

Copper/Amino Acid Catalyzed Cross-Couplings of Aryl and Vinyl Halides with Nucleophiles[†]

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RECEIVED ON JANUARY 31, 2008

CONSPECTUS

Copper-assisted Ullmann-type coupling reactions are valuable transformations for organic synthesis. Researchers have extensively applied these reactions in both academic and industrial settings. However, two important issues, the high reaction temperatures (normally above 150 °C) and the stoichiometric amounts of copper necessary, have greatly limited the reaction scope. To solve these problems, we and other groups have recently explored the use of special ligands to promote these coupling reactions.

We first showed that the structure of α -amino acids can accelerate Cu-assisted Ullmann reactions, leading to the coupling reactions of aryl halides and α -amino acids at 80–90 °C. In response to these encouraging results, we also discovered that an L-proline ligand facilitated the following transformations: (1) coupling



of aryl halides with primary amines, cyclic secondary amines, and N-containing heterocycles at 40-90 °C; (2) coupling of aryl halides with sulfinic acid salts at 80-95 °C; (3) azidation of aryl halides and vinyl halides with sodium azide at 40-95 °C; (4) coupling of aryl halides with activated methylene compounds at 25-50 °C. In addition, we found that *N*,*N*-dimethylglycine as a ligand facilitated Cu-catalyzed biaryl ether formation at 90 °C. Moreover, Sonogashira reactions worked in the absence of palladium and phosphine ligands, forming enamides from vinyl halides and amides at temperatures ranging from ambient temperature up to 80 °C.

Furthermore, we discovered that an *ortho*-amide group can accelerate some Ullmann-type reactions. This functional group in combination with other ligand effects allowed for aryl amination or biaryl ether formation at ambient temperature. The coupling between aryl halides and activated methylene compounds even proceeded at -45 °C to enantioselectively form a quaternary carbon center. Taking advantage of these results, we developed several novel approaches for the synthesis of pharmaceutically important heterocycles: 1,2-disubstituted benzimidazoles, polysubstituted indoles, N-substituted 1,3-dihydrobenzimidazol-2-ones, and substituted 3-acyl oxindoles.

Our results demonstrate that an L-proline or *N*,*N*-dimethylglycine ligand can facilitate most typical Ullmann-type reactions, with reactions occurring under relatively mild conditions and using only 2-20 mol % copper catalysts. These conveniently available and inexpensive catalytic systems not only accelerate the reactions but also tolerate many more functional groups. Thus, they should find considerable application in organic synthesis.

Introduction

Ullmann-type coupling reactions between aryl halides and N-containing reactants, phenols, and other related nucleophilic agents are now a common method for the preparation of the corresponding aromatic compounds, which are important for the pharmaceutical and material sciences. However, a significant drawback of these reactions is the requirement of a high reaction temperature, which greatly limited its scope of application. This shortcoming stimulated considerable efforts to develop relatively mild coupling **SCHEME 1.** Cul-Catalyzed Coupling Reaction of Aryl Halides with α -Amino Acids and Proposed Mechanism



conditions in recent years.¹ The successive examples are highly dependent on the use of special ligands such as *N*,*N*- or *N*,*O*-bidentate compounds. This campaign not only provided useful synthetic processes, but also shed light on mechanistic details. This Account will focus on the progress made by the use of amino acids as the ligands.

Accelerating Effect Induced by the Amino Acid Structure

During the studies exploring an efficient method to access the *N*-aryl amino acid moiety in substituted benzolactam-V8s (known protein kinase activators), we became interested in direct arylation of amino acids with aryl halides under metal catalysis.² After some experimentation, we found that copper could catalyze this coupling, leading the reaction to occur smoothly at 90 °C (Scheme 1).² Cu(I) or a related complex was found to be the active catalyst because molecular oxygen could inhibit the reaction. The lower reaction temperatures required here compared with typical Ullmann aryl amination prompted us to propose that there exists an accelerating effect induced by the structure of an α -amino acid in Cu-catalyzed Ullmann reactions.² To rationalize this effect, a mechanism involving chelates 3 that are formed from copper ions and amino acids, π -complexes **4**, and transition states **5** that result from an intramolecular nucleophilic substitution was proposed. By this means, enantiopure N-aryl- α -amino acids could be assembled in a convenient manner. Most amino acids were found suitable as coupling partners, but their solubility in DME seemed to limit the reactivity, as evident from the fact that α -amino acids with larger hydrophobic groups gave higher coupling yields, while those with smaller hydrophobic groups afforded only low yields, and no coupling products were detected for those with hydrophilic residues.

