Synlett C. S. Marques et al. Letter

Pd-Catalyzed One-Pot Borylation/Intramolecular Asymmetric Arylation on α-Ketiminoamides: Innovative Approach to Chiral 3-Amino-2-oxindoles

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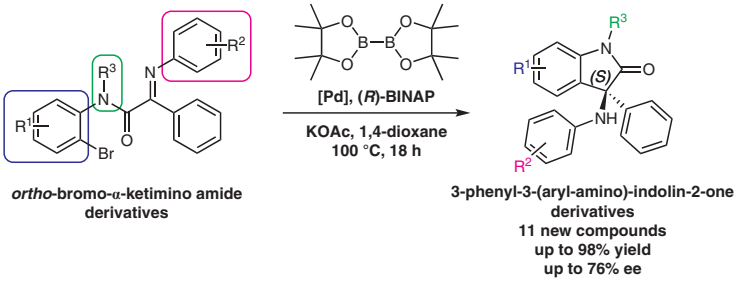


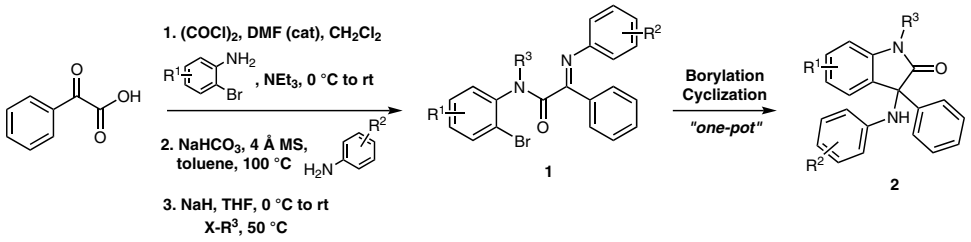
Received: 30.08.2017
Accepted after revision: 04.10.2017
Published online: 03.11.2017
DOI: 10.1055/s-0036-1590940; Art ID: st-2017-d0656-l

Abstract 3-Amino-2-oxindole derivatives are a common framework found in many natural products and medicinal compounds and thus their synthesis is of significant importance. We report for the first time a one-pot approach for the synthesis of these compounds, using a borylation/intramolecular asymmetric arylation sequence starting from *ortho*-bromo-α-ketimino amide derivatives. $Pd(OAc)_2$ was used as the pre-catalyst along with (*R*)-BINAP as the chiral source. We successfully obtained a family of 3-phenyl-3-(aryl-amino)-indolin-2-one derivatives (11 in total) with excellent yields (up to 98%) and enantioselectivities of up to 76% ee. The reaction is versatile and tolerant of a wide range of functional groups.

Key words oxindoles, intramolecular, bis(pinacolate)diboron, palladium, arylation, α-ketimines

The oxindole framework, bearing a tetrasubstituted quaternary carbon stereocenter in the 3-position, is a privileged and common substructure found in numerous natural products and biologically active molecules.[1] Our group has particular interest in the synthesis of 3-amino-2-oxindoles due to their presence in promising drug candidates, particularly for cancer and neurodegenerative diseases.[2] Very recently we reported an interesting Rh-catalyzed addition of arylboronic acids to isatin-derived *N*-Boc-protected ketimines to afford novel 3-amino-3-aryl-2-oxindoles in very good yields. Notably, this was the first catalytic enantioselective procedure with this substrate type.[3] Although some methods have been described in the literature,[4,5] we have investigated a novel one-pot borylation/intramolecular cyclization to give 3-amino-2-oxindoles. Although transition-metal-catalyzed (Rh, Pd) arylation of protected ketimines using arylboron reagents is a well-established methodology for obtaining chiral amines, particularly tetrasubstituted quaternary centers;[6] there has been very little reported on the intramolecular version. Besides our own report, the only other report is that of Ley and co-workers who disclosed an intramolecular arylation on a ketimine to afford oxindoles with an α-tertiary amine at the 3-position.[7] The methodology is interesting but limited to one type of ketimine substrate and also to one chiral phosphane ligand, namely (*R*)-DifluorPhos.

