Asymmetric Catalysis

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Asymmetric Conjugate Addition of Glycine Derivatives under Copper Catalysis**

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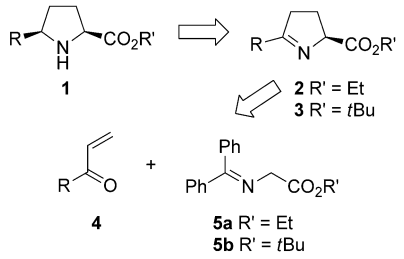
Pyrrolidines are ubiquitous substructures which are incorporated into varied pharmaceutical and natural product targets, and significant efforts have surrounded their syntheses.[1] Although many synthetic approaches have been developed for their formation,[1,2] we became interested in an inexpensive, scalable, asymmetric, and sustainable synthesis that would allow access to medicinally relevant derivatives of **1** (Scheme 1). Cycloaddition is a well-established method of

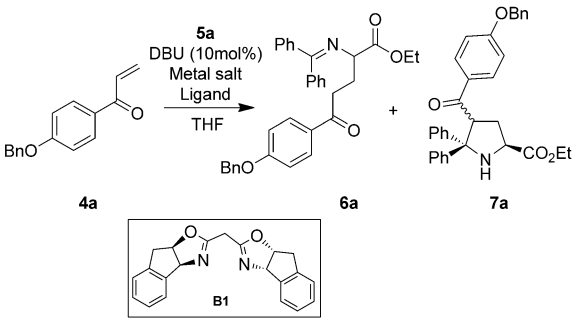


Scheme 1. Conjugate addition approach to **1**.

forming pyrrolidines with great efficiency, but few processes are capable of preparing 3,4-unsubstituted systems easily.[2] The approach highlighted in Scheme 1 was of particular interest because of the commercial availability of the glycine derivatives **5**. Standard hydrogenations of cyclic imines **2**/**3**, which have the desirable reaction features discussed above, are also known to produce *cis*-**1** with high selectively and in high yield.[3] However, the existing asymmetric methods[4] for the conjugate addition of **5** to **4** rely on expensive additives,[4b–e] high catalyst loadings (10 mol% or more),[4e–j,m,o] or the use of cesium salts,[4g,n] which are difficult to use in fixed equipment and have a high cost of disposal.[5] With this in mind, a more convenient and more economic alternative is desirable. Herein, we report a method for the reaction of **4** and **5** based on an environmentally innocuous chiral copper complex, and present evidence gained through NMR spectroscopy for the solution structure of the associated intermediates.

The conditions required for the conjugate addition of **5** to **4** (Table 1) were examined. Ketone **4a** was chosen as a test substrate,[6] along with the imine counterpart **5a**. Metal–ligand complexes were screened to obtain a selective reaction favoring the conjugate addition product **6a** over cycloaddition product **7a**. Reactions of **4** and **5** catalyzed by a calcium bisoxazoline (BOX) complex[4h–j] containing ligand **B1** produced mixtures of **6a** and **7a** (Table 1, entry 1).[7] Silver and nickel-based systems with 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) **8** as the ligand (Table 1, entries 2 and 3) afforded complex mixtures, which included products **6a** and **7a**. However, switching to a copper catalyst gave exceptional results, with only trace amounts of **7a** obtained (Table 1, entry 4). The reaction could be run at lower catalyst loadings (1 mol%) and lower temperatures resulting in a cleaner reaction and increased selectivity for **6a** (Table 1, entry 5).

Table 1: Selected screening conditions.



Entry[a]	Metal salt	Ligand	Temp. [°C]	**6a**:**7a**[b]
1	$Ca(OiPr)_2$[c]	**B1**	−20	3:2[d]
2	AgOAc	(±)-**8**	−20	1:2
3	$NiCl_2$	(±)-**8**	−20	1:1[e]
4	$[Cu(MeCN)_4]PF_6$	(±)-**8**	−20	18:1
5	$[Cu(MeCN)_4]PF_6$[f]	(±)-**8**	−78	>20:1

[a] Reactions were run at 0.2 M with 5 mol% of the catalyst for 12–18 h. [b] Based on approximate ratios of the corresponding signals in the NMR spectrum of the crude reaction mixture. [c] 10 mol% catalyst loading was used. [d] No DBU and 4 Å molecular sieves were used according to the published method.[4h–j] [e] Only a trace amount of product was detected along with multiple by-products. [f] 1 mol% catalyst loading was used.

