Direct reductive amination of aldehydes using lithium-arene(cat.) as reducing system. A simple one-pot procedure for the synthesis of secondary amines.

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Abstract

A simple one-pot procedure for the direct reductive amination of aldehydes using lithium powder and a catalytic amount of 4,4'-di-*tert*-butylbiphenyl (DTBB) or a polymer supported naphthalene as reducing system is described. The direct reductive amination of a variety of aldehydes with primary amines was achieved simply by adding a mixture of the corresponding carbonyl compound and the amine, over a solution of the lithium arenide in THF at room temperature. For most of the substrates tested the main reaction products were the secondary amines along with variable amounts of the corresponding alcohol and/or imine products. Theoretical DFT calculations have been applied in order to explain the differences in reactivity observed for aromatic substrates.

Keywords: lithium-arene, aldehydes, reductive amination, secondary amines, DFT methods

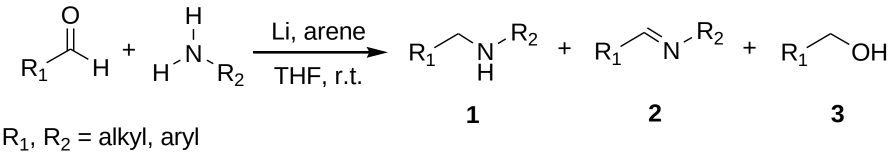
Introduction

Amines and their derivatives are present in many naturally occurring bioactive molecules such as amino acids, nucleic acids and alkaloids, among others.[1] They are known to have interesting herbicidal and fungicidal activities and they are also utilised as versatile intermediates for the synthesis of pharmaceuticals, agrochemicals,[2] and as valuable building blocks for nitrogen-containing synthetic polymers. Amines can be synthesized by many different methods including: (a) reduction of nitrogen-containing functional groups such as nitro, cyano, azide, and carboxamide derivatives; (b) alkylation of ammonia, primary or secondary amines, using alkyl halides or sulfonates as alkylating agents;[1] and (c) reaction of aldehydes or ketones with ammonia, primary or secondary amines in presence of different reducing agents.[3] This latter is the so-called *reductive amination reaction* which is described as *direct* when the carbonyl compound and the amine are mixed together with a suitable reducing agent in a single operation (one-pot), without preformation of an imine or iminium salt. On the other hand, *indirect* reductive amination involves the preformation of an imine followed by its reduction in a second step. Direct reductive amination (DRA) offers significant advantages over other amine syntheses, including simplicity of the methodolgy, wide commercial availability of substrates, mild reaction conditions, and in some cases high functional group tolerance.[4] A wide variety of reducing agents and reaction conditions have been developed to perform this transformation, all of them presenting both advantages and disadvantages. The catalytic hydrogenation, for instance, is an attractive methodology from economical and ecological points of view. It can be mediated by several heterogeneous[5] and some homogeneous metal catalysts,[6] although the presence of some functional groups such as nitro, cyano and carbon-carbon multiple bonds may limit its applicability. Hydride reducing agents are also commonly used for the DRA of carbonyl compounds, among them the Borch reduction using sodium cyanoborohydride ($NaBH_3CN$), and reductive amination using sodium triacetoxyborohydride [$NaBH(OAc)_3$] have been widely used.[3,7] Sodium cyanoborohydride is stable in relatively strong acid solutions, is soluble in hydroxylic solvents such as methanol, and presents different selectivities at different pH values; but it is expensive, highly toxic and may contaminate the product with NaCN, and generate toxic HCN upon work-up. Moreover, in some cases up to a fivefold excess of the amine is required in order to limit the competitive reduction of the C=O bond of the carbonyl compound. On the other hand, sodium triacetoxyborohydride is mild, presents a high functional group tolerance and reduces imines selectively over carbonyl compounds, but it is flammable, poorly soluble in most of the commonly used organic solvents, and has important limitations when aromatic and unsaturated ketones are used as starting carbonyl compounds. Another hydride reagent frequently used to perform the DRA reaction is sodium borohydride ($NaBH_4$). It is inexpensive, safe to handle, and can be employed for large-scale reductions,[8] nevertheless, the major drawbacks are its low selectivity, the harsh reactions conditions needed and, in many cases, the necessity of adding Brönsted acids to facilitate intermediate imine formation.[9] Many other hydride-based reducing systems have been applied to the reductive amination reaction, most of them associated with the use of complex catalysts, expensive and flammable reagents, and/or low product yield. Among them, organosilanes have the advantage to be organic soluble reducing agents, however they present some limitations in substrate compatibility.[10]

