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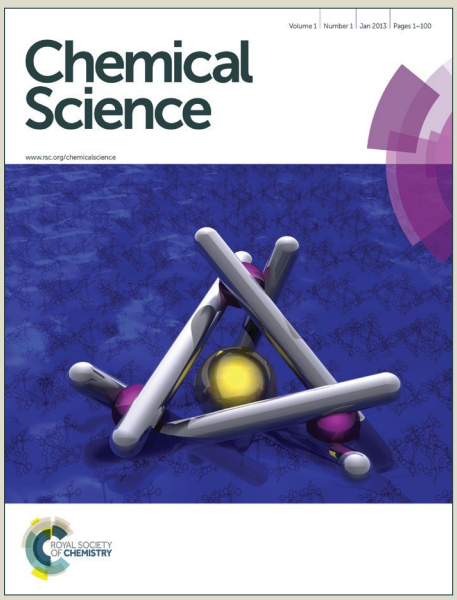

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ARTICLE

Rhodium-Catalyzed Regioselective Addition of the ortho C-H Bonds in Aromatic Amides to C-C Double Bonds in α,β-Unsaturated γ-Lactones and Dihydrofurans

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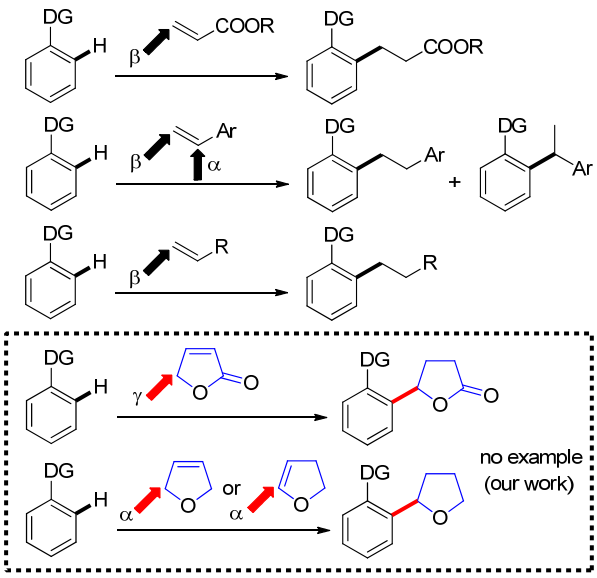
An unprecedented C-H alkylation using α,β-unsaturated γ-lactones (butenolides) and dihydrofurans was achieved by the Rh-catalyzed reaction of benzamides. C-C Bond formation occurs between the ortho-position in the benzamide derivative and the γ-position of the butenolide and the α-position of the dihydrofuran. The presence of an 8-aminoquinoline directing group is crucial for the success of the reaction. The results of deuterium labeling experiments indicate that the cleavage of C-H bonds is reversible and suggests that a migratory carbene insertion is involved as the key step.

Introduction

During the past several decades, the chelation-assisted functionalization of C-H bonds has undergone rapid development and is now used in the synthesis of a wide variety of natural products and medicinally relevant compounds.[1,2] While a wide variety of such functionalizations has been developed to date, the addition of C-H bonds to alkenes represents one of the fundamental and atom economical functionalizations of C-H bonds because of atom economy.[3,4] While various alkenes can be used as coupling partners, the range of alkenes that are applicable to C-H alkylation continue to remain limited to vinylsilanes and tert-butylethylene, which contains no allylic hydrogen, or activated alkenes, such as styrenes and α,β-unsaturated carbonyl compounds. Methodology for using various alkenes as participants in C-H alkylation is still needed. Not only the applicability of alkenes but also the control of regioselectivity regarding the addition of C-H bonds to alkenes remains to be solved. Acrylic esters exclusively undergo β-addition reactions to give linear products. In reactions with styrenes, the extent of regioselectivity depends on the catalytic system being used.[5] In many cases, terminal alkenes containing an allylic hydrogen are not applicable for the reaction, however Chang and Ackermann recently reported on the Rh- and Ru-catalyzed alkylation of C-H bonds with various terminal alkenes, in which β-addition takes place with linear products being produced.[6] We wish to report herein on the first example of the C-H alkylation of α,β-unsaturated γ-lactones and dihydrofurans, in which C-C bond formation occurs between the ortho-position in an aromatic amide and the γ-position of butenolides and the α-position of dihydrofurans, irrespective of the position of the C-C double bonds to give 5-aryl-γ-butyrolactone or 2-aryltetrahydrofuran derivatives, respectively (Scheme 1). These types of products cannot be produced by the alkylation of C-H bonds with alkyl halides. 5-Aryl-γ-butyrolactone derivatives[7] and 2-aryltetrahydrofuran derivatives[8] are key structural components of many biologically active and pharmaceutically important molecules, making the construction of such a structure synthetically important. Our strategy for constructing 5-aryl-γ-butyrolactone and 2-aryltetrahydrofuran frameworks involves the catalytic activation of C-H bonds in a benzene ring, which then add to the C-C double bond in a butenolide or dihydrofuran derivative. In addition, a directing group must be easily removed or elaborated to another useful functionality.[9]



