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Synthesis of Glutamic Acid and Highly Functionalized Pyrrolidine Derivatives by Utilizing Tunable Calcium Catalysts for Chemoselective Asymmetric 1,4-Addition and [3+2] Cycloaddition Reactions

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Abstract: A current trend in organic chemistry is the development of highly efficient, environmentally friendly and inexpensive catalysts for asymmetric transformations. Alkaline earth metals, due to their specific chemical properties and abundance in nature, provide promising and challenging catalysts in organic synthesis. This article describes the utilization of alkaline earth metals in the development of an effective catalytic system based on calcium salts in combination with Box-type ligands. We disclose asymmetric 1,4-addition and [3+2]cycloaddition reactions using simple catalytic systems consisting of calcium chloride dihydrate, chiral ligands and tetramethylguanidine. Various Box ligands were synthesized and the most effective proved to be that bearing an indane chiral backbone and a cyano group. Depending on the structure of both glycine Schiff bases and α,β-unsaturated compounds, the corresponding Michael adducts or pyrrolidine derivatives were obtained in moderate to high yields with high enantioselectivities. Modification of the catalytic system by using more Lewis acidic calcium salts such as calcium triflate and neutral Pybox-type ligands allows a tuning of the chemoselectivity and leads to suppression of the [3+2]cycloadition reactions. Various β-substituted acrylates provided 1,4-addition adducts exclusively in high yields with moderate to high diastereo- and enantioselectivities. This methodology has broadened a synthetic route to β-branched glutamic acid derivatives and established calcium salts as useful and attractive catalysts for asymmetric catalysis.

Keywords: asymmetric addition reactions; β-branched glutamic acid derivatives; chiral calcium complexes; pyrrolidine derivatives; tuning of the chemoselectivity

Introduction

The biological importance of natural and unnatural α-amino acid derivatives has been increasing over the past few years, and their synthesis in optically pure form continues to be of great interest. In particular, glutamic acid and its β-substituted derivatives, which are found in virtually all living organisms, are important not only as essential structural components of peptides and proteins,[1] but also due to their biological activities.[2] L-Glutamate is an important nutrient involved in several biochemical pathways such as gluconeogenesis and ammonia detoxification, and it is also the most abundant neurotransmitter in the central nervous systems of mammalian organisms.[3,4] Equally, glutamic acid is utilized as a valuable building block for the synthesis of drugs and their precursors,[5,6] dendrimeric drug carriers,[7] as well as for useful materials such as gelators and supramolecular columnar liquid crystals.[8,9] Recent synthetic methods have offered numerous attractive approaches towards structurally diverse β-substituted α-amino acids precursors. The most effective methodologies involve diastereoselective synthesis and stereoselective alkylation of glycine Schiff bases.[10,11] Catalytic asymmetric 1,4-additions of glycine derivatives to α,β-unsaturated carbonyl compounds or other Michael acceptors were often mediated by structurally diverse chiral phase-transfer catalysts,[12] metal salts combined with various enantiopure ligands,[13] and more recently, a chiral organic base was also successfully used as a catalyst for this transformation.[14] The current trend to develop

highly efficient and enantioselective reactions is the use of ubiquitous and green catalysts. Despite alkaline earth metals (Ca, Sr, Ba) being one of the most abundant elements on the earth, their utilization in organic chemistry, especially in catalysis, is limited. Due to their specific chemical properties and their abundance in nature, chiral complexes of these metals are promising and challenging catalysts in organic synthesis. In particular, calcium, as the fifth most frequent and easily accessible element in the earth's crust and seawater, represents a great potential for synthetic utility.[15]

