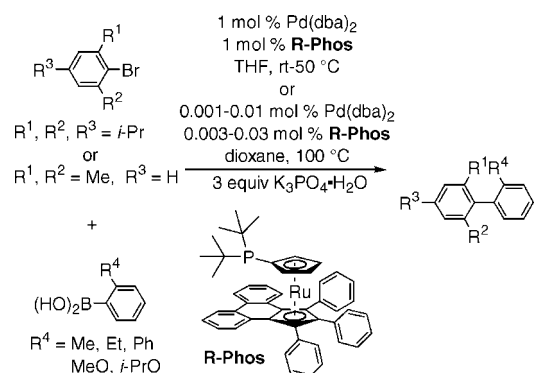# Biphenylene-Substituted Ruthenocenylphosphine for Suzuki−Miyaura Coupling of Sterically Hindered Aryl Bromides

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Toshio Suzuki,[†] Jun-ichi Sakai,[†] and Hisahiro Hagiwara*,[‡]

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A highly general, active, and stable catalytic system was realized in the palladium-catalyzed Suzuki−Miyaura reactions of sterically hindered aryl bromides with arylboronic acids using biphenylene-substituted di-*tert*-butylruthenocenylphosphine (R-Phos) as a supporting ligand.
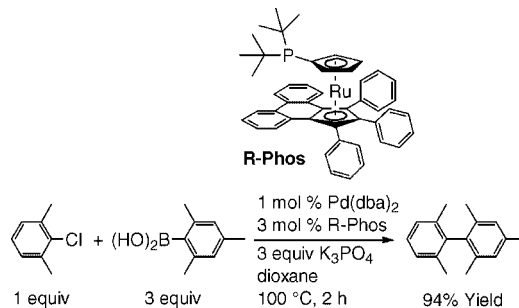
Over the past 10 years, extensive efforts aimed at reaching a high degree of efficiency in palladium-catalyzed cross-coupling processes have been devoted toward the development of new ligands with the ability to provide excellent levels of catalytic generality, activity, and longevity.[1,2] Recently, we have also reported the design, development, and high activity of biphenylene-substituted di-*tert*-butylruthenocenylphosphine (R-Phos) as a supporting ligand for palladium-catalyzed Suzuki−Miyaura reactions of aryl chlorides with arylboronic acids.[3,4] The catalyst generated from R-Phos and Pd(dba)₂ facilitates the couplings even for the construction of highly hindered tetra-ortho-substituted biaryls in good to excellent yields in short reaction

SCHEME 1. Suzuki−Miyaura Coupling of Aryl Chloride Providing Tetra-Ortho-Substituted Biphenyl Using R-Phos

times with low catalyst loadings (Scheme 1). In light of the performance of this catalyst in the reactions of sterically hindered aryl chlorides, we focused on the challenging reactions of aryl bromides containing large ortho, ortho′-substituents. In this paper, we report exceptional capabilities of this catalyst in the Suzuki−Miyaura reactions of di-ortho-substituted aryl bromides with arylboronic acids. This includes the high catalytic activity in the reactions of very hindered 2,4,6-triisopropylbromobenzene (**1a**) with ortho-substituted phenylboronic acids at 50 °C or even at room temperature, the first cross-coupling syntheses of triortho-substituted biphenyls from **1a** below 100 °C.[5] The unprecedented low catalyst loading, short reaction time, and broad scope of ortho-substituted arylboronic acids were exhibited in the couplings with 2,6-dimethylbromobenzene (**1b**) at 100 °C.[6] In addition, at this elevated temperature, the activity of this catalyst system showed a significant dependence on the L/Pd ratio which furnished a much higher activity at a 3:1 ratio of R-Phos to Pd.[7]

In our initial study, we examined the performance of the R-Phos-based palladium catalyst in the reactions of aryl

† Faculty of Engineering.
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(4) For recent reviews on Suzuki−Miyaura reaction, see: (a) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11. (b) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (c) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633. (d) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, *15*, 2419. (e) Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron* **2008**, *64*, 3047. (f) See also ref 1e.
(5) (a) Su, W.; Urgaonkar, S.; McLaughlin, P. A.; Verkade, J. G. *J. Am. Chem. Soc.* **2004**, *126*, 16433. (b) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871. (c) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685. (d) Liang, L.-C.; Chien, P.-S.; Huang, M.-H. *Organometallics* **2005**, *24*, 353.
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(7) For some examples of the beneficial effect of increasing the L/Pd ratio on catalytic activity, see: (a) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550. (b) Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 3690.