Scheme 1 The addition of C-H bonds across alkenes.

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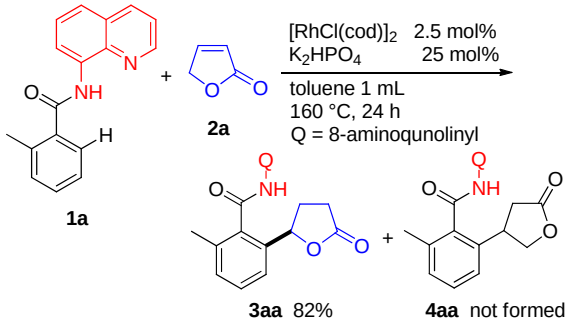
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

Results and Discussion

When the butenolide **2a** was used as the coupling partner in the reaction of **1a**, the expected product **4aa**, for which the reaction occurred at the β-position of the lactone, was not obtained, but, instead, **3aa** was produced as the sole product (Scheme 2). After screening a number of bases, it was found that the reaction is sensitive to the nature of the base used. In general, the use of Na_2CO_3 or K_2HPO_4 gave the best results.[10] To the best of our knowledge, this is the first example of C-H bond alkylation with α,β-unsaturated lactones.



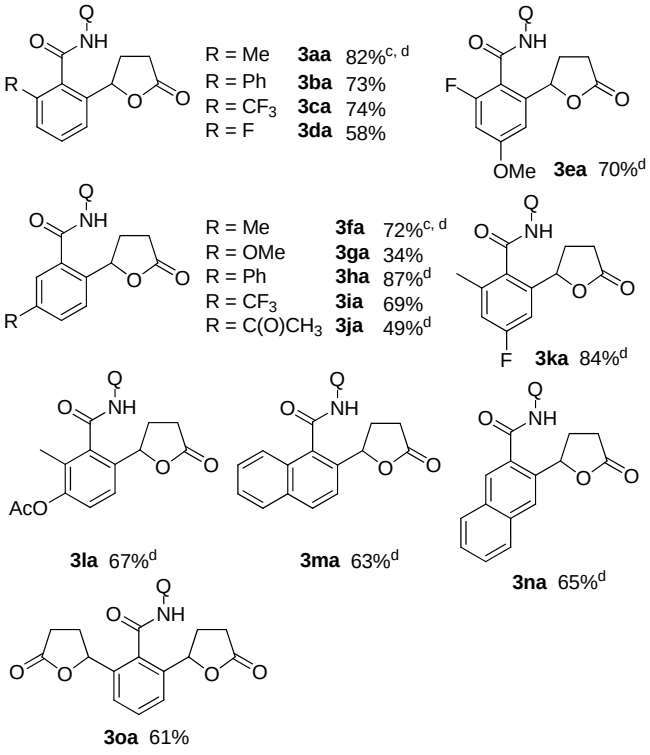
Scheme 2 Rh-Catalyzed C-H alkylation of **1a** with butenolide **2a**.

We next examined the effect of the directing group.[11] Among the directing groups examined, only an 8-aminoquinoline gave the corresponding alkylation product. Most importantly, the 2-phenylpyridine, which contains an extensively used pyridine directing group in catalytic C-H functionalization reactions, was also ineffective. Our research has recently focused on the utilization of an *N,N*'-bidentate directing chelation system in the functionalization of C-H bonds.[12,13] This result also shows the potential of such a system for exploring new types of functionalizations of C-H bonds.

