JOC*Note*

Diastereoselective Synthesis of *N*-Secondary Alkyl 2-Alkoxymethylpyrrolidines via Sequential Addition Reactions of Organolithium and -Magnesium Reagents to *N*-Thioformyl 2-Alkoxymethylpyrrolidines

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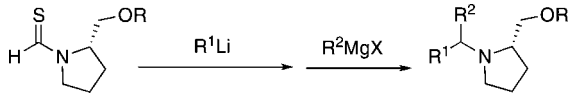


Highly efficient sequential addition reactions of organolithium and -magnesium reagents to *N*-thioformyl 2-methoxymethylpyrrolidine have been described. Various combinations of these reagents gives successful results. A highly efficient and diastereoselective addition reaction is also described. Use of the opposite combinations of substituents on organolithium and -magnesium reagents leads to the selective formation of the opposite diastereomers. The reaction was extended to *N*-thioformyl 2-siloxymethypyrrolidine and 2-methoxymethylpiperidine, and these showed similar efficiency and selectivity.

Increasing attention has been paid to *N*-secondary chiral alkyl prolinol derivatives because of their importance as synthetic intermediates[1] and optically active ligands,[2] as well as their biological activity.[3] The first synthesis was achieved via [2,3] sigmatropic rearrangement of chiral ammonium salts derived from prolinol.[4] Later, *N*-cyanoalkyl prolinol derivatives have been used as starting materials,[5] although KCN or HCN was necessary for their synthesis. Alternatively, *N*-alkylation of prolinol derivatives with secondary alkyl halides, α,β-unsaturated esters, and nitroalkenes gives the corresponding products.[6] Ti-mediated regioselective ring-opening of oxiranes with 2-methoxymethylpyrrolidine leads to *N*-chiral secondary derivatives, and their ability to act as optically active ligands has been tested.[7] Ring-opening of thiophene 1,1-dioxide with prolinol has led to *N*-dieneallyl prolinol.[8] Recently, metal-catalyzed three-component coupling reactions of aldehydes, 2-methoxymethylpyrrolidine, and terminal alkynes have been intensively studied.[9] In this case, alkynyl groups are introduced to in situ generated imines to give prolinol derivatives in which the propargyl groups are on the nitrogen atom. Similarly, the Mannich-type reaction of prolinol derivatives with organoborane reagents has been developed.[10] Very recently, we have developed three-component coupling reactions of thioiminium salts and thioformamides with organolithium and -magnesium reagents to give tertiary amines with high efficiency[11] (Scheme 1) in studies on the synthesis, properties, and reactivity of chalcogen isologues of amides.[12] In these reactions, even when excess organolithium reagents were used, the products in which 2 equiv of organolithium reagents were introduced were not obtained, and two different organometallic reagents were efficiently incorporated in the products. We report herein diastereoselective synthesis of *N*-secondary alkyl prolinol derivatives via sequential addition reactions of organolithium and -magnesium reagents to *N*-thioformyl 2-alkoxymethylpyrrolidines.

SCHEME 1. Addition Reactions of Organolithium and -Magnesium Reagents to Thioformamides

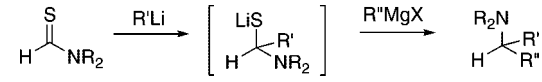
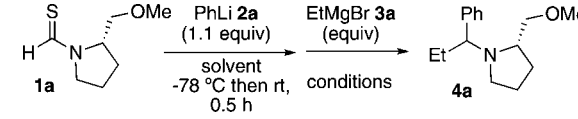


TABLE 1. Addition Reaction of Phenyllithium (2a) and Ethylmagnesium Bromide (3a) to Thioformamide 1a[a]



entry	solvent	**3a** equiv	conditions	yield[b] (%)	*dr*[c]
1	THF	2.0	rt, 5 h	93	88:12
2	THF	2.0	0 °C, 5 h	91	88:12
3	THF	2.0	−20 °C, 5 h	17	88:12
4	Et_2O	2.0	rt, 5 h	93	88:12
5	THF	1.1	rt, 5 h	86	91:9

[a] A solution of thioformamide **1a** (1 mmol, 1.0 M) was treated with organolithium **2a** (1.1 equiv) and -magnesium reagents **3a** (1.1 − 2.0 equiv), unless otherwise noted. [b] Isolated yield. [c] Ratio was determined by ^{1}H NMR analysis of crude products.