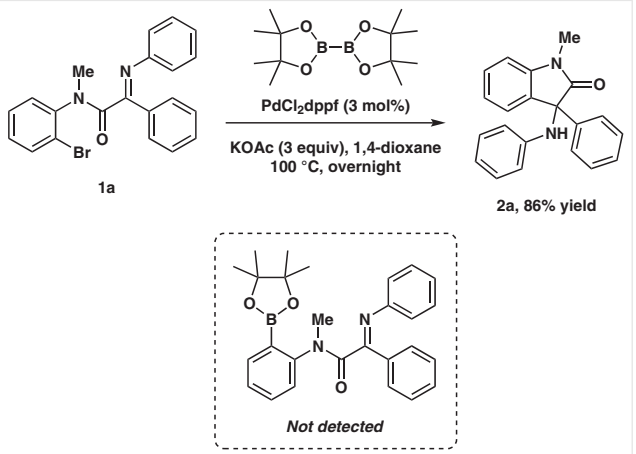
With our interest in this field,[8] we decided to use our experience to develop a new efficient methodology to access enantiomerically pure 3-amino-2-oxindole derivatives **2** (Scheme 1).



Scheme 1 Intramolecular borylation/arylation of *ortho*-bromo-α-ketimino amides **1** to give 3-amino-2-oxindoles **2**

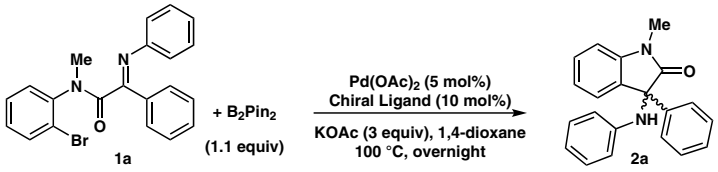
ortho-Bromo-α-ketimino amides **1** were synthesized according to the literature,[7,9] from cheap and easily accessible phenylglyoxylic acid (Scheme 1). Our first approach was to borylate substrate **1a** folllowing the well-established conditions reported by Miyaura and co-workers,[10a] using bis(pinacolate)diboron (B_2Pin_2) as the boron source, and 1,4-dioxane instead of dimethylsulfoxide (DMSO) as solvent. Gratifyingly we obtained the corresponding cyclic oxindole product **2a** in 86% yield (Scheme 2) and presume that the boronic ester was formed *in situ* and then underwent cyclization.

We also tested the borylation conditions reported by Colobert and co-workers,[10b] using $Pd(OAc)_2$ and DPEPhos ligand, pinacolborane (HBPin) and NEt_3 as base, and the cyclic compound **2a** was obtained in 64% yield, with only the presence of vestigial amounts of the borylated intermediate. We decided to study in depth this interesting reaction, where apparently the same Pd catalyst was able to catalyze the borylation of the C–Br bond carbon and the cyclization onto the C=N unit.[11] We then decided to optimize the reaction conditions and study the reaction scope. The results can be seen in Table 1.



Scheme 2 One-pot borylation of **1a** to **2a**

Table 1 Chiral Ligand Screening in the One-Pot Borylation/Intramolecular Arylation Reaction of Substrate **1a**[a]