Table 1 shows some representative results for reactions of various aromatic amides with butenolide **2a**. In the case of meta-substituted aromatic amides, contrary to the case when methyl acrylate is used in a similar chelation system,[13a] the alkylation proceeded selectively only at the less hindered position, as in **3fa**-**3ja** because the introduced lactone moiety is a sterically demanding group, compared with an acrylate moiety. In the case of the benzamide **1o**, both ortho C-H bonds underwent alkylation to give the double alkylation product **3oa** in 61% isolated yield.

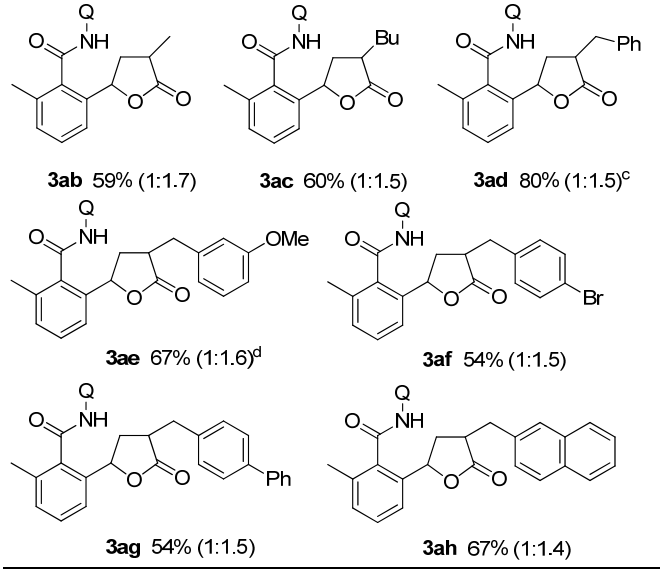
Substituted α,β-unsaturated γ-lactones **2** were also applicable to the present reaction (Table 2). Me, Bu, and benzyl substituted lactones could all be used, as in **3ab**, **3ac**, and **3ad**. In all cases, a mixture of cis and trans isomers was produced in a comparable ratio. The ratio was constant even when the reaction was stopped after a short reaction time, suggesting that the ratio obtained is a thermodynamic ratio. Lactones bearing functional groups on the phenyl ring, such as Br and MeO were tolerated under the reaction conditions.

Table 1 Rh-Catalyzed alkylation of aromatic amides **1a-1o** with butenolide **2a**[a,b]



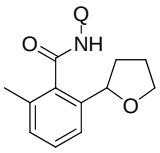
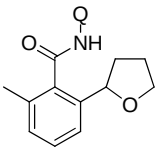
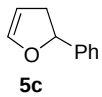
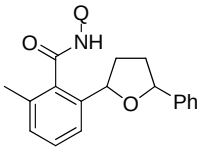
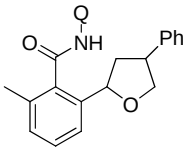
[a] Reaction conditions: amide **1** (0.3 mmol), lactone **2a** (0.9 mmol), $[RhCl(cod)]_2$ (0.015 mmol), Na_2CO_3 (0.075 mmol), toluene (1 mL), at 160 °C for 24 h. b Isolated yields. [c] Lactone (0.6 mmol), $[RhCl(cod)]_2$ (0.0075 mmol) were used. [d] K_2HPO_4 was used in place of Na_2CO_3.

Table 2 Rh-Catalyzed alkylation of aromatic amides **1a** with α,β-unsaturated γ-butyrolactones **2b**-**2h**.[a,b]



[a] Reaction conditions: amide 1 (0.3 mmol), lactone **2a** (0.9 mmol), $[RhCl(cod)]_2$ (0.015 mmol), K_2HPO_4 (0.075 mmol), toluene (1 mL), at 160 °C for 24 h. [b] Isolated yields. The number in parenthesis denotes the ratio of cis and trans isomers [c] The reaction was run for 12h. [d] KOAc was used in place of K_2HPO_4.