Initially, (*S*)-2-methoxymethyl-1-thioformylpyrrolidine (**1a**)[13] was sequentially reacted with phenyllithium (**2a**) and ethylmagnesium bromide (**3a**) (Table 1). As a result, two different organometallic reagents were selectively introduced to the thioformyl carbon atom, and the corresponding amine **4a** was obtained as a diastereomeric mixture in a ratio of 88:12 (entry

(1) (a) Kametani, T.; Kawamura, K.; Tsubuki, M.; Honda, T. *Chem. Pharm. Bull.* **1985**, *33*, 4821. (b) Pohl, M.; Thieme, M.; Jones, P. G.; Liebscher, J. *Liebigs Ann.* **1995**, 1539. (c) Ahlbrecht, H.; Kramer, A. *Chem. Ber.* **1996**, *129*, 1161. (d) Boswell, G. E.; Musso, D. L.; Davis, A. O.; Kelly, J. L.; Soroko, F. E.; Cooper, B. R. *J. Heterocycl. Chem.* **1997**, *34*, 1813. (e) Lo, V. K.-Y.; Wong, M.-K.; Che, C.-M. *Org. Lett.* **2008**, *10*, 517. (f) Nakamura, H.; Ishikura, M.; Sugiishi, T.; Kamakura, T.; Biellmann, J.-F. *Org. Biomol. Chem.* **2008**, *6*, 1471.

(2) (a) Jimeno, C.; Vidal-Ferran, A.; Moyano, A.; Pericas, M. A.; Riera, A. *Tetrahedron Lett.* **1999**, *40*, 777. (b) Almansa, R.; Guijarro, D.; Yus, M. *Tetrahedron: Asymmetry* **2007**, *18*, 2828. (c) Almansa, R.; Guijarro, D.; Yus, M. *Tetrahedron: Asymmetry* **2008**, *19*, 1376.

(3) Ducray, P.; Cavaliero, T.; Lohrmann, M.; Bouvier, J. *PCT WO 2008062006*, 2008.

(4) Hiroi, K.; Nakazawa, K. *Chem. Lett.* **1980**, 1077.

(5) (a) Enders, D.; Lotter, H. *Tetrahedron Lett.* **1982**, *23*, 639. (b) Maigrot, N.; Mazaleyrat, J. P.; Welvart, Z. *J. Chem. Soc., Chem. Commun.* **1984**, 40. (c) Enders, D.; Lotter, H.; Maigrot, N.; Mazaleyrat, J. P.; Welvart, Z. *Nouv. J. Chim.* **1984**, *8*, 747. (d) Ahlbrecht, H.; Dollinger, H. *Synthesis* **1985**, 743. (e) Ahlbrecht, H.; Sommer, H. *Chem. Ber.* **1990**, *123*, 829. (f) Trost, B. M.; Spagnol, M. D. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2083. (g) Myers, A. G.; Kung, D. W.; Zhong, B.; Movassaghi, M.; Kwon, S. *J. Am. Chem. Soc.* **1999**, *121*, 8401.

