of the routes reported in the Amgen patent[21c] and without the use of any noble metal catalysts or pyrophoric organometallic reagents.

In conclusion, these results highlight the importance of considering the aggregation state of reactive intermediates involved in iron-catalyzed cross-coupling reactions. The conditions that were found to be most successful to effect the Suzuki−Miyaura reaction were those that avoided formation of iron aggregates. A secondary but important factor for the success of these reactions was the involvement of anionic ligands and the use of amide bases, both of which make transmetalation from boron to iron more facile. Importantly, while these results demonstrate that mononuclear iron species are critical for successful cross-coupling reactions between alkyl halides and unactivated arylboronic esters, it is likely true that other iron-catalyzed cross coupling reactions require higher ordered iron species. Exemplifying this point are recent findings pertaining to iron-catalyzed cross-coupling of vinyl halides and aryl Grignard reagents, which involve iron cluster intermediates.[22] While extensive mechanistic investigations are still needed to rationalize these preferences, aggregation state is nevertheless important to consider when designing new iron-based catalysts for cross-coupling reactions.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02184.

Full experimental procedures, computational models, and additional experiments (PDF)

*XYZ* coordinates (PDF)

### Accession Codes

CCDC 1854710 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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### Notes

The authors declare no competing financial interest.

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