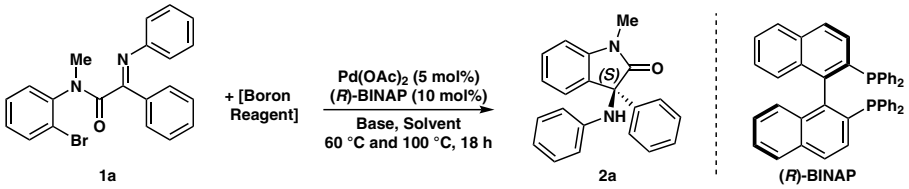


Entry	Chiral ligand	Conversion (%)[b]	ee (%)[b,c]
1	(*R*)-BINAP	>99	68 (*S*)
2	(*R*)-Tol-BINAP	>99	37 (*S*)
3	(*R*)-SegPhos	72	29 (*S*)
4	(*R*,*R*)-ChiraPhos	83	18 (*S*)
5	(*S*)-*i*Pr-MeOBIHEP	99	15 (*R*)
6	(*S*,*S*)-BDPP	98	16 (*R*)
7	(*R*)-PhanePhos	65	<10
8	(*R*)-DifluorPhos	>99	23 (*S*)
9	(*S*)-JosiPhos	67	<5
10	JosPOPhos	14	23 (*R*)
11	(*R*,*R*,*S*,*S*)-DuanPhos	33	21 (*S*)
12	(*R*)-MonoPhos	<10	<5 (*S*)
13	(*R*)-Diox-MonoPhos	93	58 (*R*)
14	(*R*,*R*)(+)-Box	14	<10
15	(*R*)(+)-PyBox	<10	<10
16	(*S*,*S*)-diene	<10	<5

[a] Reaction conditions: $Pd(OAc)_2$ (5 mol%), chiral ligand (10 mol%; see Supporting Information for structure details), and 1,4-dioxane (1 mL) were stirred for 30 min at room temperature. After that, **1a** (0.25 mmol), B_2Pin_2 (0.28 mmol), and KOAc (0.76 mmol) were added sequentially to the reaction vessel. Additional 1,4-dioxane (1 mL) was added, and the reaction mixture stirred at 100 °C for 18 h.
[b] Determined by chiral stationary phase HPLC (see Supporting Information for further details).
[c] The absolute configuration of **2a** was determined using X-ray crystallography (see Supporting Information for further details).

Several chiral phosphane ligands were screened (Table 1, entries 1–11) and, in general, excellent to moderate conversions were achieved. Almost full conversion into **2a** was obtained using BINAP ligands,[12] (*S*)-*i*Pr-MeOBIHEP, (*S*,*S*)-BDPP, and (*R*)-DifluorPhos[7] (Table 1, entries 1, 2, 5, 6, and 8, respectively). Very low conversion was obtained with the phosphane-oxide ligand JosPOPhos (Table 1, entry 11). Phosphoramidite-type ligands[13] were also screened (Table 1, entries 12 and 13), but despite (*R*)-MonoPhos giving very poor results, the analogous phosphane ligand (*R*)-Diox-MonoPhos gave much better results (Table 1, entry 13). We also screened bisoxazoline ligands[14] (Table 1, entries 14 and 15), but these were not very efficient. A chiral diene ligand[15] containing a bicyclo[2,2,2]octa-2,5-diene core gave the product in only trace quantities (Table 1, entry 16). Regarding the enantioselectivity, the best values were obtained using (*R*)-BINAP ligand (68% ee, Table 1, entry 1) and the phosphoramidite type (*R*)-Diox-MonoPhos (58% ee, Table 1, entry 13). An X-ray crystal-structure determination on compound **2a**[16] (see Supporting Information), showed that it had the *S* absolute configuration, which is in agreement with the results of Ley's group[7] for an analogous system. We decided to run further reaction screenings using $Pd(OAc)_2$ and (*R*)-BINAP to optimize the conditions further. Boron reagent, base, and solvent were screened in this new one-pot borylation/intramolecular arylation reaction using substrate **1a**. The results are shown in Table 2.