Apart from hydride-based reagents, the Hantzsch 1,4-dihydropyridine system is a mild, inexpensive and nontoxic reducing agent that has been used for the reductive amination of carbonyl compounds. Nevertheless, the reduction step proceeds in low yield, thus requiring long reaction times and the use of Lewis acids for the imine activation.[11] Some interesting related systems, using the Hantzsch ester as transfer hydrogenating agent and thioureas for selective imine activation, have recently been reported.[12]

On the other hand, alkali metals are known to be strong reducing agents, among them, lithium metal has been widely used for many reduction reactions in organic synthesis.[13] The reducing systems based on the use of alkali-metals in combination with arenes in aprotic media, with the arene acting as electron carrier via the generation of its radical anion, have received much attention. In the last years, some of us have been actively working on the preparation of transition metal nanoparticles by fast reduction of the corresponding transition metal chlorides with lithium and a catalytic amount of an arene [naphthalene, 4,4´-di-*tert*-butylbiphenyl (DTBB)] as electron carrier, for their application in many useful organic transformations.[14]

During the course of our studies on the reductive amination of aldehydes and ketones mediated by copper nanoparticles, we have found that the lithium-arene(cat.) system alone, in the absence of the copper nanoparticles, was capable of performing the desired transformation. In this work we want to introduce a simple and efficient procedure for the direct reductive amination of aromatic and aliphatic aldehydes for the one-pot synthesis of secondary amines, using primary amines of several nature as starting materials in the presence of lithium powder and a catalytic amount of an arene (DTBB or a polymer supported naphthalene) in tetrahydrofuran as solvent and at room temperature (Scheme 1). The methodology reported in this work is simple, mild, economic, nontoxic, and does not need the use of any additives or acids. As far as we know, there are no reports on the direct reductive amination of aldehydes using lithium and arenes as promoters.



Scheme 1. Reductive amination of aldehydes with primary amines.

Results and discussion

The direct reductive amination of a variety of aldehydes with primary amines of different nature, was achieved simply by adding a mixture of the corresponding carbonyl compound (1.0 mmol) and the amine (1.0 mmol) in THF (4 mL), over a solution of the lithium arenide obtained from the reaction of an excess of lithium powder (3.0 mmol) with a catalytic amount of DTBB (0.1 mmol) in THF (2 mL). The reaction mixture was stirred at room temperature, under nitrogen atmosphere, until total conversion of the starting carbonyl compound (TLC, GLC). For most of the substrates tested the main reaction products were the corresponding secondary amines (**1**) along with variable amounts of the direct reduction products of the starting carbonyl compounds (alcohols **3**). In some cases, the corresponding imines (**2**) were formed in very good yields but were resistant to further reduction. On the other hand, ketones remained unreacted under the same reaction conditions, even at higher reaction temperature (reflux of THF).

Table 1 summarizes the results obtained in the DRA of a series of aldehydes with different primary amines under the above described conditions. Benzylamine and *p*-methylbenzaldehyde were used as model substrates for determining the optimal reaction conditions. When DTBB was used as electron carrier the corresponding secondary amine was obtained in excellent yield and in only 1.5 h of reaction time (Table 1, entry 1). The same reaction performed below room temperature (0 to 15° C) did not show conversion of the starting aldehyde. We then tested naphthalene as electron carrier in the same reaction conditions. After 1.5 h of reaction time the secondary amine was obtained in a lower yield compared with that of using DTBB (Table 1, entry 2), together with a considerable amount of 1,1'-binaphthyl as a side reaction product. These observations are in agreement with the fact that DTBB is better than naphthalene as mediator in electron transfer processes, mainly due to its lower reduction potential and its low tendency to coupling because of the steric hindrance caused by the *tert*-butyl groups. In the absence of an arene (DTBB or naphthalene), the secondary amine was obtained in much lower yield and the corresponding benzylic alcohol was formed in 20% yield (Table 1, entry 3), thus demonstrating the necessity of using an electron carrier for the DRA to occur. As reported by Compton *et. al.*, the use of an arene as mediator in lithium reductions offers a very large rate increase over the non mediated route.[13b] On the other hand, in the last years we have been interested in the use of macromolecular structures as stabilizers for metal nanoparticles and, in connection with this goal, we have synthetized a copolymer of styrene and 2-vinylnaphthalene (PS-2VN) by anionic polymerization, which could act both as electron carrier and as stabilizer. Interestingly, the use PS-2VN (20 mg) and lithium (3.0 mmol) in the DRA of benzaldehyde (1.0 mmol) and cyclohexylamine (1.0 mmol) quantitatively gave the desired secondary amine (Table 1, entry 4), which was recovered from the reaction mixture simply by filtration without needing further purification. The use of the same copolymer in the DRA of *p*-methylbenzaldehyde with cyclohexylamine gave the corresponding secondary amine in a similar yield to that obtained using DTBB as electron carrier (Table 1, entry 5).