So far, chiral complexes of alkaline earth metals have been successfully utilized as catalysts in several asymmetric bond forming reactions.[16] Previously, in our laboratory, an effective catalyst system based on chiral calcium alkoxides was developed and applied for the asymmetric additions of azomethine imines to various α,β-unsaturated compounds. This methodology has extensively widened the field of synthesis of glutamic acid derivatives.[16b] However, calcium alkoxides, phenoxides, and hexamethyldisilylamide, which are commonly used as basic precursors for the preparation of chiral calcium complexes, are relatively moisture sensitive. Moreover, calcium alkoxides-catalyzed 1,4-additions of glycine Schiff bases are limited to α-substituted acrylates due to the undesired [3+2] cycloaddition that predominates when crotonates and other β-substituted α,β-unsaturated esters are employed. We report here the development of an effective catalytic system based on calcium chloride dihydrate as an inexpensive, harmless, and environmental friendly metal source.[17] In combination with bis(oxazoline) (Box) ligands and organic bases, this innovative methodology was applied to the asymmetric Michael addition and [3+2]cycloaddition of glycine Schiff bases to α,β-unsaturated carbonyl compounds. Structurally variable substrates, even secondary amides bearing an acidic proton, can be employed with high efficiency by using only 5 mol% of the catalyst. Notably, slight modification of the catalytic systems facilitates chemoselective 1,4-addition reactions of glycine Schiff bases with crotonates. Suppression of the [3+2]cycloaddition pathway broadens the substrate scope of this methodology to include β-substituted α,β-unsaturated esters to provide β-branched glutamic acid derivatives in a facile manner with excellent enantiopurity.

Results and Discussion

We initiated our investigation for the enantioselective 1,4-addition reaction of Schiff base **2a** with methyl acrylate (**3a**) by using 10 mol% of calcium chloride dihydrate in combination with various optically active Box ligands (Figure 1). In our preliminary investigations, we employed common tertiary amines in THF with molecular sieves at −30 °C, but could not obtain the desired 1,4-adducts. We hypothesized that the basicity of the tertiary amines were insufficient to either deprotonate **2a** and/or the chiral Box ligands, which is a critical step for the formation of the chiral calcium complexes responsible for the stereoselective catalysis. Guanidines are well known to be relatively strong bases and, in the last decade, have found wide utility in organic synthesis.[18] After initial trials, tetramethylguanidine (TMG) was found to be an effective base and was subsequently utilized in our optimization studies (Table 1). We screened various Box ligands and found that the 1,4-addition reaction proceeded smoothly, but unfortunately, almost no stereoselective induction was observed in most cases. Low enantioselectivity was obtained with (*S*)-Ph-Box (**1a**) as well as with its methylated (*R*)-analogues **1b–1d** (entries 1–4). Comparable low enantioselectivity was also observed when methylene-substituted derivative **1e** was used (entry 5). On the other hand, a breakthrough was achieved when commercially available (*4S*)-(+)-phenyl-α-[(*4S*)-phenyloxazolidin-ylidene]-2-oxazoline-acetonitrile [(*S*)-CN-Ph-Box, (*S*)-**1f**] provided the desired glutamic acid derivative **4aa** with moderate enantiopurity (entry 6).[19] These results suggested that an electron-withdrawing substituent on the methylene bridge of the bis(oxazoline) framework is necessary to facilitate its deprotonation and subsequent formation of the desired chiral calcium complex. The formation of the anionic ligand is a key requirement for the strong coordination of the chiral ligand to the metal center, and chiral calcium complexes derived from **1a–e** were most likely not formed due to the insufficient acidity of the ligand. Based on this assumption, we performed control studies and found that a competitive background reaction proceeded in the absence of a ligand and that the 1,4-addition reaction also proceeded with catalytic amounts of TMG. In addition to the background reaction, a second undesired

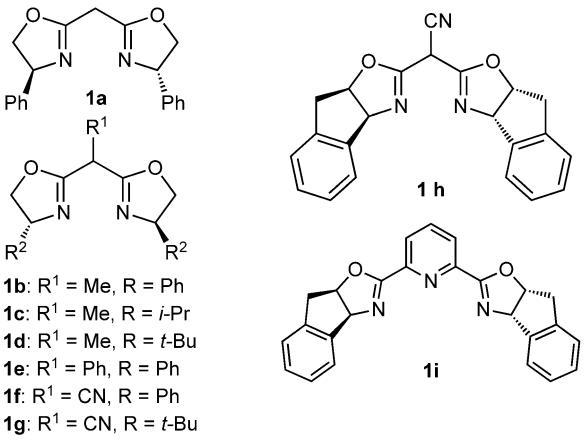
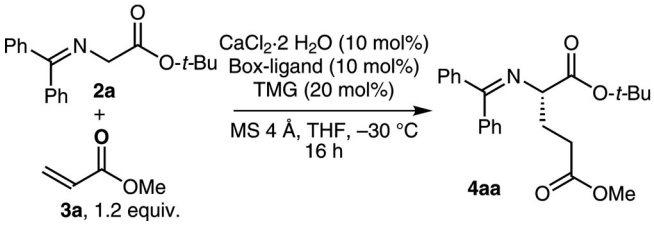