SCHEME 2. Cul-Catalyzed Coupling Reaction of Aryl Halides with β -Amino Acids and Its Application in the Synthesis of SB214857 and Martinellic Acid



Based on the intramolecular nucleophilic substitution mechanism, we next explored the possibility to couple aryl halides to other types of amino acids and found that β -amino acids had a similar effect to give the corresponding coupling products at 100 °C (Scheme 2),³ while γ -amino acids did not show a remarkable accelerating effect because little conversion was determined at 110 °C. Leveraging this effect displayed by β -amino acids, we developed a novel route to the potent GPIIb/IIIa receptor antagonist SB214857³ and a first total synthesis of martinellic acid,⁴ a naturally occurring bradykinin receptor antagonist. The former synthesis was carried out via an intramolecular coupling (from **9** to **10**), while the latter one used an intermolecular coupling between 1,4-diiodobenzene and the β -amino acid generated from ester **11**.

Amino Acid Promoted Ullmann-Type Coupling Reactions

Between 1999 and 2002, several groups reported that some bidentate compounds like 1,10-phenanthroline, 1,2-diamines, and 1,2-diols could serve as ligands to facilitate Ullmann-type aryl amination at relatively low temperatures.⁵ Stimulated by these results, we realized that the amino acids might be suitable ligands for similar reactions. To our delight, after screening some amino acids, we found that both α - and β -amino

SCHEME 3. Possible Catalytic Cycle for Amino Acid Promoted Reactions



acids could promote the coupling reaction of aryl iodides and benzylamine.⁶ However, only some secondary and tertiary amino acids such as *N*-methylglycine, L-proline, and *N*,*N*-dimethylglycine were selected for further studies, mainly because they were less reactive toward the coupling with aryl halides in competition with the reactants.^{6a} Using the coupling of iodobenzene and benzylamine at 40 °C as a testing point, we found the following order of ligand efficiency: *N*-methylglycine > L-proline > *N*,*N*-dimethylglycine. This order probably arises from the difference in steric hindrance of the related copper chelates.

In general, our reactions may go through an oxidative addition/reductive elimination pathway as depicted in Scheme 3.^{6b} The chelation of Cu(I) with an amino acid makes Cu(I) species more reactive toward the oxidative addition or stabilizes the oxidative addition intermediates **B**, thereby promoting the coupling reaction. The capability of amino acids to promote coupling reactions might be dependent on their reactivity as coupling agents and coordination ability as bidentate additives. Based on their steric hindrance, the order for coordination ability is *N*-methylglycine > L-proline > *N*,*N*-dimethylglycine, which is consistent with the order of ligand efficiency mentioned above. However, for the ability toward the coupling with substrates, N-methylglycine is greater than L-proline, while N,N-dimethylglycine has little. Thus, for amino acid ligand design, one should consider both coupling ability with aryl halides and steric hindrance.

C–**N Bond Formation.** After we had explored the scope and limitations of Cul/amino acid catalyzed N-arylation, we found that *N*-methylglycine only worked well for the coupling reaction of electron-deficient aryl iodides with aliphatic primary amines. In these cases, the reaction occurred at 40 °C to give aryl amines in good yields (Table 1, entry 1). However, for other aryl halides, incomplete conversion was encountered, which presumably resulted from the easy coupling between this ligand and aryl halides. Fortunately, L-proline was found to be a universal promoter, which led to the following results:^{6b}

- (1) Coupling reactions of aryl iodides or aryl bromides with aliphatic primary amines, acyclic secondary amines, or electron-rich primary aryl amines take place at 60−90 °C (entries 2−7).
- (2) Coupling reactions of aryl iodides with indole, pyrrole, carbazole, imidazole, or pyrazole can be carried out at 75–90 °C (entries 9–12).
- (3) Coupling reactions of electron-deficient aryl bromides with imidazole or pyrazole run to completion at 60–90 °C (entry 13).