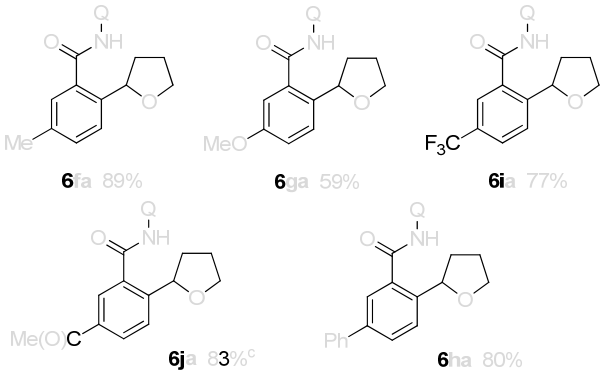
Table 3 Rh-Catalyzed alkylation of aromatic amides **1a** with dihydrofurans **5a**-**5d** [a,b,c]

alkene	product	
 **5a**		**6aa** 69%[a] **6aa** 80%[b]
 **5b**		**6aa** 74%[a] **6aa** 68%[b]
 **5c**		**6ac** 76% (1:1.3)[a] **6ac** 70% (1:1.5)[b,d]
 **5d**		**6ad** 79% (1:1.1)[a] **6ad** 76% (1:1.3)[b]

[a] Reaction conditions: **Method A:** amide **1a** (0.3 mmol), dihydrofuran (0.6 mmol), $[RhCl(cod)]_2$ (0.0075 mmol, KOAc (0.075 mmol), toluene (1 mL), at 160 °C for 12 h. [b] Reaction conditions: **Method B:** amide **1a** (0.3 mmol), dihydrofuran (0.6 mmol), $[Rh(OAc)(cod)]_2$ (0.0075 mmol), PivOH (0.3 mmol), toluene (1 mL), at 160 °C for 12 h. [c] Isolated yields. The number in parenthesis denotes the ratio of cis and trans isomers. [d] NMR yield.

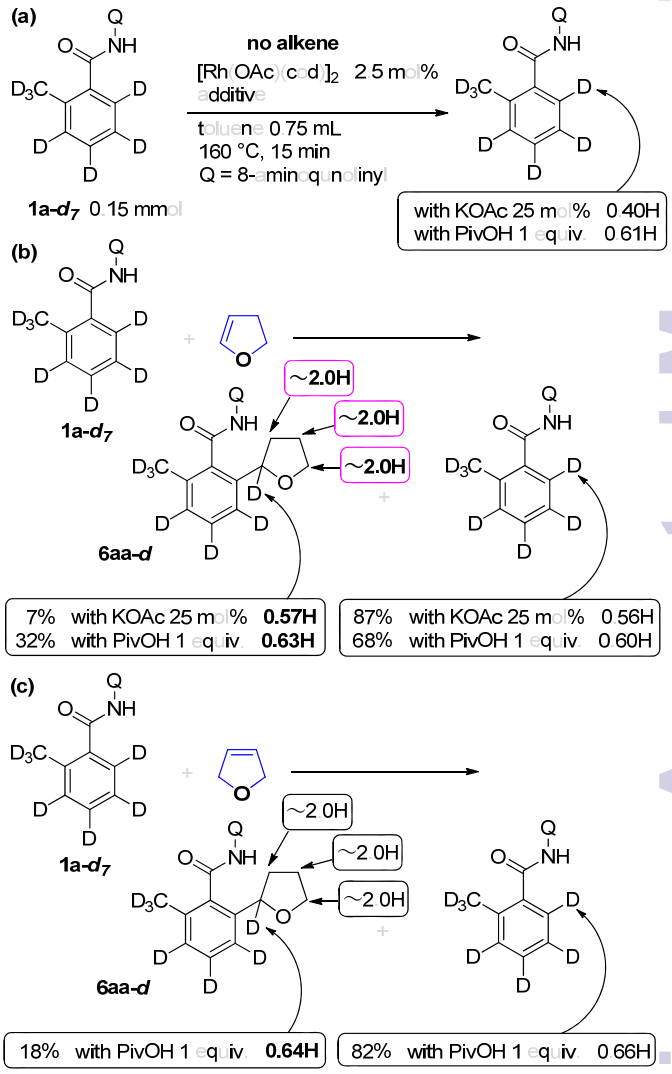
The 2,3-dihydrofuran **5a** and the 2,5-dihydrofuran **5b** also participated in the alkylation reaction (Table 3). While the reaction was carried out under two different conditions, i.e. Method A and B, marginal effects were observed. Irrespective of the position of the olefins as in **5a** and **5b**, C-C bond formation took place at the α-position (next to the oxygen atom) of dihydrofurans.[14]