Figure 1. Employed chiral ligands

Table 1. Screening of bis(oxazoline) ligands and the optimization of reaction conditions.



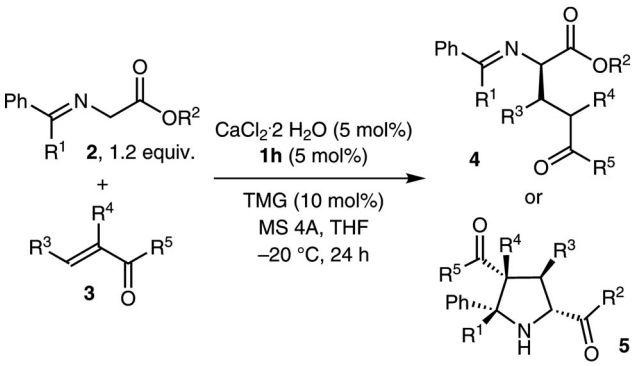
Entry	Ligand	Yield [%]	*ee* [%]
1[a]	**1a**	70	4
2	**1b**	78	8
3	**1c**	85	0
4	**1d**	74	0
5	**1e**	62	8
6[a]	(*S*)-**1f**	64	44
7[b]	**1f**	64	77
8[b]	**1g**	39	0
9[a,b]	**1h**	73	96
10[a]	**1h**	77	95
11[a,c]	**1h**	73	96
12[a,c,d]	**1h**	87	98

[a] Opposite enantiomer of the product.
[b] **3a** (0.54 M) was added over 10 h using a syringe pump and the resulting mixture was stirred for 6 h.
[c] 5 mol% of $CaCl_2 \cdot 2H_2O$, 5 mol% of **1h** and 10 mol% of TMG were used, and the reaction was carried out at −20 °C for 24 h.
[d] Reversed ratio of reagents **2a**/**3a**.

Michael addition of the product **4aa** to methyl acrylate also took place. Despite these discouraging results, we continued our investigation and began a detailed exploration on the use of cyano-Box derivatives as chiral ligands.[20] With the aim to suppress the predominant background reaction, the effect of slow addition of **3a** was examined. To our delight, when **3a** was added to the reaction mixture over 10 h at −30 °C, the enantioselectivity increased dramatically (entry 7). Further effort to improve both the enantioselectivity and the yield by employing ligand **1g** failed (entry 8). However, when **1h**, bearing an indane backbone, was employed, the desired 1,4-adduct was obtained in good yield with excellent enantioselectivity (entry 9). By utilizing **1h**, the reaction proceeded smoothly without the slow addition of **3a** (entry 10), and the catalyst loading could be reduced to 5 mol% at −20 °C without any significant drop in the yield and the enantioselectivity (entry 11). The yield of **4aa** was improved further by the addition of a slight excess of **2a** to suppress the undesired second Michael reaction (entry 12).

With the optimized conditions in hand, the substrate scope for the chiral calcium-complex catalyzed asymmetric 1,4-addition of various Schiff bases with α,β-unsaturated compounds such as acrylic acid esters and amides was investigated (Table 2). The reactions of **2a** with both methyl acrylate (**3a**) and benzyl acrylate (**3b**) proceeded in high yields with excellent enantioselectivities (entries 1 and 2). Under the same conditions, lower reactivity was observed with Weinreb amide **3c**, but the product was obtained with high enantioselectivity (entry 3). In comparison with **2a**, Schiff base **2b** bearing a methyl ester group turned out to be less reactive. However, reducing the steric bulk on the ester did not affect the enantioselectivity significantly, and the reaction of **2b** with **3a** provided the corresponding dimethyl pentanedioate (**4ba**) with high *ee*. A similar result was also obtained for the 1,4-

Table 2. Substrate scope of 1,4-addition and [3+2] cycloaddition reactions.