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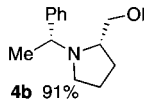
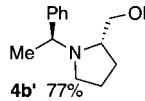
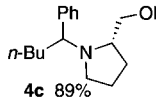
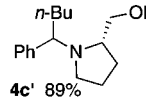
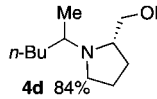
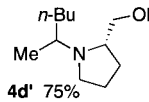
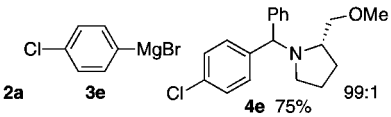
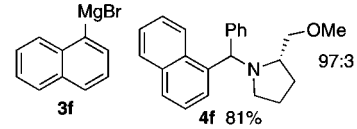
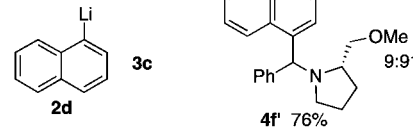
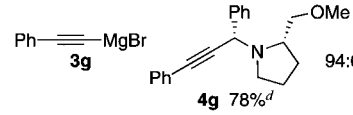
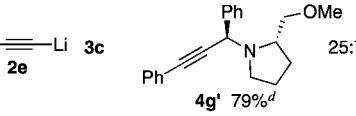
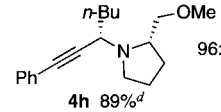
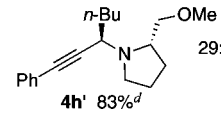
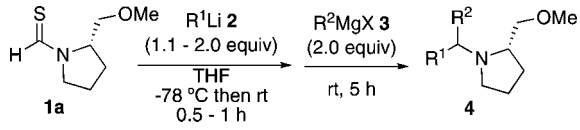
TABLE 2. Addition Reaction of Organolithium 2 and -Magnesium Reagents 3 to Thioformamide 1a[a]

entry	2	3	product yield (%)[b]	dr[c]
1	PhLi **2a**	MeMgBr **3b**	 **4b** 91%	95:5
2	MeLi **2b**	PhMgBr **3c**	 **4b'** 77%	10:90
3	**2a**	*n*-BuMgBr **3d**	 **4c** 89%	91:9
4	*n*-BuLi **2c**	**3c**	 **4c'** 89%	7:93
5	**2c**	**3b**	 **4d** 84%	92:8
6	**2b**	**3d**	 **4d'** 75%	12:88[e]
7	**2a**	**3e**	 **4e** 75%	99:1
8	**2a**	**3f**	 **4f** 81%	97:3
9	**2d**	**3c**	 **4f'** 76%	9:91
10	**2a**	**3g**	 **4g** 78%[d]	94:6
11	**2e**	**3c**	 **4g'** 79%[d]	25:75
12	**2c**	**3g**	 **4h** 89%[d]	96:4
13	**2e**	**3d**	 **4h'** 83%[d]	29:79

[a] For details, see Supporting Information. [b] Isolated yield. [c] Ratio was determined by ^{1}H NMR or GC analyses of crude products. [d] The stereochemistry of the products was determined by comparing their NMR data with those in the literature (ref 9a).

SCHEME 2. Addition Reactions of Organolithium and -Magnesium Reagents to Thioformamide 1a



1). The reaction temperature did not influence the ratio of diastereomers (entries 2 and 3), but the reaction at lower temperature was very slow (entry 3). The use of Et_2O as a solvent showed an efficiency and stereoselectivity equal to those in the reaction with THF (entry 4). The reaction with 1.1 equiv of EtMgBr gave **4a** with a slightly higher selectivity but in lower yield (entry 5).

Various combinations of organolithium and -magnesium reagents were applied to the addition reaction to **1a**. The results are listed in Scheme 2 and Table 2.

In all cases, the reaction was highly stereoselective. For example, the addition of PhLi (**2a**) to **1a** followed by the addition of MeMgBr (**3b**) gave the amine **4b** exclusively as a single diastereomer, whereas the sequential addition reaction of MeLi (**2b**) and PhMgBr (**3c**) to **1a** led to the opposite diastereomer **4b′** as a major product (entries 1 and 2). The stereochemistries of **4b** and **4b′** were determined by comparing their NMR spectroscopic data with those in the literature.[5b] A similar trend in stereoselectivity was observed not only for butyl and phenyl metallic reagents (entries 3 and 4), but also for two different alkyl metallic reagents (entries 5 and 6), although the relative stereochemistry of the products has not yet been determined. The combination of aryllithium and -magnesium reagents also shows high stereoselectivity (entries 7−9). In particular, diarylmethylamines such as **4e** and **4f** are not readily accessible, and the development of their synthetic methods via

(6) (a) Brand, M.; Drewes, S. E.; Emslie, N. D.; Khan, A. A. *Synth. Commun.* **1991**, *21*, 727. (b) Morris, M. L.; Sturgess, M. A. *Tetrahedron Lett.* **1993**, *34*, 43. (c) Uenish, J.; Hamada, M. *Tetrahedron: Asymmetry* **2001**, *12*, 2999. (d) Uenishi, J.; Hamada, M.; Aburatani, S.; Matsui, K.; Yonemitsu, O.; Tsukube, H. *J. Org. Chem.* **2004**, *69*, 6781.