TABLE 1. Suzuki–Miyaura Coupling of Aryl Bromide at Room Temperature[a]

entry	ArBr	Ar'B(OH)₂	t (h)	product	yield (%)
1	**1c**	**2a**	1	**3a**	100
2	**1d**	**2a**	1.5	**3b**	93
3	**1e**	**2a**	0.5	**3c**	91
4	**1d**	**2b**	0.5	**3d**	96
5	**1f**	**2a**	2	**3e**	95
6	**1f**	**2b**	1	**3f**	100
7	**1b**	**2b**	1	**3g**	95

[a] Conditions: 1 equiv of aryl bromide, 1.5 equiv of arylboronic acid, 1 mol % of Pd(dba)₂, 1 mol % of R-Phos, 3 equiv of K₃PO₄·H₂O, THF, room temperature.

TABLE 2. Suzuki–Miyaura Coupling of 1a with *Ortho*-Substituted Phenylboronic Acid under Mild Conditions[a]

entry	ArBr	Ar'B(OH)₂	t (h)	product	yield (%)
1[b]	**1a**	**2b**	18	**3h**	52[c]
2[d]	**1a**	**2b**	1	**3h**	92
3	**1a**	**2c**	1	**3i**	94
4	**1a**	**2d**	2	**3j**	95
5	**1a**	**2e**	21	**3k**	19
6	**1a**	**2f**	24	**3l**	22

[a] Conditions: 1 equiv of aryl bromide, 1.5 equiv of arylboronic acid, 1 mol % of Pd(dba)₂, 1 mol % of R-Phos, 3 equiv of K₃PO₄·H₂O, THF, 50 °C. [b] 1 mol % of Pd(dba)₂, 3 mol % of R-Phos, room temperature. [c] ¹H NMR yield. [d] 0.5 mol % of Pd(dba)₂, 0.5 mol % of R-Phos.

bromides at room temperature. As shown in Table 1, in the presence of 1 mol % of the catalyst containing equimolar amounts of R-Phos and Pd(dba)₂, an array of sterically and electronically different aryl bromides underwent efficient couplings with phenylboronic acid (**2a**) or 2-methylphenylboronic acid (**2b**) to afford the corresponding biphenyls in excellent yields in short reaction times. Particularly noteworthy is the ability of this catalyst to promote coupling reactions with a comparable rate regardless of the steric character of the substrate even for the construction of hindered tri-ortho-substituted biphenyl **3g**, indicating the high activity of this catalyst toward sterically hindered aryl bromides even at room temperature.

Given the high catalytic activity toward sterically hindered aryl bromides, we explored the possibility of carrying out the coupling reaction of **1a**, the quite difficult aryl bromide substrate for the cross-coupling reactions due to its extremely increased steric hindrance imparted by two large *o*-isopropyl groups.[5,8,9] In fact, to the best of our knowledge, Buchwald's S-Phos has been reported as the only successful ligand for the Suzuki–Miyaura couplings of **1a** with ortho-substituted arylboronic acids to date.[5b,c] In addition, previous cross-coupling syntheses of tri-ortho-substituted biphenyls from **1a** were carried out at 100 °C