2a: R^1 = Ph, R^2 = *t*-Bu
2b: R^1 = Ph, R^2 = Me
2c: R^1 = H, R^2 = *t*-Bu
2d: R^1 = H, R^2 = Me

3a: R^3 = R^4 = H, R^5 = OMe
3b: R^3 = R^4 = H, R^5 = OBn
3c: R^3 = R^4 = H, R^5 = NMe(OMe)
3d: R^3 = R^4 = H, R^5 = NMe_2
3e: R^3 = R^4 = H, R^5 = $N(CH_2)_3CH_2$
3f: R^3 = Me, R^4 = H, R^5 = OMe
3g: R^3 = H, R^4 = Me, R^5 = OMe
3h: R^3 = R^4 = H, R^5 = $N(CH_2)_2OCH_2CH_2$
3i: R^3 = R^4 = H, R^5 = NHPh

Entry	**2**	**3**	**4**	Yield [%]	*ee* [%]
1	**2a**	**3a**	**4aa**	87	98
2	**2a**	**3b**	**4ab**	90	90
3	**2a**	**3c**	**4ac**	41	94
4	**2b**	**3a**	**4ba**	65	94
5	**2b**	**3c**	**4bc**	66	83
6[a]	**2a**	**3d**	**5ad**	91	99
7	**2a**	**3e**	**5ae**	76	99
8	**2c**	**3b**	**5cd**	86	64
9[b]	**2c**	**3f**	**5cf**	85	95
10	**2d**	**3f**	**5df**	89	96
11[b,c]	**2c**	**3g**	**5cg**	71	89
12	**2c**	**3c**	**5cc**	59	89
13	**2d**	**3h**	**5dh**	63	92
14	**2d**	**3i**	**5di**	98	96

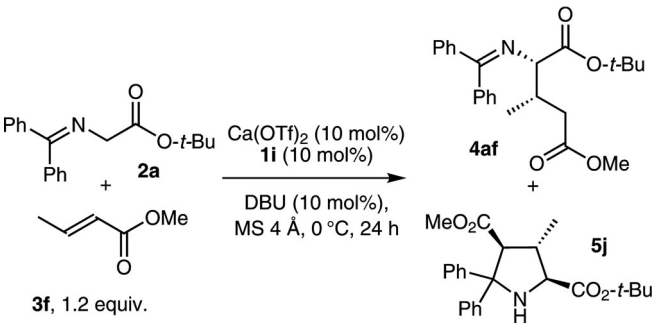
[a] 10 mol% of catalyst and ligand were used.
[b] 48 h.
[c] −30 °C.