(7) Vidal-Ferran, A.; Moyano, A.; Pericas, M. A.; Riera, A. *J. Org. Chem.* **1997**, *62*, 4970.

(8) Tsirk, A.; Gronowitz, S.; Hornfeldt, A.-B. *Acta Chem. Scand.* **1998**, *52*, 533.

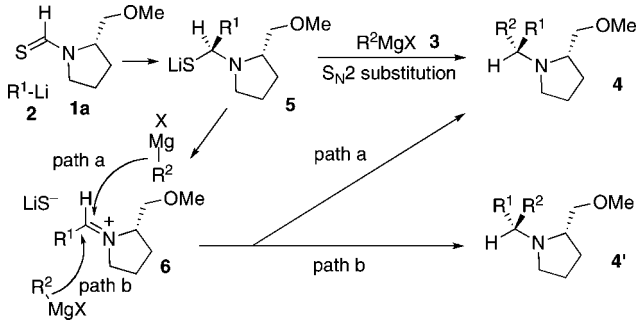
(9) (a) Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763. (b) Xu, Q.; Rozners, E. *Org. Lett.* **2005**, *7*, 2821. (c) Lo, V. K.-Y.; Liu, Y.; Wong, M.-K.; Che, C.-M. *Org. Lett.* **2006**, *8*, 1529. (d) Gommermann, N.; Knochel, P. *Chem.—Eur. J.* **2006**, *12*, 4380. (e) Zhang, X.; Corma, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4358.

(10) (a) Suginome, M.; Uehlin, L.; Murakami, M. *J. Am. Chem. Soc.* **2004**, *126*, 13196. (b) Nanda, K. K.; Wesley, T. B. *Tetrahedron Lett.* **2005**, *46*, 2025. (c) Tanaka, Y.; Hasui, T.; Suginome, M. *Synlett* **2008**, 1239.

(11) (a) Murai, T.; Mutoh, Y.; Ohta, Y.; Murakami, M. *J. Am. Chem. Soc.* **2004**, *126*, 5968. (b) Murai, T.; Toshio, R.; Mutoh, Y. *Tetrahedron* **2006**, *62*, 6312. (c) Murai, T.; Asai, F. *J. Am. Chem. Soc.* **2007**, *129*, 780.

(12) For recent examples, see: (a) Mutoh, Y.; Murai, T.; Mutoh, Y. *J. Organomet. Chem.* **2007**, *692*, 129. (b) Shibahara, F.; Suenami, A.; Yoshida, A. *Chem. Commun.* **2007**, 2354. (c) Murai, T.; Nogawa, S.; Mutoh, Y. *Bull. Soc. Chem. Jpn.* **2007**, *80*, 2220. (d) Murai, T.; Fukushima, K.; Mutoh, Y. *Org. Lett.* **2007**, *9*, 5295. (e) Shibahara, F.; Yoshida, A.; Murai, T. *Chem. Lett.* **2008**, *37*, 646.