In the optimized reaction conditions, using DTBB as arene, the DRA of benzaldehyde with aliphatic and aromatic amines such as dodecylamine, cyclohexylamine, aniline and benzylamine, gave the desired secondary amines in less than 3 h and in very good yields (Table 1, entries 6-9, respectively). Aliphatic aldehydes showed to be less reactive than their aryl counterparts, leading to the corresponding secondary amines in moderate yield and in longer reaction times (Table 1, entries 10 and 11).

Table 1. Direct reductive amination of aldehydes with primary amines.[a]

Entry	R_1	R_2	Time (h)	Yield (%)[b]		
				1	**2**	**3**
1	p-CH_3-Ph	$PhCH_2$	1.5	76 (**1a**)	-	-
2[c]	p-CH_3-Ph	$PhCH_2$	1.5	45 (**1a**)	22	7
3[d]	p-CH_3-Ph	$PhCH_2$	1.5	30 (**1a**)	7	20
4[e]	Ph	c-C_6H_{11}	0.5	100 (**1b**)	-	-
5[e]	p-CH_3-Ph	c-C_6H_{11}	2	70 (**1c**)	-	12
6	Ph	n-$C_{12}H_{25}$	2	74 (**1d**)	-	7
7	Ph	c-C_6H_{11}	2	73 (**1b**)	-	8
8	Ph	Ph	8	87 (**1e**)	-	-
9	Ph	$PhCH_2$	3	60 (**1f**)	9	8
10	$(CH_3)_2C{=}CH(CH_2)_2CH(CH_3)CH_2$	c-C_6H_{11}	10	64 (**1g**)	16	-
11	c-C_6H_{11}	$PhCH_2$	12	58 (**1h**)	14	5
12	Ph	p-CH_3-Ph	5	71 (**1i**)	8	-
13	p-CH_3-Ph	n-$C_{12}H_{25}$	3	70 (**1j**)	-	8
14	p-CH_3-Ph	c-C_6H_{11}	2	75 (**1c**)	4	8
15	p-$(CH_3)_2N$-Ph	n-$C_{12}H_{25}$	3	72 (**1k**)	7	8
16	p-$(CH_3)_2N$-Ph	c-C_6H_{11}	2	68 (**1l**)	-	7
17	p-$(CH_3)_2N$-Ph	$PhCH_2$	3	82 (**1m**)	5	6
18	p-CH_3O-Ph	c-C_6H_{11}	6	40 (**1n**)	4	29
19	Ph	3,5-$(CF_3)_2$-Ph	8	-	50 (**2o**)	-
20	p-CF_3-Ph	Ph	8	-	45 (**2p**)	-

[a] Reaction conditions: aldehyde (1.0 mmol), amine (1.0 mmol), Li (3.0 mmol), DTBB (0.1 mmol), in THF as the solvent (6 mL), at 25 ºC, unless otherwise stated.

[b] Yield determined by ^{1}H-RMN or CG-MS using internal standard method.

[c] Reaction conditions: aldehyde (1.0 mmol), amine (1.0 mmol), Li (3.0 mmol), naphthalene (0.15 mmol), in THF as the solvent (6 mL), at 25ºC.

[d] Reaction conditions: aldehyde (1.0 mmol), amine (1.0 mmol), Li (3.0 mmol), in THF as the solvent (6 mL), at 25ºC.