For some inactive coupling substrates, higher reaction temperatures were required to ensure good conversions. In these cases, L-proline was less effective because self-coupling occurred predominantly. However, *N*,*N*-dimethylglycine was found to be suitable. This ligand could, for example, promote the coupling reactions of electron-rich aryl bromides with imidazole or pyrazole to afford the corresponding *N*-aryl imidazoles or pyrazoles at 110 °C (entry 14). It is noteworthy that poor conversions were observed when acyclic secondary amines were used (entry 8).

Compared with Pd-catalyzed aryl amination,⁷ the scope of the present method is still narrow. For example, most aryl chlorides and sterically hindered secondary amines are not compatible with our conditions. Thus, further investigations to explore more powerful ligands are required.

When other groups investigated the coupling of amides and carbamates with aryl halides catalyzed by Cul/amino acid,⁸ we examined the coupling reaction of vinyl halides with amides,⁹ and found that *N*,*N*-dimethylglycine is a better promoter for this transformation, and dioxane is a better solvent than DMF or DMSO (Scheme 4).9a Besides amides, oxazolidinones were found to be suitable coupling partners as shown, for example, by the formation of 14 and 15. The geometry of the C=C double bond was retained in this process, as evident from the fact that trans-16 and cis-17 were obtained from the corresponding bromides with the same geometry. In addition, compound **18** was prepared from $cis-\alpha$ -bromocinnamic acid methyl ester, which could be a potential precursor for the asymmetric synthesis of amino acids. The coupling reaction between vinyl iodide 19 and amide 20 delivered enamide 21 in 75% yield, which led to the first total synthesis of the antiplasmodial natural product ziziphine N.¹⁰

With the assistance of L-proline, the coupling of aryl halides with sodium azide proceeded smoothly to give aryl azides (Scheme 5).¹¹ Both aryl iodides and bromides were suitable substrates, but they required different reaction conditions. For iodides, using DMSO as solvent gave better results, while EtOH/water was suitable for bromides. Using this method, we



elaborated aryl azides bearing hydroxyl, amine, or carboxylate functions (**22**–**26**). A sterically hindered aryl bromide also worked well to provide azide **27**, while vinyl azide **28** was prepared from the corresponding vinyl iodide.







SCHEME 5. Cul/L-Proline-Catalyzed Coupling Reaction of Aryl Halides and Vinyl Iodides with Sodium Azide



C–**O Bond Formation.** For the promotion of Cu-catalyzed couplings of aryl halides and phenols, ¹² *N*,*N*-dimethylglycine was found to be an ideal ligand, while *N*-methylglycine and L-proline gave rise to poor conversions. ^{12a} For aryl iodides, the coupling reaction was completed at 90 °C in dioxane using only 2 mol % of Cul and 7.5 mol % of *N*,*N*-dimethylglycine (Scheme 6). However, the catalyst loading had to be increased to 10 mol % of Cul and 30 mol % of *N*,*N*-dimethylglycine in the case of aryl bromides to ensure good yields. This reaction is of general use, and a wide range of biaryl ethers were assembled, as exemplified by the formation of **29–32**. Importantly, under these conditions the coupling between L-tyrosine-derived phenol **33** and L-phenylalanine-derived iodide **34**

SCHEME 6. Biaryl Ether Synthesis via Cul/*N*,*N*-Dimethylglycine Catalyzed Coupling



proceeded well to afford **35**, which led to a new and concise synthesis of ACE inhibitor K-13.¹³ The protecting groups in these amino acid derivatives played a key role in preventing racemization, as evident from the fact that partial racemization occurred when *N*-Boc, *N*-Cbz, or monobenzyl-protected amino esters were used (**36a**–**c**), while *N*-trityl- and *N*,*N*-dibenzyl-protected aromatic amino esters afforded coupling products **36d** and **36e** without concomitant loss of optical purity. The electronic nature and steric hindrance of these protecting groups can be used for rationalizing these differences.