Twenty-four commercially available chiral ligands were then screened at −20 °C and positive hits were identified on the basis of enantioselectivity versus cost. Selected ligands from the Josiphos and ferrocenyloxazolinylphosphines (FOXAP) families[8] which were used in this screen are depicted in Scheme 2.[9] The best selectivity was obtained by using **J1**. It is important to note that most of the ligands

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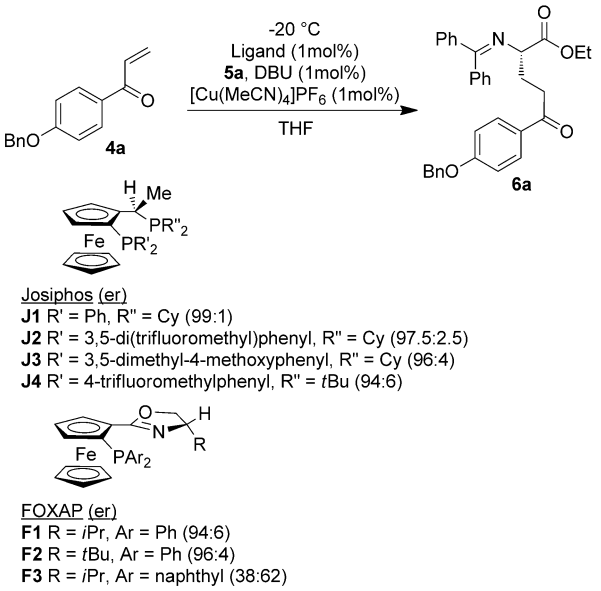
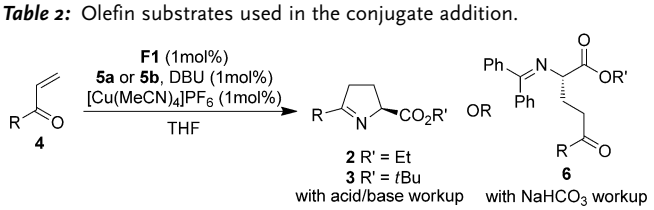


Scheme 2. Selected chiral ligands with the enantiomer ratios of **6a** produced in parentheses.

Table 2: Olefin substrates used in the conjugate addition.



Entry[a]	Olefin	R′	Product	Yield [%](e.r.)[b]
1	**4a** R = *p*-BnOC$_6$H$_4$	Et	**2a**	81 (99:1)
2		Et	**2a**	84 (94:6)[c]
3		*t*Bu	**3a**	79 (96:4)
4	**4b** R = Ph	Et	**2b**	85 (98:2)
5		*t*Bu	**3b**	88 (94:6)
6	**4c** R = *p*-CF$_3$C$_6$H$_4$	Et	**2c**	78 (97:3)
7		*t*Bu	**3c**	77 (95:5)
8	**4d** R = Me	Et	**2d**	70 (96:4)
9		*t*Bu	**3d**	71 (95:5)
10	**4e** R = *t*Bu	Et	**2e**	78 (96:4)
11	**4a**	Et	**6a**	88 (99:1)
12	**4e** R = *t*Bu	Et	**6e**	81 (99:1)
13	**4f**	Et	**6f**	82 (99:1)[d]

[a] Reactions were run under the standard conditions (**5a** at −78 °C, **5b** at −20 °C) using the appropriate workup to produce either **2**/**3** or **6**. [b] The enantiomer ratio (e.r.) was determined by HPLC analysis. [c] The reaction was run at −20 °C. [d] A 56:44 ratio of diastereomers was obtained, both diastereomers were 99:1 e.r.[9]