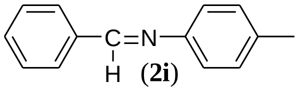
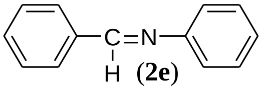
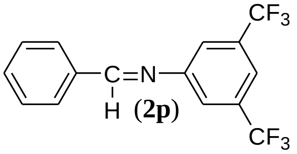
[e] Reaction conditions: aldehyde (1.0 mmol), amine (1.0 mmol), Li (3.0 mmol), co-polymer (20 mg), in THF as the solvent (6 mL), at 25ºC.

Then, we examined the scope of the reaction for aromatic substrates by reacting various substituted benzaldehydes and anilines. We observed that those substrates bearing electronreleasing groups attached to the aromatic ring were more reactive, leading to the corresponding secondary amines in good yield (Table 1 entries 12-17). In the case of *p*-methoxybenzaldehyde (Table 1, entry 18) the lower yield obtained is attributed to the partial cleavage of the methoxy group under the reaction conditions. On the other hand, the reaction of benzaldehydes or anilines bearing electron-withdrawing groups, gave the corresponding imines as major reaction products (Table 1, entries 19 and 20). Although electron-poor anilines are poor nucleophiles, the fact that the reaction stops at the imine stage indicates that the intial nucleophilic attack on the carbonyl carbon indeed takes place, but the imine intermediate do not undergo subsequent reduction under the reaction conditions.

These observations prompted us to study in more detail the electron transfer process involved, using density functional theory (DFT) calculations. For this purpose, we theoretically study the neutral imines and the corresponding radical anions of compounds **2e**, **2i** and **2p**. The ab initio calculations were performed with the B3LYP[15] DFT[16] functional and the 6-31+G* basis set, which is known to be an appropriate methodology for the theoretical study of the electronic properties of radical anions.

The LUMO MOs of the neutral imines have $\pi-$symmetry (shown in Figure 1 for imine **2e**) and, as expected, this MOs showed differences in energy for each imine (Table 2). An electron-withdrawing group attached to the aromatic ring at the amine moiety of the imine increases the stability of the π-system and lowers its LUMO, favouring the electron transfer (ET) process by increasing the electron affinity of the substrate.

Table 2. LUMO MOs energy for different imines

Imine	LUMO energy (eV)
 (**2i**)	-0.068
 (**2e**)	-0.070
 (**2p**)	-0.091

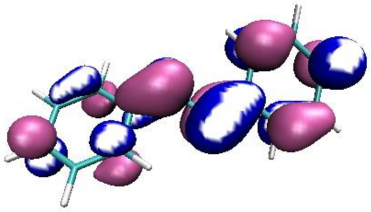


Figure 1. LUMO for imine **2e**.

On the other hand, the DFT calculations showed significant differences for the corresponding radical anions of these imines. In these species, the unpaired electron is located mainly on the C=N $\pi-$system. When comparing the C=N bond of the neutral imines with that of the corresponding radical anions, the main geometric change observed for this π-system is the elongation of the C=N bond, which have a length of 1.28 Å for the imines and 1.33 Å for the corresponding radical anions. For the radical anions of imines **2i** and **2e**, the excess spin is mainly located on the nitrogen center, however, for **2p** radical anion, as a consequence of the electron-withdrawing groups attached to the aromatic ring, the spin density at the same center is considerably low. The unpaired spin distribution for the radical anions of these imines is shown in Figure 2. It should be mentioned that, when the reaction solvent (THF) was included in the calculations as a polarizable continuum model, the spin density remained almost unchanged.