SCHEME 3. Plausible Reaction Pathway

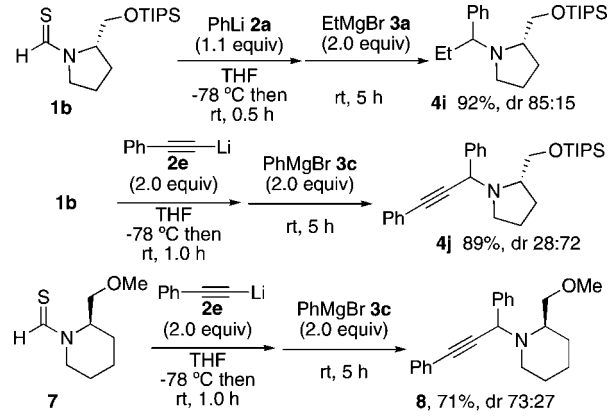


asymmetric addition of organometallic reagents to imines is one of the great topics.[15] Finally, the combination of alkynyl and aryl or alkyl metallic reagents was tested. The use of alkynylmagnesium reagents in the second step gave the products with high diastereoselectivity (entries 10 and 12). In contrast, the initial addition of lithium acetylide **2e** to **1a** decreased the selectivity to some extent, although the desired products **4g′** and **4h′** were obtained in good yields (entries 11 and 13).[16] This may be because alkynyl groups are the least sterically hindered substituents. Therefore, the stereochemistry of the products is not determined thermodynamically but rather is kinetically controlled.

Although details of the reaction mechanism can not yet be discussed, the presumed reaction pathway is shown in Scheme 3. Organolithium reagents **2** may attack the thiocarbonyl carbon atom of the major conformer of **1a** from the side opposite the methoxymethyl group in the pyrrolidinyl group to form lithium thiolates **5**. An S_N2 substitution reaction may then occur at the carbon atom adjacent to the nitrogen atom in **5** with elimination of a LiS group. The results in Table 2 show that diastereoselectivity is controlled not solely by the organolithium reagents, but also by the organomagnesium reagents. Therefore, the step from **5** to **4** may partly involve an S_N1 mechanism. Prior to the attack of organomagnesium reagents, a LiS group is eliminated from **5** to exclusively form *E*-iminium salts **6**. Then, **3** adds to the iminium carbon atom from the side opposite the methoxymethyl group to lead to the major isomers **4** (path a), whereas the addition of **3** to **6** from the same side of the methoxymethyl group gives the minor isomers **4′** (path b). In fact, the generation of **6** has been postulated in the reaction of *N*-1-cyanophenylmethyl 2-methoxymethylpyrrolidine with MeMgBr.[5b] In this case, the product **4b** is obtained with a diastereoselectivity of 90:10.

Finally, thioformamides **1b** and **7** were used as starting materials (Scheme 4). The combinations of phenyllithium (**2a**) and ethylmagnesium bromide (**3a**) and of lithium acetylide (**2e**) and phenylmagnesium bromide (**3c**) were used. The reaction

SCHEME 4. Reaction of Thioformamide 1b and 7



showed efficiency and diastereoselectivity similar to those observed in Table 1 and entry 11 in Table 2.

In summary, sequential addition reactions of widely used organolithium and -magnesium reagents[17] to *N*-thioformyl 2-alkoxymethylpyrrolidine have been demonstrated. Various combinations of these two different types of organometallic reagents have been shown to be useful. The reaction shows high efficiency and diastereoselectivity. The synthesis of diastereomers with opposite stereochemistries can be achieved by simply reversing the order of introduction of the substituents on organolithium and -magnesium reagents. Further studies on the sequential addition of organometallic reagents to thioamides and on the application of the products obtained as optically active ligands are in progress.