or above. The ability to undergo the reaction under milder conditions is of great synthetic importance. Thus, we examined the reactions of **1a** with a series of ortho-substituted phenylboronic acids at lower temperatures (Table 2). Initially, the reaction with the most simple **2b** was executed at room temperature with 1 mol % of the catalyst, and we obtained the desired biphenyl **3h** in 52% yield after 18 h (Table 2, entry 1). When heated at 50 °C, this transformation was dramatically accelerated to afford a nearly quantitative yield in only 1 h with 0.5 mol % of Pd (Table 2, entry 2). By using 1 mol % of the catalyst, more sterically hindered 2-ethylphenylboronic acid (**2c**) and 2-methoxyphenylboronic acid (**2d**) could also be coupled with **1a** in excellent yields in short reaction times (Table 2, entries 3 and 4). Although further sterically hindered 2-isopropoxyphenylboronic acid (**2e**) and 2-phenylphenylboronic acid (**2f**) resulted in a significant loss in yield (Table 2, entries 5 and 6), a range of tri-ortho-substituted biphenyls from **1a** could be obtained at 50 °C with the catalyst based on R-Phos. We also found that the coupling of 2,4,6-trimethylphenylboronic acid (**2g**) with **1b**, one of the most difficult Suzuki–Miyaura substrate combinations,[10] occurred at this low temperature. Though full conversion was not observed, the corresponding biphenyl with four *o*-methyl substituents **3m** was obtained in an acceptable yield (eq 1).

$$\text{1b} + (HO)_2B-\!\!\!\begin{array}{c}\text{2g}\\3\text{ equiv}\end{array} \xrightarrow[\substack{3\text{ equiv K}_3\text{PO}_4\cdot\text{H}_2\text{O}\\ \text{THF, 50 °C, 4 h}}]{\substack{0.5\text{ mol \% Pd(dba)}_2\\0.5\text{ mol \% R-Phos}}} \begin{array}{c}\text{3m}\\54\%\text{ Yield}\end{array} \quad (1)$$

The catalyst generated from R-Phos and Pd(dba)₂ demonstrated a beneficial effect of increasing the L/Pd ratio on the catalyst activity at 100 °C, as previously reported in the reaction

(8) For Suzuki–Miyaura reactions of **1a** with ortho-unsubstituted arylboronic acid, see: (a) Feuerstein, M.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* **2002**, *42*, 6667. (b) Kwong, F. Y.; Chan, K. S.; Yeung, C. H.; Chan, A. S. C. *Chem. Commun.* **2004**, 2336. (c) Lipshutz, B. H.; Petersen, T. B.; Abela, A. R. *Org. Lett.* **2008**, *10*, 1333. (d) See also refs 5b and 5c.
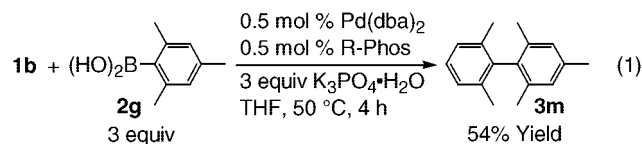
(9) For Mizoroki–Heck reactions of **1a**, see: (a) Feuerstein, M.; Doucet, H.; Santelli, M. *Synlett* **2001**, 1980. (b) Feuerstein, M.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* **2002**, *43*, 2191. (c) Battace, A.; Zair, T.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* **2006**, *47*, 459. (d) Berthiol, F.; Doucet, H.; Santelli, M. *Appl. Organometal. Chem.* **2006**, *20*, 855. (e) Battace, A.; Zair, T.; Doucet, H.; Santelli, M. *Synthesis* **2006**, 3495. (f) Lemhadri, M.; Doucet, H.; Santelli, M. *Synlett* **2006**, 2935. (g) Battace, A.; Feuerstein, M.; Lemhadri, M.; Zair, T.; Doucet, H.; Santelli, M. *Eur. J. Org. Chem.* **2007**, 3122. (h) Kantchev, E. A. B.; Peh, G.-R.; Zhang, C.; Ying, J. Y. *Org. Lett.* **2008**, *10*, 3949.