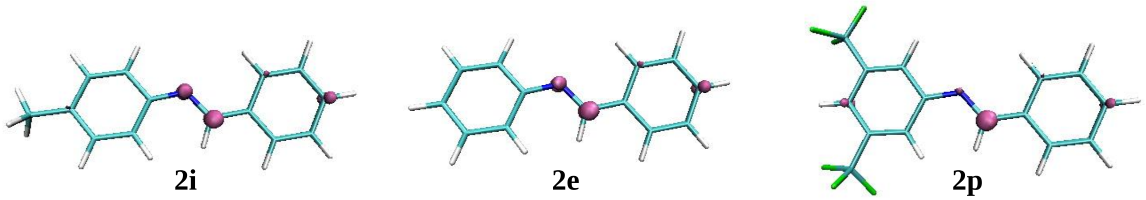
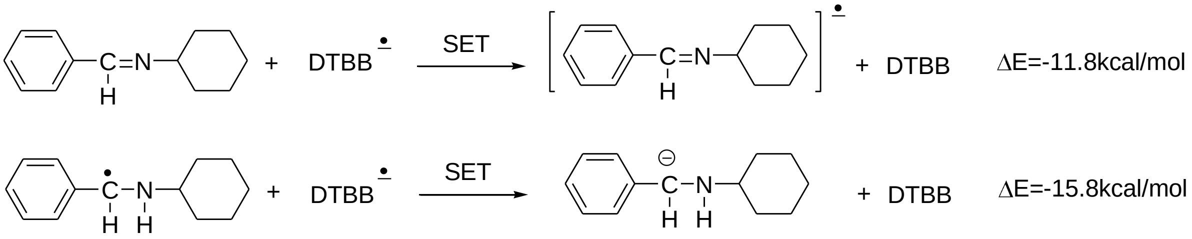

2i **2e** **2p**

Figure 2. Gas phase B3LYP/6-31+G* spin density (pink) for radical anions of imines **2i**, **2e** and **2p**.

The calculated spin distribution shown in Figure 2, could *a priori* be interpreted as consistent with a favoured formation of a radical anion intermediate in which the negative charge is located at the nitrogen atom. An intermediate of this type would be also consistent with the experimentally observed lack of reactivity of imines bearing an electron withdrawing group on the aromatic ring of the aldehyde moiety of the imine. It has been shown that the unpaired spin density distribution is a relevant factor for reactions that proceed through ET processes. As can be seen from the graphics in Figure 2, the higher spin distribution is placed on the nitrogen, thus, the protonation of this radical anion would result in the formation of a benzylic type radical that would be easily reduced to the corresponding benzylic anion, and finally protonated to yield the amine product.

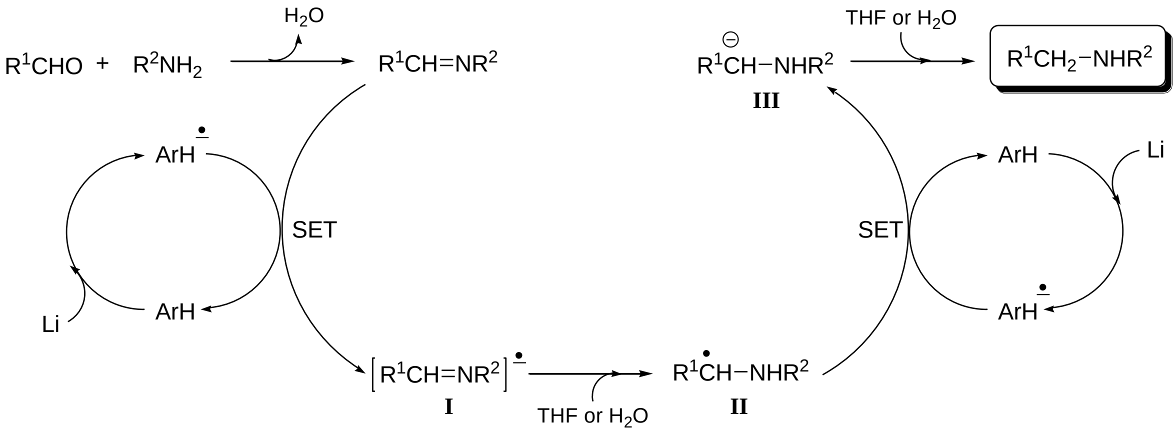
In order to study the thermodynamic feasibility for the different steps involved in the proposed reaction pathway, DFT calculations for imine **2b** as model compound, including THF as the solvent, were carried out. The results are shown in Scheme 2.



Scheme 2.

It is noteworthy that the formation of a dianion, as a possible intermediate, would be endothermic in about 27.3 kcal/mol.

