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Undergraduate Research Experience on CAmpus

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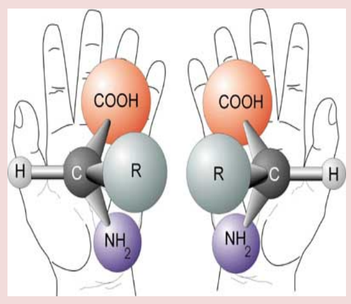
Development of new organocatalytic reactions

Introduction

Chirality and asymmetric synthesis

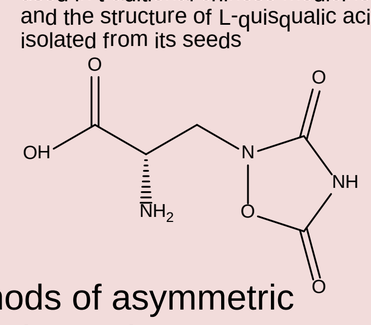
Chirality is an interesting phenomenon in nature. A lot of objects such as hands, shells and even molecures possess this property. For example, chiral amino acids are frequently found in many biologically active peptides and natural products. Asymmetric synthesis of useful chiral molecules has been an important part in pharmaceutical industry since the last century.



Non-proteinogenic amino acids

As building blocks of many biologically active compounds, chiral non-proteinogenic amino acids, esspeciallyα,β-diamino acids, such as quisqualic acid, were found to possess biological significance, therapeutic uses, and other useful applications. However, as an atypical kind of amino acids, α,β-diamino acids were less well studied, especially with regard to their asymmetric synthesis.

Quisqualis indica L. (its seeds are used in traditional chinese medicine.) and the structure of L-quisqualic acid isolated from its seeds



A green approach

The conventional and still commonly used methods of asymmetric synthesis of chiral molecules involve heavy metal complexes as catalysts since they provide very good yields and selectivities. However, the use of these heavy metals has a significant negative impact on the our living environment. Thus, our research aimed to achieve a more efficient, economical and operationally simple approach towards the asymmetric synthesis of protected α,β-diamino acids.

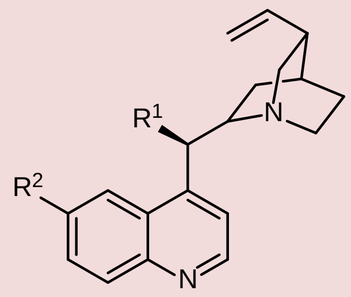
Methodology and results

Design of reaction

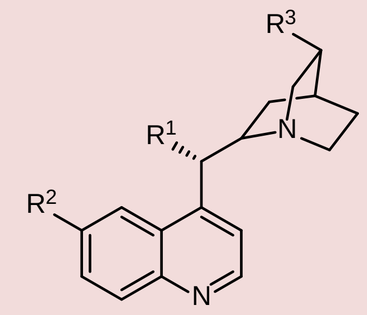
In the presense of suitable catalyst, enantioselective Mannich reations of protected imines and α-isothiocyanato imide might proceed to afford the protected α,β-diamino acids.

PMP- and Boc-protected phenylimines were first examined with 10 mol% catalyst 4e. However, no reaction occurred. This was probably due to the reduced electrophilicity of those imines toward α-isothiocynato imide 1. When more reactive Ts-protected phenyl imine 2 was employed, to our delight, the reaction proceeded smoothly to give the desired product with 92% yield, though no enantioselectivity was achieved. Encouraged by this promising result, different kinds of catalysts were designed and synthesized for the reaction. Catalyst 4d proved to be powerful enough to afford product 3 with excellent yield (98%), enantio-(98%) and good diastereoselectivity (90:10 dr), even with a low catalyst loading.

Catalysts screened

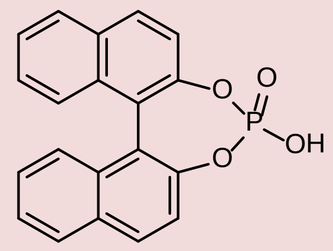


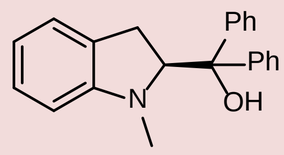
4a R^1 = OH, R^2 = OMe
4b R^1 = OH, R^2 = OH
4c R^1 = $OSiPh_3$, R^2 = OMe
4d R^1 = OBz, R^2 = OH



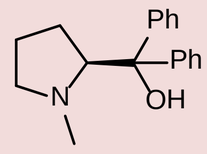
4e R^1 = NH_2, R^2 = OMe, R^3 = $CHCH_2$
4f R^1 = OH, R^2 = OMe, R^3 = $CHCH_2$
4g R^1 = OH, R^2 = OH, R^3 = $CHCH_2$
4h R^1 = OH, R^2 = OMe, R^3 = CH_2CH_3

4i





4j



4k

Optimization of reaction conditions

The effect of catalyst loading, solvent and reactant concentration for this transformation was further investigated, with solvent to be m-xylene giving the best result in the presence of 2.5mol% catalyst 4d, at room temperature, in 99% yield, >99% ee and 95:5 dr). With the optimal reaction conditions obtained, the substrate scope of Ts-protected imines was explored as shown below. Aromatic, heteroaromatic and aliphatic Ts-protected imines were good substrates for this reaction, affording the desired adducts in high yields and stereoselectivities.

Substrate scope

Entry	R	t (h)	Yield (%)	dr	ee (%)
1	Ph	5	90	96:4	>99
2	4-MeC_6H_4	4	99	97:3	>99
3	4-ClC_6H_4	3	97	96:4	>99
4	4-BrC_6H_4	5	92	97:3	>99
5	3-MeC_6H_4	4	98	97:3	>99
6	3-ClC_6H_4	2	99	93:7	95
7	3-furyl	6	96	89:11	98
8	2-MeC_6H_4	72	80	91:9	91
9	2-FC_6H_4	10	91	67:33	97
10	2-thienyl	6	99	93:7	99
11	2-naphthyl	5	90	95:5	97
12	Cinnamyl	30	97	80:20	98
13	n-butyl	48	90	83:17	86

Conclusion

In summary, we have developed a highly efficient organocatalytic asymmetric protocol for the preparation of enantiomerically pure protected α,β-diamino acids, through the Mannich reaction between Ts-protected imines and α-isothiocynato imide, catalyzed by readily available and environment-friendly quinine derived catalyst 4d under mild conditions.

Project Title: Development of new organocatalytic reactions
Supervisor: Assoc Prof Zhong Guofu **Collaborators: Shi Zugui, Chua Pei Juan**