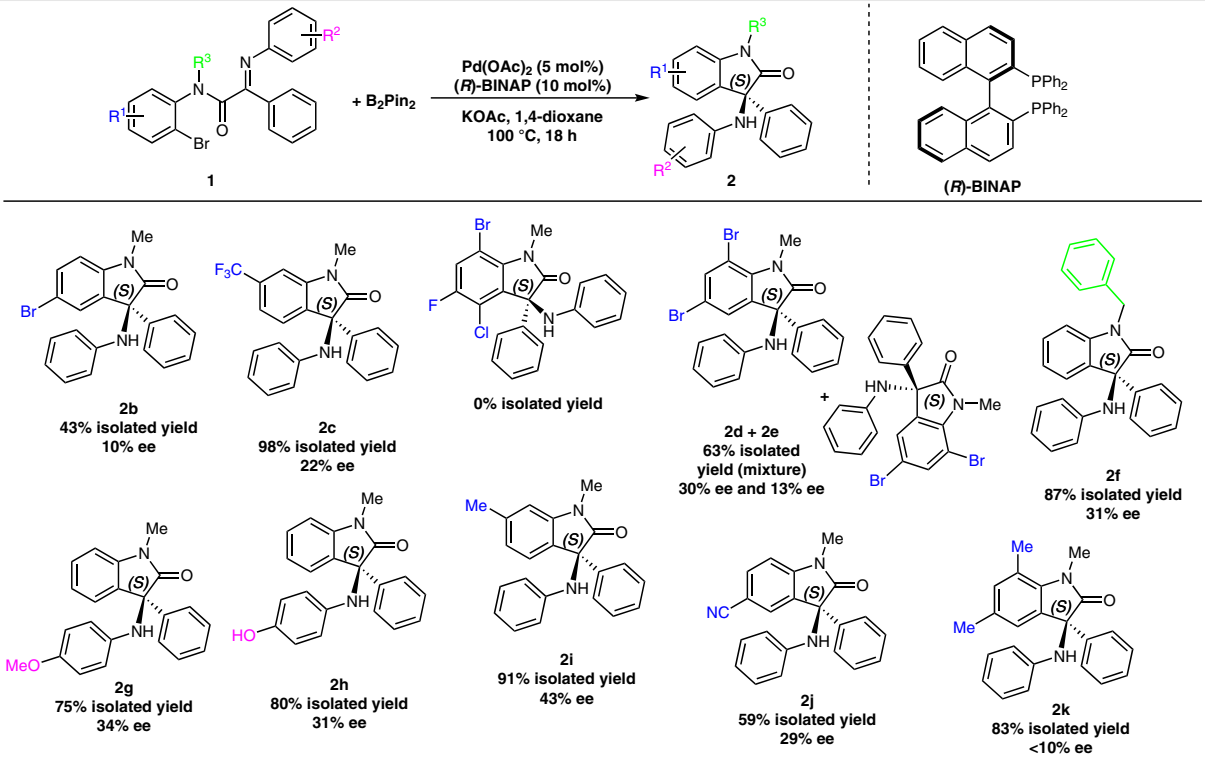
Table 2 Boron Reagent, Base and Solvent Screening in the One-Pot Borylation/Intramolecular Arylation of **1a**[a]



Entry	Boron reagent	Base	Solvent	Conversion (%)[b]	ee (%)[b]
1	HBPin	KOAc	dioxane	54	76
2	$B_2(cat)_2$	KOAc	dioxane	77	68
3	$B_2(npg)_2$	KOAc	dioxane	97	68
4	$B_2(OH)_4$	KOAc	dioxane	63	57
5[c]	HBPin	KOAc	dioxane	99	60
6	B_2Pin_2	Cs_2CO_3	dioxane	90	47
7	B_2Pin_2	NEt_3	dioxane	<10	67
8	B_2Pin_2	KO*t*Bu	dioxane	99	30
9	B_2Pin_2	K_2CO_3	dioxane	91	18
10	B_2Pin_2	K_3PO_4	dioxane	87	15
11	B_2Pin_2	DIPEA	dioxane	53	44
12[d]	B_2Pin_2	KOAc	CH_2Cl_2	<1	n.d.
13	B_2Pin_2	KOAc	toluene	86	36
14	B_2Pin_2	KOAc	CH_3CN	12	26
15	B_2Pin_2	KOAc	DME	45	75
16	B_2Pin_2	KOAc	DCE	<1	n.d.[g]
17	B_2Pin_2	KOAc	THF	19	38
18[d,e]	B_2Pin_2	KOAc	MeOH	31	10
19[d,f]	B_2Pin_2	KOAc	dioxane	24	44
20[f]	B_2Pin_2	KOAc	toluene	99	21

[a] Reaction conditions: $Pd(OAc)_2$ (5 mol%), (*R*)-BINAP (10 mol%), and solvent (1 mL) were stirred for 30 min at room temperature. After that, **1a** (0.25 mmol), Boron reagent (0.28 mmol), and base (0.76 mmol) were added sequentially to the reaction vessel. Additional solvent (1 mL) was added and the reaction mixture stirred at 100 °C for 18 h.
[b] Determined by chiral stationary phase HPLC (see Supporting Information for further details).
[c] Reaction run with 0.53 mmol of HBPin.
[d] Reaction run at 60 °C.
[e] $Pd(OAc)_2$ and (*R*)-BINAP were pre-stirred in CH_2Cl_2.
[f] $Pd(OAc)_2$ and (*R*)-BINAP were pre-stirred in DME.
[g] n.d. = not determined.