Based on our experimental results, and those previously reported by other authors,[17] in conjunction with the results obtained from DFT calculations, we suggested a possible reaction pathway, involving two successive single-electron transfer (SET) steps from the lithium-arenide to the *in situ* formed imine, as depicted in Scheme 3. According to DFT calculations, the first SET might led to the formation of radical anion **I**, which would be protonated by the solvent (THF) or water (produced during the formation of the imine), to give the radical intermediate **II**. A second SET from the lithium-arenide to **II** would lead to carbanion **III**, which would be rapidly protonated to give the secondary amine product.



Scheme 3. Proposed reaction pathway

Conclusions

In summary, we have described herein a simple one-pot procedure for the direct reductive amination of aromatic and aliphatic aldehydes for the synthesis of secondary amines, using lithium-arene(cat.) as reducing system. The methodology reported is simple, mild and avoid the use of any additives or acids. On the other hand, DFT calculations have shown to be a successful approach for studying the ET reduction of imines as well as to explain the proposed reaction mechanism.

Experimental

General

All moisture sensitive reactions were carried out under nitrogen atmosphere. Anhydrous tetrahydrofuran was freshly distilled from sodium/benzophenone ketyl. Other solvents used were treated prior to use by standard methods.[18] All starting materials were of the best available grade (Aldrich, Merck) and were used without further purification. Column chromatography was performed with Merck silica gel 60 (0.040–0.063 μm, 240–400 mesh). Thin layer chromatography (TLC) was performed on precoated silica gel plates (Merck 60, F254, 0.25 mm).

Instrumentation and analysis

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker ARX-300 spectrophotometer using $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal reference. Mass spectra (EI) were obtained at 70 eV on a Hewlett Packard HP-5890 GC/MS instrument equipped with a HP-5972 selective mass detector. The purity of volatile compounds and the chromatographic analyses (GC) were determined with a Shimadzu GC-9A instrument equipped with a flame-ionization detector and a 2 m column (1.5% OV17 9_A SUS Chrom 103 80/1000), using nitrogen as carrier gas.

General procedure for the reductive amination of aldehydes with primary amines

A mixture of lithium sand (21 mg, 3.0 mmol) and DTBB (26 mg, 0.1 mmol) in THF (2 mL) was stirred at room temperature under nitrogen atmosphere. When the reaction mixture turned dark green (5-20 min), indicating the formation of the lithium arenide, a solution of the primary amine (1.0 mmol) in THF (2 mL) was slowly added by syringe, followed by the addition of the corresponding aldehyde (1.0 mmol) in THF (2 mL). After total conversion of the starting material (TLC, GC-MS), the resulting suspension was diluted with ethyl ether (10 mL) and washed with

H_2O (3x10 mL). The combined extracts were dried over anhydrous Na_2SO_4 and evaporated (20 mbar). The resulting residue was purified by flash column chomatography (silica gel, hexane-ethyl acetate) to give the corresponding secondary amine.

Computational Procedure

The calculations were performed with Gaussian03.[19] The initial conformational analysis of compounds was performed with the semiempirical AM1 method. The geometry of the most stable conformers thus obtained was used as starting point for the B3LYP studies of the imines and their radical anions. The zero point energy corrections were made at the 6-31+G* level for the thermodynamic quantities. The energies in solution were obtained with full geometry optimization within the Tomasi's polarized continuum model (PCM)[20] as implemented in Gaussian03. Figures were built with the GaussView program using a spin density isosurface of 0.02.

Synthesis of PS-P2VN copolymer

The synthesis of PS-P2VN copolymer was achieved by anionic copolymerization, using high vacuum techniques, as described below.[21]

A clean glass reactor containing destilled THF was placed in a liquid N_2/isopropanol bath, and then the styrene (2 mL of a solution in benzene, 0.43 g/mL) and 2-vinylnaphthalene (0.49 g) monomers were added. The solution turned yellow. After the initiator (*sec*–Bu^-Li^+) was added, the reaction mixture turned bright orange. The polymerization was left to proceed under continuous stirring at room temperature. After 24 h of reaction time, the resulting solution turned deep red. No changes were observed when methanol was added to stop the polymerization. The crude reaction product was precipitated in chilled methanol, and the copolymer was obtained as a finely pale yellow powder (50% yield). The SEC analysis of the copolymer showed a molar mass of 2,800 g/mol, and a polydispersity index (PD) of 1,9.

Acknowledgements

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