(10) (a) Yin, J.; Rainka, M. P.; Zhang, X.-X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1162. (b) Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *J. Am. Chem. Soc.* **2004**, *126*, 15195. (c) Demchuk, O. M.; Yoruk, B.; Blackburn, T.; Snieckus, V. *Synlett* **2006**, 2908. (d) See also refs 5b and 5c.

TABLE 3. Effect of R-Phos/Pd Ratio on Suzuki−Miyaura Coupling of Aryl Bromide and Arylboronic Acid[a]

1a: R^1, R^2, R^3 = i-Pr
1b: R^1, R^2 = Me, R^3 = H

Pd(dba)$_2$
R-Phos

3g: R^1, R^2 = Me, R^3 = H
3h: R^1, R^2, R^3 = i-Pr

(HO)$_2$B—

2b

entry	ArBr	Pd (mol %)	R-Phos/Pd	T (°C)	time	product	yield (%)
1[b,c]	1b	0.1	1:1	100	45 min	3g	94
2[b,d]	1b	0.1	3:1	100	15 min	3g	98
3[b,e]	1b	0.01	1:1	100	4.5 h	3g	11[f]
4[b,g]	1b	0.01	3:1	100	30 min	3g	97
5[b,h]	1b	0.001	3:1	100	2 h	3g	83
6[i,j]	1b	1	1:1	rt	2 h	3g	97
7[i,k]	1b	1	3:1	rt	2 h	3g	87
8[j,l]	1a	1	1:1	50	1 h	3h	88
9[k,l]	1a	1	3:1	50	1 h	3h	92

[a] Conditions: 1 equiv of aryl bromide, 1.5 equiv of arylboronic acid, 3 equiv of K$_3$PO$_4$·H$_2$O. [b] Dioxane, 100 °C. [c] 0.1 mol % of Pd(dba)$_2$, 0.1 mol % of R-Phos. [d] 0.1 mol % of Pd(dba)$_2$, 0.3 mol % of R-Phos. [e] 0.01 mol % of Pd(dba)$_2$, 0.01 mol % of R-Phos. [f] ^{1}H NMR yield. [g] 0.01 mol % of Pd(dba)$_2$, 0.03 mol % of R-Phos. [h] 0.001 mol % of Pd(dba)$_2$, 0.003 mol % of R-Phos. [i] THF, room temperature. [j] 1 mol % of Pd(dba)$_2$, 1 mol % of R-Phos. [k] 1 mol % of Pd(dba)$_2$, 3 mol % of R-Phos. [l] THF, 50 °C.

TABLE 4. Suzuki−Miyaura Coupling of Sterically Hindered Aryl Bromide and Arylboronic Acid with 0.01 mol % of Pd[a]

entry	ArBr	Ar'B(OH)$_2$	t	product	yield (%)
1	1b	2c	15 min	3n	97
2	1b	2d	15 min	3o	99
3	1b	2h	30 min	3p	97
4	1b	2e	1 h	3q	80
5	1b	2f	1 h	3r	95
6	1g	2f	30 min	3s	100
7	1a	2b	3 h	3h	52

[a] Conditions: 1 equiv of aryl bromide, 1.5 equiv of arylboronic acid, 0.01 mol % of Pd(dba)$_2$, 0.03 mol % of R-Phos, 3 equiv of K$_3$PO$_4$·H$_2$O, dioxane, 100 °C.