C−S Bond Formation. Subsequent to our studies, Guo and co-workers demonstrated that some amino acids could be used for reducing the reaction temperature of the coupling reaction between aryl halides and thiols.¹⁴ At the same time, we revealed that L-proline or its sodium salt could make the Cul-catalyzed reaction of aryl halides with sulfinic acid salts occur readily at 80–95 °C, thereby offering a convenient method for assembling biologically important aryl sulfones (Scheme 7).¹⁵ As a solvent, DMSO was superior to DMF and dioxane, although the latter also gave good yields. A variety of functional groups (hydroxyl, amido, amine, ketone, ester, and heterocycles) were found to tolerate these conditions, giv-



SCHEME 8. Coupling of Aryl Halides and Vinyl lodides to 1-Alkynes



ing sulfones **37–40** in good yields. As usual, aryl iodides were better substrates because their coupling reaction with sodium methanesulfinate took place at 80 °C, while aryl bromides required temperatures over 95 °C to reach complete conversion. When the less reactive sodium benzenesulfinate was employed, aryl iodides gave good coupling reaction yields of products **38b** and **39** at 90 °C, while the reaction was very sluggish for aryl bromides even at 95 °C.

C–C Bond Formation. The Sonogashira reaction has become a standard method for the elaboration of aryl acetylenes and conjugated enynes. The requirement of two metals (Pd and Cu) is a major drawback for its application in industry because of great difficulties in catalyst recovery. We discovered that Cul alone could catalyze the coupling of aryl halides with 1-alkynes (Scheme 8) if *N*,*N*-dimethylglycine was used as a ligand.^{16a} Compared with typical Sonogashira reactions, our method required higher reaction temperatures. However, it is still very attractive for practical usage owing to its less expensive catalytic system.¹⁶ Vinyl iodides seemed to be more active coupling partners, because their reaction worked at 80 °C, although different solvent and base were used.¹⁷

The arylation of activated methylene compounds in the presence of copper or copper salts, the Hurtley reaction, is a convenient transformation with a long history. The scope of this reaction is very narrow, because only *o*-bromobenzoic acid and closely related bromides are reactive.¹⁸ We revealed that the reaction scope could be greatly enlarged if L-proline was used as a ligand (Scheme 9).^{18a} The coupling reaction of various aryl halides generally occurs at 40 °C (for iodides) or 50 °C (for bromides) in DMSO under the catalysis of 20 mol

SCHEME 9. Couplings of Aryl Halides and Activated Methylene Compounds







% Cul and 40 mol % L-proline. Both β -keto esters and malonates are suitable coupling partners, giving the arylation products in good to excellent yields, as exemplified by the assembly of **41–44** from the corresponding aryl halides.

The *ortho*-Substituent Effect of Amido Groups

Room-Temperature Couplings between Aryl Halides and Phenois. During the studies of Cul/N,N-dimethylglycine catalyzed biaryl ether synthesis, we discovered that there is an accelerating effect caused by an *ortho*-amide group,¹⁹ and its combination with ligand effects enables this reaction to take place at room temperature. As indicated in Table 2, all examined carboxylic amides displayed the ortho-substituent effect with an efficiency order of $CF_3CO > CH_3CO > PhCO$, while no similar effect was observed in case of a sulfonamide as the substrate.^{19a} Other groups, like methoxy, have no similar effect. A possible mechanism was proposed to rationalize this novel effect, as depicted in Scheme 10. Oxidative addition of the chelated Cu(I) 48 to ArX produces complex 49, in which the oxygen of the NHCOR group may coordinate to Cu to provide additional stabilization. After reaction of 49 with cesium phenoxide to give 50, reductive elimination occurs to afford the biaryl ethers and regenerate the catalyst.









The room-temperature biaryl ether formation gave us the opportunity to elaborate biaryl ethers bearing carbamate-protected amino ester moieties. As we had expected, the coupling products **51** were obtained in enantiopure form when Boc- or Cbz-protected L-tyrosine derivatives were utilized (Scheme 11).^{19a} In case of the easily racemized Boc-protected 4-hydroxyphenylglycine derivative, coupling product **52a** was obtained with 91% ee. Switching the protecting group to trityl could prevent the racemization completely (**52b**). We next tried macrocyclization using our method and were pleased that 14-membered macrolactam **54** was formed from **53** in 42% yield. This macrolactam is a potential building block for the assembly of natural cyclopeptides with a wide range of biological activities.