As HBPin had already been shown to be successful in this reaction by Colobert and co-workers,[10b] we decided to test this boron reagent with the chiral (*R*)-BINAP ligand (Table 2, entries 1 and 5). Gratifyingly, we obtained a higher enantioselectivity (76% ee, compared with 68% using B_2Pin_2, compare Table 2, entry 1 with Table 1, entry 1), although the conversion was lower. We decided to increase the quantity of HBPin to 2.1 equivalents and almost full conversion of **2a** was obtained, despite a slight decrease in ee (Table 2, entry 5). Other commercially available diboron reagents, such as arylboronate esters and acids,[17] were also evaluated (Table 2, entries 2–4). We speculated that the steric bulk of the tetra(alkoxy)diboron reagent might play an important role in the reaction, but no significant alterations in conversion and enantioselectivity were noted when the less sterically hindered bis(neopentyl glycolato)diboron ($B_2(npg)_2$) was used (Table 2, entry 3). Less expensive tetrahydroxydiboron ($B_2(OH)_4$) was also tested, but lower conversions were achieved (Table 2, entry 4). The same happened with bis(catecholato)diboron ($B_2(cat)_2$). There was no change in the enantioselectivity but the conversion only reached a maximum of 77% (Table 2, entry 2). We decided to conduct a base-screening study, maintaining the other reagents, i.e., ($Pd(OAc)_2$ and (*R*)-BINAP) and B_2Pin_2 (Table 2, entries 6–11). Generally, organic bases such as NEt_3 and *N*,*N*-diisopropylethylamine (DIPEA) are not the best choice for this reaction, since low conversions of **2a** were obtained (Table 2, entries 7 and 11). High conversions were obtained with the inorganic bases Cs_2CO_3, KO*t*Bu, and K_2CO_3 (Table 2, entries 6, 8, and 9, respectively). Unfortunately, there was no improvement in the reaction enantioselectivity. Finally, we decided to evaluate the effect of the solvent (Table 2, entries 12–20). None of the desired product **2a** was obtained using chlorinated solvents such as CH_2Cl_2 and 1,2-dichloroethane (DCE, Table 2, entries 12 and 16). We conducted the same reaction with CH_2Cl_2 in a sealed tube at 100 °C and again no product **2a** was obtained. For good conversions, apolar aprotic solvents were the best. For example, toluene afforded the product with a conversion of 86% (Table 2, entry 13), albeit with low enantioselectivity. However, upon using 1,2-dimethoxyethane (DME) as solvent, an enantioselectivity of 75% ee was obtained, despite a low conversion (Table 2, entry 15). So, we decided to use DME in the pre-complexation step between the $Pd(OAc)_2$ and (*R*)-BINAP and then run the reaction in dioxane and toluene, after evaporation of the DME (Table 2, entries 19 and 20, respectively). No significant variations were observed in the conversions and enantioselectivities. At this point we established the following conditions to be the optimized conditions for this reaction: $Pd(OAc)_2$ and (*R*)-BINAP as ligand, B_2Pin_2 as the boron source, KOAc as base, and dioxane as the solvent (see Table 1, entry 1).[18] The next step was to study the reaction scope and this study is shown in Scheme 3.



Scheme 3 One-pot borylation/intramolecular asymmetric arylation reaction on *ortho*-bromo-α-ketimino amide substrates **1–k** affording 3-amino-2-oxindoles **2–k**