of aryl chlorides in which the exceptionally higher activity could be induced at a 3:1 ratio of R-Phos to Pd(dba)$_2$ (Table 3).[3] When the coupling of 1b with 2b was conducted in the presence of 0.1 mol % of Pd, the reaction proceeded about 3 times faster at a 3:1 ratio than at a 1:1 ratio (Table 3, entries 1 and 2). This L/Pd ratio-dependent catalytic activity was observed more clearly with more than 1 order of magnitude lower catalyst loadings. In actuality, when the palladium loading was reduced to 0.01 mol %, the catalyst system containing equimolar amounts of R-Phos and Pd(dba)$_2$ resulted in only 11% yield (Table 3, entry 3). In contrast, increasing the L/Pd ratio to 3:1 furnished an excellent yield of the same coupling product in only 30 min (Table 3, entry 4). Furthermore, the exceptionally low catalyst loading of 0.001 mol % of Pd was also sufficient to induce this transformation in 83% yield after 2 h, corresponding to a turnover number (TON) and a turnover frequency (TOF) of 83000 and 41500 h^{-1}, respectively (Table 3, entry 5).[6] To the best of our knowledge, this result represents more than 10 and 100 times higher TON and TOF than any of these observed for this sterically difficult transformation to date. In contrast, there was no observation of the influence of the L/Pd ratio on the catalytic activity below 50 °C (Table 3, entries 6−9).

The ability to operate for a range of substrates at low catalyst loading is of great importance in metal-catalyzed processes. Thus, we proceeded to assess the efficiency of this catalyst system in the couplings of 1b with a sterically diverse set of ortho-substituted arylboronic acids in the presence of 0.01 mol % of Pd (Table 4). 2-Ethylphenylboronic acid (2c), 2-methoxyphenylboronic acid (2d), and 1-naphthylboronic acid (2h) also underwent couplings with 1b in excellent yields in less than 30 min (Table 4, entries 1−3). Further sterically demanding isopropoxyphenylboronic acid (2e) and 2-phenylphenylboronic

acid (2f) slightly retarded the rates of the reactions, whereas coupling products could also be obtained in good to excellent yields within 1 h (Table 4, entries 4 and 5). This catalyst system was also effective for generating tri-ortho-substituted biaryls from other hindered aryl bromides with only this low catalyst loading. For example, 9-bromoanthracene (1g) underwent the facile coupling even with 2f in quantitative yield in 30 min (Table 4, entry 6). Furthermore, although a longer reaction time was required, extremely hindered 1a could also be coupled with 2b in acceptable yield (Table 4, entry 7).

In summary, we have demonstrated the excellent generality, activity, and stability of the catalyst generated from R-Phos and Pd(dba)$_2$ for the sterically difficult Suzuki−Miyaura reactions of di-ortho-substituted aryl bromides with arylboronic acids. The catalyst works well even for the couplings of extremely hindered 2,4,6-triisopropylbromobenzene (1a) with ortho-substituted phenylboronic acids not just with the most simple 2-methyl derivative to provide tri-ortho-substituted biphenyls in excellent yields under mild conditions. When heated at 100 °C, 2,6-dimethylbromobenzene (1b) couples with a sterically diverse set of ortho-substituted arylboronic acids in good to excellent yields and short reaction times in the presence of only 0.001−0.01 mol % of this catalyst. The operational simplicity of our process without the need of special handling such as the use of a glovebox is also noteworthy.

Experimental Section

General Procedure A for Suzuki−Miyaura Couplings below 50 °C. A flame-dried two-necked flask was charged with R-Phos, arylboronic acid, Pd(dba)$_2$, and K$_3$PO$_4$·H$_2$O, capped with a rubber septum, and then evacuated and backfilled with argon

(three cycles). To the flask were sequentially added aryl bromide and THF via syringe through a septum, and then the reaction mixture was stirred at the indicated temperature for the indicated amount of time.