Table 4 Rh-Catalyzed alkylation of aromatic amides with 2,3-dihydrofuran **5a**[a,b]



[a] Reaction conditions: amide **1** (0.3 mmol), dihydrofuran (0.6 mmol), $[Rh(OAc)(cod)]_2$ (0.0075 mmol), PivOH (0.3 mmol), toluene (1 mL), at 160 °C for 12 h. [b] Isolated yields. [c] $[Rh(OAc)(cod)]_2$ (0.015 mmol) for 24 h.

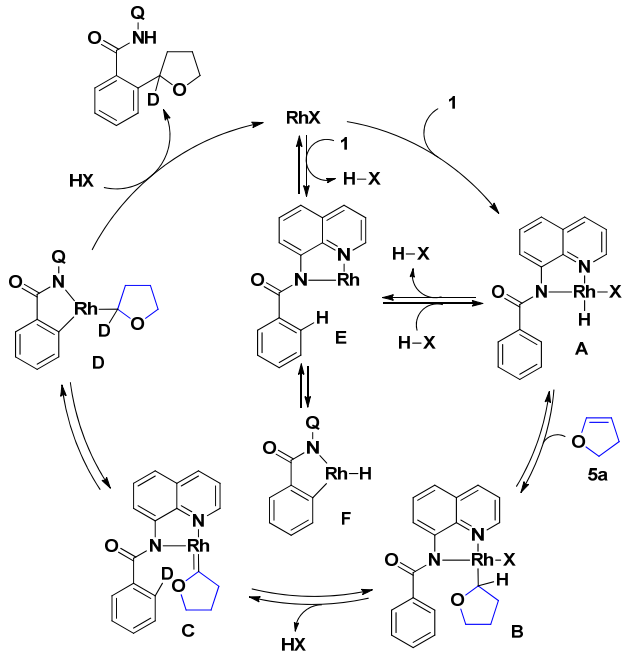
The results for the reaction of meta-substituted benzamides with **5a** are shown in Table 4. The reaction was carried out under the reaction conditions of Method B. Irrespective of the electronic nature of the substituent, only the less hindered C-H bonds reacted.



Scheme 3 Deuterium labeling experiments.

To gain insights into the reaction mechanism, deuterium labeling experiments were carried out in the absence of alkenes (Scheme 3a). Irrespective of the reaction conditions (Method A:KOAc and Method B:PivOH), a significant amount of H/D exchange occurred even within a short reaction time (15 min) and the exchange occurred only at the ortho position (Scheme 3a), indicating that the cleavage of C-H bonds is reversible and does not appear to be the rate-determining step. The reaction of **1a** in toluene-d_8 was carried out. No deuterium atom was incorporated into the product, indicating that in the H/D exchange reaction, the proton source is not the solvent, but rather, comes from NH bond in the substrate (Scheme being not shown). When the reaction was carried out in the presence of dihydrofuran **5a** (Scheme 3b), alkylation

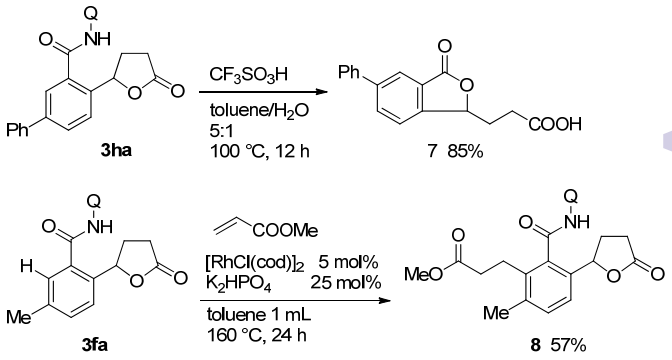
product **6aa-*d*** was obtained in 7% and 36% NMR yield, depending on the additive used, along with the starting **1a-d_7** being recovered. Curiously and unexpectedly, a deuterium atom was incorporated into the THF ring only at the α-position and no deuterium atoms were detected at any of the other positions in the THF ring by ^{1}H NMR. Both the ortho-carbon and hydrogen atom in benzamides attach to the α-carbon of the THF ring. A similar result was obtained even when 2,5-dihydrofuran (**5b**) was used as the coupling partner (Scheme 3c). To exclude the possibility that H/D exchange occurs at the α-position of the THF ring under the reaction conditions employed, **6aa** was reacted with CD_3COOD at 160 °C in the presence of a rhodium complex. However, no deuterium atom was introduced into **6aa** (Scheme being not shown). These results suggest that the ortho C-H bonds appear to undergo a migratory carbene insertion, as discussed later.