Enantioselective Creation of α **-Aryl All-Carbon Quaternary Centers.** By combining the *ortho*-substituent effect of the NHCOCF₃ group and ligand effects, we found that the coupling reaction of aryl halides and activated methylene compounds could be carried out at -45 °C (Scheme 12).²⁰ Introducing a trace amount of water into this reaction system was found to be essential for this low-temperature reaction, although the reason for this action is not yet clear. It is noteworthy that these results represent a new record low in reaction temperatures for Ullmann-type coupling reactions. When 2-methyl acetoacetates are used, this coupling reactions



tion creates an α -aryl all-carbon quaternary center. Gratifyingly, it was found that asymmetric induction was effected by chiral ligands; for example, β -keto esters **55** were obtained with 81–93% ee. This stereochemical outcome is strong evidence for the participation of the Cu(I)–amino acid chelate in the transition state of the reaction. Noteworthy is that *trans*-4-hydroxy-L-proline was employed here because it showed better asymmetric induction than L-proline.

Assembly of Heterocycles via Cul/Amino Acid Catalyzed Couplings

Our mild coupling conditions not only provide a facile manner to synthesize basic chemical intermediates but also grant access to more advanced compounds. To this end, assembly of heterocycles via our coupling reactions was investigated. Some results are highlighted here.

Synthesis of Polysubstituted Indoles. The coupling products of 2-halotrifluoroacetanilides and activated methylene compounds are obviously ideal intermediates for assembling substituted indoles²¹ because their liberated amine group could easily attack neighboring carbonyl groups to form heterocycles (Scheme 13). With this idea in mind, we developed two methods for the one-pot synthesis of 2,3-substituted indoles. The first one was based on *in situ* base-induced hydrolysis, which limited the substrates to those bearing a strong electron-withdrawing group in the 4-position (for **56a–c**). The second one used acid-induced hydrolysis, which proved to be suitable for both electron-rich (to furnish indoles **56d–f**) and electron-deficient 2-halotrifluoroacetanilides.²²

While we were screening the optimum reaction conditions for indole synthesis, we found that 2-(trifluoromethyl)indoles **57** were formed exclusively if anhydrous DMSO was used and the coupling reaction mixture was heated at 40–80 °C. By carefully analyzing the scope of this reaction, we noticed that the ketone moiety in the initial products **58** was necessary for further transformation into **57**. Consequently a possible mechanism was proposed, as depicted in Scheme 14.²³ Using this method, we assembled 5-, 6-, and 7-substituted 2-(trifluoro-



SCHEME 14. Synthesis of 2-(Trifluoromethyl)indoles



methyl)indoles in good to excellent yields, as exemplified by formation of **57a**–**d**.

The coupling reaction of 2-bromotrifluoroacetanilides with 1-alkynes was found to occur at 80 °C to afford 2-substituted indoles, the reaction being catalyzed by 2 mol % Cul and 6 **SCHEME 15.** Indole Synthesis by Coupling of 2-Bromotrifluoroacetanilides with 1-Alkynes



mol % L-proline (Scheme 15).¹⁷ This conversion involves a Cul/L-proline-catalyzed coupling between aryl bromides and the 1-alkynes followed by a Cul-mediated cyclization process. The relatively low catalyst loading and reaction temperature (in comparison to the coupling of bromobenzene and 1-alkynes) indicated that the *ortho*-substituent effect directed by NHCOCF₃ also existed in this transformation. Both aryl acetylenes (to give **58a**–**d**) and O-protected propargylic alcohols (to provide **58e** and **58f**) could be applied, leading to 5-, 6-, or 7-substituted 2-aryl and protected 2-hydroxymethyl indoles in good yields. However, lower yields were observed with simple aliphatic alkynes.

Assembly of 1,2-Disubstituted Benzimidazoles. 1,2-Disubstituted benzimidazoles are an important class of heterocyclic compounds that show a wide range of biological activities. The conventional methods for their synthesis suffer from the limited availability of the starting materials. Taking advantage of the ortho-substituent effect of the NHCOR groups and ligand effects, we developed a new approach to elaborate these heterocycles as depicted in Scheme 16.²⁴ Coupling of 2-haloacetanilides and amines proceeded smoothly at rt to 50 °C to afford the initial aryl amination products, which underwent cyclization to provide benzimidazoles 59 under three possible conditions: (1) prolonged reaction time in the case of less sterically hindered amines and 2-halotrifluoroacetanilides as substrates, such as formation of 59a; (2) addition of HOAc to the reaction mixture with subsequent heating at 40–90 °C, as demonstrated by production of **59b**-e; (3) heating the coupling reaction mixture at 120-150 °C, as exemplified by formation of 59f. In the initial coupling step, both 2-iodotrifluoroacetanilides and 2-bromotrifluoroacetanilides react at rt, which so far represents the



SCHEME 17. 1,3-Dihydrobenzimidazol-2-one Synthesis



lowest temperature ever used for a Cu-catalyzed aryl amination and indicates that the $NHCOCF_3$ group exhibits a strong *ortho*-substituent effect.