addition reaction with Weinreb amide **3c** (entries 4 and 5). During our previous investigation of chiral calcium alkoxide-catalyzed 1,4-addition reactions of glycine ester Schiff bases with crotonates, an unexpected [3+2] cycloaddition reaction occurred,[16c,e] and the same tendency was observed when Schiff base **2a** reacted with acryl amides **3d** and **3e** using the newly developed $CaCl_2$-based catalytic system. In both cases, the corresponding pyrrolidine derivatives **5ad** and **5ae** were obtained as single diastereoisomers in high yields with extremely high enantioselectivities (entries 6 and 7). [3+2] Cycloaddition of azomethine imines with substituted alkenes represents one of the most efficient methods for the synthesis of optically active polyfunctionalized pyrrolidines,[21] which are common substructures of a number of naturally occurring and medicinally important compounds.[22,23] Furthermore, optically active pyrrolidines are widely used as chiral inductors and organocatalysts in asymmetric synthesis.[24] Encouraged by our previous results, we decided to explore the substrates scope of the [3+2] cycloaddition under the conditions that were optimized for the catalytic 1,4-addition reactions (Table 1). Various α,β-unsaturated compounds were examined for the asymmetric [3+2] cycloaddition reactions with Schiff bases **2c** and **2d**. Benzyl acrylate (**3b**) gave the corresponding pyrrolidine in high yield with moderate enantioselectivity (entry 8). To our delight, the reaction of α- and β-substituted unsaturated esters such as methyl crotonate (**3f**) and methyl methacrylate (**3g**), which were unreactive in the previous 1,4-addition, with Schiff bases **2c** and **2d** proceeded smoothly to afford the desired products in high yields with excellent enantioselectivities (entries 9–11). Tertiary amides **3c** and **3h** provided moderate yields but high *ee* of the desired pyrrolidines were achieved (entries 12 and 13). Interestingly, in the case of *N*-phenylacrylamide (**3i**), the product was isolated in near quantitative yield with excellent enantioselectivity (entry 14). Compounds bearing secondary *N*-phenylamide group represent a useful class of compounds with potential biological activity and utilization in industry.[25] Basic calcium catalysts, such as $Ca(O\text{-}i\text{-}Pr)_2$ and $Ca(HMDS)_2$, are known to easily deprotonate mildly acidic *N*-phenylamides.[26] Due to the potential quenching of the catalyst by this acid-base process, catalytic applications of these complexes are limited. However, in the case of using the calcium chloride-based catalyst, the reaction proceeded smoothly with excellent results.

Using the catalytic system consisting of $CaCl_2 \cdot 2H_2O$ and ligand **1h**, the reactions of methyl crotonate (**3f**) as well as some other β-substituted α,β-unsaturated esters with Schiff base **2a** did not afford the 1,4-addition products, but gave [3+2] cycloaddition products. With an aim to broaden the range of this methodology for the synthesis of β-substituted glutamic acids derivatives, we next focused on other suitable calcium-based catalytic systems. Due to mild Lewis acidity of Ca^{2+} ions, anionic or strongly coordinative ligands are often employed to form stable complexes and used as catalysts for various transformations.[16a,17,27] Based on our previous good results obtained with **1h** bearing a chiral indane backbone, we decided to investigate the use of a related neutral inda-Pybox ligand **1i** (Table 3). In a preliminary screening, we found that calcium halides did not work well as catalysts. On the other hand, the reaction catalyzed by calcium triflate [$Ca(OTf)_2$] proceeded smoothly with high selectivity for the 1,4-adduct as well as with high diastereoselectivity, albeit with moderate enantioselectivity (entries 1–3).[28] The use of tetrahydrofuran (THF) instead of *tert*-butyl methyl ether (TBME) as a solvent led to a dramatic improvement of the enantioselectivity, but the selectivity for the 1,4-adduct was decreased. High chemical yield, 1,4/[3+2] ratio, diastereo- and enantioselectivity were achieved by using 1,2-diethoxyethane (DEE) as solvent. The yield and the selectivities were improved further by lowering the temperature to −20 °C (entries 4–6). Additional optimization by using calcium bis(trifluoromethylsulfonyl)amide [$Ca(NTf_2)_2$] led to a higher yield and diastereoselectivity, but the enantioselectivity was decreased (entry 7).

The substrate scope involving different α,β-unsaturated compounds was surveyed and is summarized in

Table 3. Preliminary screening of reaction conditions for addition of **2a** to **3f**.

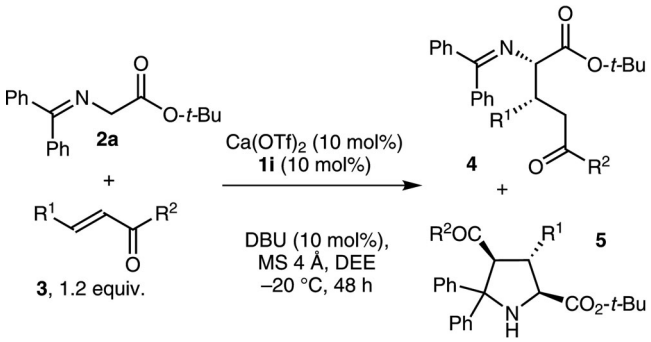


Entry	Solvent	Yield [%]	**4af/5j**	*dr*[a]	*ee* [%]
1[b]	THF	<5	–	–	–
2[c]	THF	<5	–	–	–
3	THF	76	94/6	97/3	53
4	TBME	88	96/4	85/15	91
5	DEE	87	92/8	91/9	90
6[d]	DEE	89	96/4	96/4	92
7[d,e]	DEE	96	96/4	98/2	70