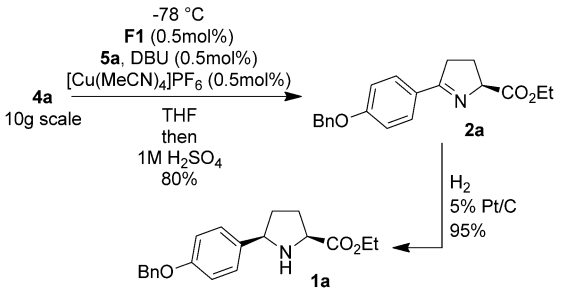
belonging to these families that were tested in this reaction gave acceptable levels of enantioselectivity for our purposes, especially since running the reaction at −78 °C improved the selectivity. Ligands **J1** (87% yield of isolated **6a**, 99:1 enantiomer ratio at −20 °C) and **F1** (86% yield of isolated **6a**, 94:6 enantiomer ratio at −20 °C and a 99:1 enantiomer ratio at −78 °C) were the most attractive based on cost and performance. However, **F1** was selected for further development work, based on its availability on a larger scale. Ethyl acetate, acetonitrile, toluene, methyl *tert*-butyl ether, dichloromethane, and hexanes, along with NEt_3 or tetramethylpiperdine were screened as solvent and base combinations with **F1**, but nothing improved the selectivity of the reaction or the reaction profile over THF and DBU.

We determined that **6a** could be converted in situ into **2a** by using an acid/base workup. Treatment of a reaction mixture containing **6a** with aqueous 1 M H_2SO_4 cleaved the protecting group efficiently. The majority of the ligand and benzophenone was removed by extraction with *tert*-butyl methyl ether at this stage. After neutralization with aqueous sodium bicarbonate, a dehydrative cyclization occurred to afford **2a**, with less than 2% epimerization of the stereocenter. The *S* configuration of the stereocenter was established by comparing the **2a** obtained from the copper-catalyzed reaction with a sample of **2a** with known stereochemistry, which was prepared from pyroglutamic acid.[3c]

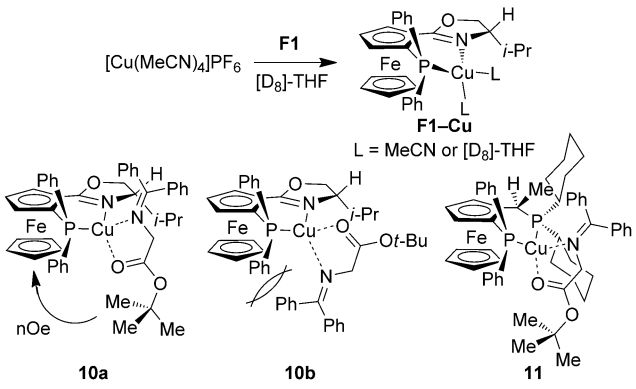
Alkyl- and arylvinyl ketones both proved to be viable substrates for the conjugate addition/dehydrative cyclization sequence (Table 2). Although both the ethyl (**5a**) and *tert*-butyl (**5b**) esters were used, **5b** required a higher temperature (−20 °C) because of solubility issues and a slower rate of reaction. The higher temperature resulted in a lower selectivity for **6** when compared with the reaction with **5a**, which was run at −78 °C. Electronic differences between aryl rings on the α,β-unsaturated ketone (Table 2, entries 1–7) seemed to play little role in the outcome of the reaction, although more electron-rich systems gave a higher selectivity. In addition, increasing the size of alkyl substituents on the ketone did not affect the overall rate of the reaction or the selectivity (Table 2, entries 8–10). It is important to note that although *E*- and *Z*-crotonyl systems based on **4a** did not react, the reaction with ketone **4f** furnished **6f** effectively (Table 2, entry 13). Attempts to use acrylonitrile, methylacrylate, or phenylvinyl sulfone dramatically altered the reaction pathway and afforded cycloaddition products, similar to **7a**, almost exclusively.