In general, moderate to very good yields were obtained using substrates containing both electron-rich and electron-deficient substituents. The best yield was obtained with **1c** – containing a CF_3 electron-withdrawing group – to give **2c**, in a yield of 98% (Scheme 3). The yield decreased slightly, when halogen substituents were present as the R^1 substituent in the substrate (see, for example, compounds **2b**,**d**,**e**). When several halogen substituents (C, F, Br) were present in the same ring no reaction occurred. We believe that in the borylation step, there is competition between these sites and the *ortho*-Br site for the boron unit.[19] When we conducted the reaction with **1e** it gave a mixture of **2d** and **2e**, which would be expected (Scheme 3). Unfortunately, it was impossible to separate the two isomers by silica gel chromatography. Low enantioselectivities were observed for compounds **2b**,**d**,**e**,**i**,**j**,**k**, the best being 43% ee (**2i**, Scheme 3). Unfortunately, the only R^2 substituents that we could introduce into the imine phenyl unit were the electron-donating 4-OMe and 4-OH groups (as in **1g** and **1h**). However, gratifyingly both **2g** and **2h** were obtained in very good yields, despite giving low enantioselectivities (Scheme 3). In the case of functionalization of the amide (substituent R^3) we could only manage to introduce a benzyl group as is the case for **1f** (Scheme 3). The product **2c** was obtained in high yield and low enantioselectivity (87% and 31% ee, respectively). Since the absolute configuration of **2a** was determined, all of our products **2b–k** are expected to have the same *S* configuration.

In conclusion, we have developed a catalytic approach to the synthesis of chiral 3-amino-2-oxindoles in high yields and good enantioselectivities using a hitherto unknown one-pot borylation/intramolecular asymmetric arylation sequence.

Funding Information

We are grateful for the award of a post-doctoral grant to C.S.M. (FRH/BPD/92394/2013) from the Fundação para a Ciência e a Tecnologia (FCT). The authors gratefully acknowledge Fundo Europeu de Desenvolvimento Regional (FEDER)-INALENTEJO for funding the program INMOLFARM – Molecular Innovation and Drug Discovery (ALENT-07-0224-FEDER-001743) and for financing the acquisition of the NMR equipment, project LADECA (ALENT-07-0262-FEDER-001878). S.E.L. thanks University College Cork 2013 Research Fund and Science Foundation Ireland under grant no. 05/PICA/B802/EC07.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1590940.

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(16) CCDC 1571646 contains the supplementary crystallographic data for **2a**. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

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(18) **General Procedure for the Asymmetric Synthesis of Chiral 3-Amino-2-oxindoles**

In a Radley's® 12 position carousel reactor under a nitrogen atmosphere was added $Pd(OAc)_2$ (0.0125 mmol, 5 mol%), chiral ligand (0.025 mmol, 10 mol%), and 1,4-dioxane (1 mL). The mixture was stirred for 30 min at room temperature, then the corresponding *ortho*-bromo-α-ketimino amide substrate **1** (0.25 mmol), B_2Pin_2 (0.28 mmol, 1.1 equiv), KOAc (0.76 mmol), and 1,4-dioxane (1 mL) were added sequentially to the reaction vessel. The reaction was left stirring at 100 °C during 18 h. After cooling to room temperature, the crude mixture was purified by silica gel chromatography using hexane/AcOEt (5:1) as eluent to afford the desired 3-phenyl-3-(aryl-amino)-indolin-2-one derivatives **2**.

Compound **2a**: Pale yellow solid; mp 86.2–87.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.26 (s, CH_3, 3 H), 6.34–6.36 (d, Ar, 2 H, *J* = 8 Hz), 6.67–6.71 (t, Ar, 1 H, *J* = 8 Hz), 6.92–6.94 (d, Ar, 1 H, *J* = 8 Hz), 6.98–7.02 (t, Ar, 2 H, *J* = 8 Hz), 7.08–7.12 (t, Ar, 1 H, *J* = 8 Hz), 7.33–7.42 (m, Ar, 5 H), 7.55–7.57 (d, Ar, 2 H, *J* = 8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 26.80, 68.08, 108.90, 115.54, 119.40, 123.32, 125.42, 126.73, 128.73, 129.07, 129.12, 129.51, 130.37, 140.19, 143.28, 145.09, 177.05. FTIR: 1499, 1722, 3055, 3373 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{21}H_{18}N_2O$: 314.14191; found for $C_{21}H_{18}N_2ONa$: 337.13113 [M^+ + Na]. HPLC: Daicel Chiralpak IA column, *n*-hexane/*i*-PrOH = 90:10, 1.0 mL/min, 220 nm; t_R = 32.447 min (*R*, minor), 38.080 min (*S*, major).

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