Experimental Section

Typical Experimental Procedure for the Sequential Addition Reaction of Organolithium and -Magnesium Reagents to Thioformamides 1. To a solution of (*S*)-2-methoxymethyl-1-thioformylpyrrolidine (**1a**; 0.16 g, 1.0 mmol) in THF (1.0 mL) was slowly added 1.00 M solution of phenyllithium in cyclohexane−Et_2O (1.1 mL, 1.1 mmol) at −78 °C. After the addition was complete, the mixture was stirred for 0.5 h at room temperature. To this was added a 1.0 M solution of ethylmagnesium bromide in THF (2.0 mL, 2.0 mmol) at room temperature, and this mixture was stirred at this temperature for 5 h. The resulting mixture was poured into a saturated aqueous solution of NH_4Cl and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexane/EtOAc/Et_3N = 5:1:0.01) to give (2*S*)-2-(methoxymethyl)-1-(1-phenylpropyl)pyrrolidine (**4a**) (0.170 g, 73% as a major isomer; 0.021 g, 9% as a mixture of isomers; 0.025 g, 11% as a minor isomer) as a yellow oil; *dr* = 88:12. Major isomer: $[\alpha]_D^{20} = -34.0$ (c = 0.73, $CHCl_3$); IR (neat) 2963, 2931, 2873, 2823, 1492, 1452, 1197, 1116, 762, 704 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.68 (t, J = 7.6 Hz, 3H), 1.45−1.71 (m, 5H), 1.85−1.92 (m, 1H), 2.18−2.24 (m, 1H), 2.68−2.81 (m, 2H), 3.16 (dd, J = 9.4, 7.6 Hz, 1H), 3.31 (s, 3H), 3.38 (dd, J = 9.4, 4.4 Hz, 1H), 3.49 (dd, J = 9.6, 5.6 Hz, 1H), 7.14−7.25 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 11.3, 23.0, 27.8, 28.6, 49.8, 58.8, 59.1, 67.9, 76.9, 126.7, 127.8, 128.9, 140.6; MS (EI) *m/z* 232 (M^+ − H): HRMS (EI) Calcd for $C_{15}H_{22}NO$ (M^+ − H): 232.1701. Found: 232.1719. Minor isomer: IR (neat) 2963, 2931, 2873, 2807, 1453, 1196, 1114, 768 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.58 (t, J = 7.2 Hz, 3H), 1.63−1.74 (m, 5H),

(13) Pyrrolidine **1a** was prepared by thionation of *N*-formyl 2-methoxymethyl pyrrolidine[14] with Lawesson reagent.

(14) Enders, D.; Fey, P.; Kipphardt, H. *Organic Syntheses*; Wiley and Sons: New York, 1993; Collect. Vol. No. 8, p 26.

(15) For recent examples, see: (a) Le Fur, N.; Mojovic, L.; Ple, N.; Turck, A.; Reboul, V.; Metzner, P. *J. Org. Chem.* **2006**, *71*, 2609. (b) Jagt, R. B. C.; Toullec, P. Y.; Geerdink, D.; de Vries, J. G.; Feringa, B. L.; Minnaard, A. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2789. (c) Duan, H.-F.; Jia, Y.-X.; Wang, L.-X.; Zhou, Q.-L. *Org. Lett.* **2006**, *8*, 2567. (d) Berthon-Gelloz, G.; Hayashi, T. *J. Org. Chem.* **2006**, *71*, 8957. (e) Wang, Z.-Q.; Feng, C.-G.; Xu, M.-H.; Lin, G.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 5336. (f) Marelli, C.; Monti, C.; Gennari, C.; Piarulli, U. *Synlett* **2007**, 2213. (g) Nakagawa, H.; Rech, J. C.; Sindelar, R. W.; Ellman, J. A. *Org. Lett.* **2007**, *9*, 5155.

(16) In contrast to these successful results, the combination of lithium acetylides and alkynylmagnesium reagents gave the corresponding products in only low yields along with the formation of unidentified byproducts.

(17) For reviews, see: (a) *Main Group Metals in Organic Synthesis*; Yamamoto, H., Oshima, K., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 1. (b) *Handbook of Functionalized Organometallics*; Knochel, P., Ed.; Wiley-VCH: Weinheim, 2005; Vol. 1.

1.88−1.94 (m, 1H), 2.41−2.47 (m, 1H), 2.72−2.81 (m), 2.87−2.90 (m, 1H), 2.98−3.03 (m, 1H), 3.01 (s, 3H), 3.28 (dd, J = 10.8, 4.0 Hz, 1H), 7.14−7.25 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 11.1, 23.7, 26.3, 28.6, 52.4, 58.6, 60.4, 71.0, 76.1, 127.0, 128.0, 128.8, 142.8; MS (EI) m/z 232 ($M^+ - H$); HRMS (EI) Calcd for $C_{15}H_{22}NO$ ($M^+ - H$): 232.1701. Found: 232.1698.

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Supporting Information Available: Experimental procedures and characterization of new compounds **1**, **4**, **7**, and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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