The conjugate addition method also appears to be scalable. Starting with 10 grams of **4a**, product **2a** was isolated as a crystalline solid in 80% yield and greater than 99:1 enantiomer ratio from a reaction (Scheme 3). On this scale, we found that only 0.5 mol% of catalyst was necessary because of lower levels of adventitious water and oxygen. The resulting imine product was then hydrogenated with Pt/C into the corresponding pyrrolidine **1a**. Acyclic products **6**, which do not contain the benzyloxy group, were converted directly into **1** by Pd/C hydrogenation.[3d]

To gain more understanding about ligand efficiency and the structure of the associated copper complexes, intermediate species were studied by ^{1}H NMR and ^{31}P NMR spectroscopy. As a result of the poor solubility of $[Cu(MeCN)_4]PF_6$ in $[D_8]$-THF and the fact that copper ligation is a fast process,[10] formation of **F1**–**Cu** (Scheme 4) should drive the dissolution of $[Cu(MeCN)_4]PF_6$. This appeared to be the case, since



Scheme 3. Conversion of **4a** into **1a**.



Scheme 4. Intermediate complexes.

F1–Cu formed quantitatively upon dissolution of both **F1** and $[Cu(MeCN)_4]PF_6$, whereas $[Cu(MeCN)_4]PF_6$ would not completely dissolve without the ligand present. The protons of the MeCN moieties (integration = 12) were detected at the same chemical shift as unbound MeCN in the ^{1}H NMR spectrum, which indicated some amount of fast exchange, or nearly complete $[D_8]$-THF ligation of the complex. Two signals were present in the ^{31}P NMR spectrum. One septet at $\delta = -144.3$ ppm corresponded to PF_6,[11] and one singlet at $\delta = -19.8$ ppm corresponded to complex **F1–Cu**. The singlet at $\delta = -19.8$ ppm had shifted from the signal detected for free **F1** at $\delta = -17.6$ ppm. It appears that a 1:1 complex of **F1**:Cu forms, since models (Maruzen HGS Stereochemistry) indicated that severe steric interactions would preclude dimer formation, and all of the $[Cu(MeCN)_4]PF_6$ dissolved. Furthermore the addition of other chelating ligands to **F1–Cu** resulted in facile exchange and produced one species in each case, which was detected by ^{31}P NMR spectroscopy (Scheme 4).

Our attention turned to the imine complex **10a** (Scheme 4). Upon dissolution of **5b** in a solution of **F1–Cu**, the initial copper complex (**F1–Cu**) could no longer be detected by ^{1}H NMR or ^{31}P NMR spectroscopy. A single new peak in the ^{31}P NMR spectrum was detected at $\delta = -20.5$ ppm. The formation of **10a** instead of **10b** was confirmed by the detection of a nOe interaction between the *tert*-butyl group and the lower ferrocene ring (Scheme 4). This interaction provides strong experimental evidence for the top face orientation of the imine phenyl substituents relative to the ligand–metal complex.

Only one diamagnetic species was detected by ^{31}P NMR spectroscopy, which indicated that **10a** exists as the major complex in solution (approximately 9:1 or greater). This corresponds to an estimated energy difference of approximately 1.3 kcal mol^{-1}[12] or more, between **10a** and **10b**. Similar results from the NMR spectrum of a mixture of **J1**, **5b**, and $[Cu(MeCN)_4]PF_6$ revealed that complex **11** forms, which corresponds to the analogous binding of **5b** to **F1–Cu**.

Density functional theory (DFT) full structure optimizations were performed for **10a** and **10b** by using the B3LYP functional with the LANL2DZ basis set for all transition metals with effective core potentials and 6-31G* for all other elements.[13] Both optimized structures in Figure 1 have a distorted tetrahedral geometry around the copper center. The phosphine and imine phenyl groups in **10a** assume an offset, approximately coplanar conformation, with the *tert*-butyl group below the complex. The *tert*-butyl group in **10b** tips the substrate into a more angled position relative to the ferrocene moiety, with the imine and phosphine phenyl planes perpendicular. The electronic energy difference between the two optimized structures was calculated to be −0.42 and −0.31 kcal mol^{-1} at the HF and B3LYP level with the above basis set, respectively. However, the difference was calculated to be −2.39 kcal mol^{-1} using Møller-Plesset perturbation theory (MP2), which is in accord with the experimental observations. It is known that HF and B3LYP are not suitable to account for attractive van der Waals interactions, as encountered in π stacking, and the observed difference between HF, DFT, and perturbation theory is in accord with π stacking energies reported in the literature.[14] Hence, the differences between HF, B3LYP, and MP2 calculations provide evidence that van der Waals interactions have a