2,4,6-Triisopropyl-2′-ethylbiphenyl (3i). Following procedure A, a mixture of R-Phos (3.8 mg, 5 μmol), Pd(dba)$_2$ (3.0 mg, 5 μmol), 2-ethylphenylboronic acid (114.0 mg, 0.76 mmol), 2,4,6-triisopropylbromobenzene (138.6 mg, 0.49 mmol), and K$_3$PO$_4$·H$_2$O (350.6 mg, 1.52 mmol) in THF (1 mL) was stirred at 50 °C for 1 h. The reaction mixture was diluted with *n*-hexane (5 mL), filtered through a thin pad of silica gel (*n*-hexane), and concentrated under reduced pressure. The crude material obtained was purified by flash chromatography on silica gel (*n*-hexane) to provide the title compound (141.5 mg, 0.46 mmol, 94%) as a white solid: mp = 79−81 °C; ^{1}H NMR (CDCl$_3$, 270 MHz) δ 1.00 (d, J = 6.8 Hz, 6H), 1.07 (t, J = 7.3 Hz, 3H), 1.11 (d, J = 6.6 Hz, 6H), 1.31 (d, J = 6.8 Hz, 6H), 2.30 (q, J = 7.6 Hz, 2H), 2.44 (sept, J = 6.8 Hz, 2H), 2.94 (sept, J = 6.8 Hz, 1H), 7.03−7.06 (m, 3H), 7.16−7.25 (m, 1H), 7.31−7.33 (m, 2H); ^{13}C NMR (CDCl$_3$, 67.5 MHz) δ 14.2, 23.3, 24.2, 25.2, 25.7, 30.4, 34.2, 120.5, 125.0, 126.8, 127.3, 130.1, 135.5, 139.4, 142.1, 146.2, 147.5; IR (CHCl$_3$, cm^{-1}) 3019, 2964, 2932, 2870, 1465, 1362; MS (EI) *m/z* 308 (M$^+$, 72), 223 (61), 209 (81), 181 (100); HRMS found 308.2498, calcd for C$_{23}$H$_{32}$ 308.2504.

General Procedure B for Suzuki−Miyaura Couplings at 100 °C. A flame-dried, two-necked flask was charged with arylboronic acid and K$_3$PO$_4$·H$_2$O, capped with a rubber septum, and then evacuated and backfilled with argon (3 cycles). To the flask were sequentially added aryl bromide (9-bromoanthracene (**1g**) was added during the initial charge), dioxane, and the indicated amount of a catalyst solution composed of R-Phos, Pd(dba)$_2$, and dioxane via syringe through a septum, and then the reaction mixture was stirred at 100 °C for the indicated amount of time.

2,6-Dimethyl-2′-ethylbiphenyl (3n). Following procedure B, a mixture of 2-ethylphenylboronic acid (226.0 mg, 1.51 mmol), 2,6-dimethylbromobenzene (181.3 mg, 0.98 mmol), K$_3$PO$_4$·H$_2$O (693.3 mg, 3.01 mmol), and 10 μL of a catalyst solution composed of R-Phos (11.6 mg, 15 μmol), Pd(dba)$_2$ (2.9 mg, 5 μmol), and dioxane (0.5 mL) in dioxane (2 mL) was stirred at 100 °C for 15 min. The reaction mixture was diluted with *n*-hexane (5 mL), filtered through a thin pad of silica gel (*n*-hexane), and concentrated under reduced pressure. The crude material obtained was purified by flash chromatography on silica gel (*n*-hexane) to provide the title compound (200.0 mg, 0.95 mmol, 97%) as a colorless oil: ^{1}H NMR (CDCl$_3$, 270 MHz) δ 1.05 (t, J = 7.6 Hz, 3H), 1.96 (s, 6H), 2.28 (q, J = 7.6 Hz, 2H), 6.99 (d, J = 8.1 Hz, 1H), 7.08−7.18 (m, 2H), 7.20−7.28 (m, 2H), 7.30−7.35 (m, 2H); ^{13}C NMR (CDCl$_3$, 67.5 MHz) δ 14.6, 20.7, 25.8, 125.9, 126.8, 127.1, 128.1, 129.0, 135.9, 139.7, 140.8, 141.4; IR (CHCl$_3$, cm^{-1}) 3062, 3010, 2969, 2933, 2874, 1463, 1379, 1006; MS (EI), *m/z* 210 (M$^+$, 68), 195 (100), 181 (40), 180 (39), 165 (52); HRMS found 210.1403, calcd for C$_{16}$H$_{18}$ 210.1409.

Supporting Information Available: Experimental procedures and full spectroscopic data and copies of ^{1}H NMR and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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