Scheme 4 Proposed mechanism.

Based on our previously reported studies[13a,b] and the results obtained in the present work, a proposed mechanism for the reaction is shown in Scheme 4. The coordination of the quinoline nitrogen in the aromatic amide **1** to give a Rh(I)X species, followed by the oxidative addition of an N-H bond gives complex **A**.[15] The insertion of **5a** into the H-Rh bond in **A** gives complex **B**, which, after the elimination of HX affords the carbene complex **C**.[16] The migratory insertion of the ortho C-H bond to a carbene moiety in the complex **C** through the oxidative addition of the ortho C-H bond followed by α-hydride migration gives **D**,[17,18] which undergo reductive elimination followed by protonation to give the final product with the regeneration of the Rh(I) species. An alternative mechanism for generating the complex **A** involves the coordination of a quinolone nitrogen to the Rh(I) center, a ligand exchange to generate the Rh(I) complex **E** with the concomitant generation of HX, followed by the reaction of the complex **E** with HX. The ortho C-H bond of complex **E** then undergoes a reversible oxidative addition to the rhodium center to form the cyclometalated Rh-H complex **F**, the formation of which accounts for the reversibility of the cleavage of C-H bonds at the ortho position of benzamides.[19] As shown in Scheme 3b, a deuterium atom was only incorporated at the α-position of the THF ring of the product. The proposed mechanism involving the formation of the intermediate carbene complex **C** is consistent with deuterium labelling data shown in Scheme 3b, although no direct experimental evidence for this exist. To better understand the details of the reaction mechanism, more experiments including DFT calculations will be needed.

Scheme 5 shows the potential synthetic utility of the C–H bond alkylation reaction. The treatment of **3ha** under acidic conditions gave the isobenzofuran-1(3H)-one derivative **7** in 85% isolated yield. The present protocol was also applicable to the preparation of highly substituted and/or functionalized 5-aryl-γ-butyrolactone derivatives. Then, the lactone **1f** was used in the reaction, the mono-alkylated product **3fa** was exclusively formed, as shown in Table 1. The remaining hindered *ortho*-C-H bond in **3fa** could be successfully alkylated with methyl acrylate in the presence of a rhodium catalyst[13a] to give compound **8** which contains three different adjacent carbonyl-functional groups on the benzene ring.



Scheme 5 Synthetic applications.

Conclusion

In summary, this reaction represents the first example of the C-H alkylation with butenolides, in which C-C bond formation occurs between the ortho-position in an aromatic amide and the γ-position of a butenolide derivative. In addition, dihydrofurans can also be used in the alkylation reaction, in which case, C-C bond formation occurs between the ortho-position in an aromatic amide and the α-position of a dihydrofuran, irrespective of the position of C-C double bond. The use of an 8-aminoquinoline moiety as a directing group is crucial for the success of the reaction. In fact, the reaction of 2-phenylpyridine, which has extensively been used as a substrate for a wide variety of functionalization of C-H bonds, did not react. The functionalization of C-H bonds using an *N,N*'-bidentate directing group began to appear in the literature only in the last ten years, since Daugulis reported on the Pd(II)-

catalyzed arylation of C-H bonds in aliphatic amides in 2005.[20] Since then, it has been shown that various transition metal complexes can be used in the *N,N*'-bidentate chelation system.[12] As more mechanistic information emerges, new and more exciting advances can be anticipated.[21]

Acknowledgements

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