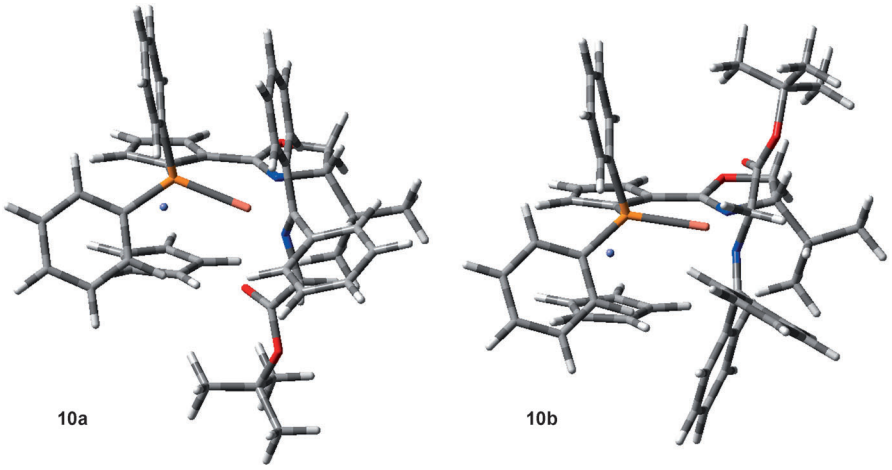


Figure 1. B3LYP 6-31G*/LANL2DZ geometry optimized structures. Fe blue sphere, Cu pink, P orange, O red, N blue.

significant stabilizing effect in **10a**. This effect is likely to be caused by the coplanar phenyl π stacking that is absent in **10b**.

Based on molecular orbital calculations and NMR experiments, binding of the imine is favored for a coplanar orientation of the imine and phosphine phenyl groups, allowing for π stacking (as drawn for **10a** in Scheme 4 and Figure 1). Alternate binding results in the higher energy conformer **10b**, because of the lack of attractive π stacking interactions. These results emphasize the importance of the phosphine groups for complex stability and, hence, the selectivity of the reaction.[9] Taking this binding geometry and the product stereocenters into account, **4** must approach the associated anion from the si-face and eclipse the Ph groups.

In summary, we have described an inexpensive and practical procedure for the enantioselective reaction between glycine derivatives **5** and α,β-unsaturated ketones **4** under copper catalysis. The products from these reactions can be directly isolated (**6** with a basic workup or **2** with an acidic workup) and transformed into the pyrrolidine **1**. This method uses low catalyst loadings (down to 0.5 mol%) and both enantiomers of the catalyst are commercially available. Additionally, the insights gained from NMR spectroscopy and molecular orbital calculations, which supports the binding orientation of **5b** to the chiral copper catalyst, should be useful for other catalytic systems that utilize rigid chiral ligands, such as FOXAP and Josiphos.

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[5] Efficient mixing of CsOH on a manufacturing scale is difficult because of its density. Also, waste disposal is more than 500-times more expensive when the waste contains cesium.

[6] Ketone **4a** is a bench-stable crystalline solid. See the Supporting Information for a preparative procedure.

[7] The ratios obtained by Kobayashi et al. for conjugate addition versus [3+2] cycloaddition were heavily dependent upon the structure of the substrate. To favor conjugate addition, the structure of **5** was modified (see Ref. [4i]), but for our purposes this is prohibitively expensive, and still requires 10 mol% of catalyst to proceed efficiently.

[8] All of these ligands were purchased from Solvias. For FOXAP ligands, see Y. Miyake, Y. Nishibayashi, S. Uemura, *Synlett* **2008**, 1747, and references therein.

[9] See the Supporting Information for more details.

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[12] $\Delta G = -RT\ln K = -(0.001986\ \text{kcal mol}^{-1}\text{K}^{-1})(298\ \text{K})\ln(1/9) = -1.3$.

[13] All calculation were performed with Gaussian 03 (Gaussian 03, revision D.02, M. J. Frisch et al.). See the Supporting Information.

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