Preparation of N-Substituted 1,3-Dihydrobenzimidazol-2-ones. The 1,3-dihydrobenzimidazol-2-ones are a class of pharmaceutically important heterocycles. The known synthetic approaches often require a number of steps from commercially available starting materials. We developed a cascade coupling/condensation process to assemble these heterocycles starting from methyl *o*-haloarylcarbamates and primary amines (Scheme 17).²⁵ For aryl bromides, the coupling step needed reaction temperatures above 70 °C for good conversions, demonstrating that the carbamate provided weak *ortho*-assistance in this case. A variety of functional groups including vinyl, nitro, carboxylate, amide, ester, ketone, and silyl ether groups were tolerated under these reaction conditions as shown by the formation of **60a**–**e**.



Construction of 3-Acyl Oxindoles. 3-Acyl oxindoles are the key scaffolds of many enzyme inhibitors. The common synthetic approach to these compounds involves the acylation of the corresponding oxindoles, a step that is hampered by the poor solubility of the latter compounds. By an intramolecular coupling of β -keto 2-iodoanilides catalyzed by Cul/L-proline in DMSO at room temperature, 3-acyl oxindoles could be easily assembled with great diversity, as exemplified by the elaboration of **61a**-**e** (Scheme 18).²⁶ The starting materials were prepared from Meldrum's acid, acyl chlorides, and 2-io-doanilines in a one-pot procedure.

Conclusion

In summary, we have demonstrated that some amino acids could serve as both coupling partners and ligands for Ullmann-type coupling reactions and in several cases NHCOR groups can provide an ortho-substitution effect. Owing to their participation, the reaction is greatly facilitated, because several room-temperature and even low-temperature reactions have been developed. L-Proline has proven to be a highly versatile ligand that can promote the aryl amination, coupling of aryl halides to sodium azide, sulfinic acid salts, and activated methylene compounds, and the formation of indoles from 2-bromotrifluoroacetanilides and 1-alkynes. N,N-Dimethylglycine turned out to be a superior ligand for biaryl synthesis, coupling of aryl halides or vinyl iodides to 1-alkynes, and coupling of vinyl halides to amides and carbamates. These newly developed coupling reactions have given rise to novel approaches for heterocycle synthesis. Taking into account the relatively low cost of the amino acids and their facile removal from reaction mixtures, our reactions are very attractive for synthetic applications.

We thank our enthusiastic co-workers Jiangchao Yao, Yongda Zhang, Chengfeng Xia, Hui Zhang, Xianhua Pan, Wei Zhu, Feng Liu, Benli Zou, Biao Lu, Xiaoan Xie, Yu Chen, Gang He, Jing Wang, and Qiliang Yuan for their dedicated contributions and Dr. Sascha Breeger for help revising the manuscript. I also thank Chinese Academy of Sciences, National Natural Science Foundation of China, and Science and Technology Commission of Shanghai Municipality for their financial support.

BIOGRAPHICAL INFORMATION

Dawei Ma received his Ph.D. in 1989 under the guidance of Xiyan Lu at SIOC and did postdoctoral studies with Alan P. Kozikowski at University of Pittsburgh and Mayo Clinic. In 1994, he returned to Shanghai Institute of Organic Chemistry, where he was appointed research professor in 1995. He is presently the director of the State Key Laboratory of Bioorganic and Natural Products Chemistry and joint professor of Fudan University. His research interests currently focus on the discovery of small modulators for target proteins and special biological processes, the total synthesis of complex natural products and their SAR and action mode studies, and the development of new synthetic methodologies.

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FOOTNOTES

[†]Dedicated to Professor Xiyan Lu on the occasion of his 80th birthday. *E-mail: madw@mail.sioc.ac.cn.

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