[a] *dr* of **4af**.
[b] $CaCl_2 \cdot 2H_2O$.
[c] CaI_2.
[d] The reaction was carried out at −20 °C for 48 h.
[e] $Ca(NTf_2)_2$.

Table 4. Under the optimized conditions for the reaction of methyl crotonate ethyl analogue **3j** gave the desired product with similar selectivities. On the other hand, an excellent 1,4/[3+2] ratio was observed in the case of vinyl ester **3k**, although only moderate enantioselectivity was obtained. Amide **3l** provided higher reactivity in comparison with esters, and the product was obtained with reasonable enantioselectivity (entries 1–4). In contrast to the crotonic acid derivatives, the reaction with (*E*)-methyl pent-2-enoate (**3m**) proceeded slowly and even when the reaction time was prolonged up to 60 h, the Michael adduct **4am** was obtained in 60% yield with high *ee*. These results led to further modification of the reaction conditions. Using $Ca(NTf_2)_2$ as the catalyst, the yield and the 1,4/[3+2] ratio of the desired adducts were improved significantly, but the enantioselectivity dropped from 95 to 83% *ee* (entries 5 and 6). The sterically more demanding substrate **3n** proved to be less reactive, and moreover, the yield of the desired 1,4-adduct was influenced by [3+2] cycloaddition (entry 7). According to the assumed reaction mechanism, the pyrrolidine derivative is formed from an intermediate of a 1,4-addition product *via* an intramolecular Mannich reaction (*vide infra*). We assumed that this side reaction could be suppressed in the presence of a suitable proton source. We also attempted to modify the calcium catalyst by using appropriate additives. It is well established that hexafluorophosphate additive can significantly affect the properties of a catalyst by an anion exchange.[29] We screened several tetrabutylammonium salts and found that the addition of Bu_4NPF_6 improved the enantioselectivity of the product (entry 8). The sterically more difficult substrate **3o** provided the desired product with excellent enantioselectivity, but with lower selectivity for the 1,4-adducts and slightly reduced chemical yield (entry 9). Finally, the undesired [3+2] cycloaddition was partially suppressed using [DBUH]OTf as an additional proton source (entry 10).

Table 4. Scope of α,β-unsaturated compounds.

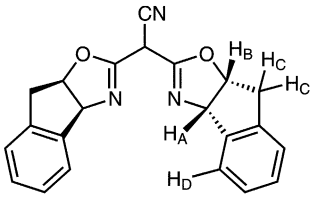


3f: R^1 = Me, R^2 = OMe
3j: R^1 = Me, R^2 = OEt
3k: R^1 = Me, R^2 = OCH=CH_2
3l: R^1 = Me, R^2 = NMe(OMe)
3m: R^1 = Et, R^2 = OMe
3n: R^1 = $Ph(CH_2)_2$, R^2 = OMe
3o: R^1 = $(CH_3)_2CHCH_2$, R^2 = OMe

Entry	3	4	Yield [%]	4/5	*dr*[a]	*ee* [%]
1	**3f**	**4af**	89	96/4	96/4	92
2	**3j**	**4aj**	50	83/17	95/5	92
3	**3k**	**4ak**	70	99/1	87/13	55
4	**3l**	**4al**	95	98/2	98/2	75
5[b]	**3m**	**4am**	60	81/19	99/1	95
6[c]	**3m**	**4am**	91	93/7	99/1	83
7	**3n**	**4an**	44	72/28	85/15	93
8[d]	**3n**	**4an**	88	88/12	85/15	87
9[e]	**3o**	**4ao**	53	83/17	89/11	97
10[f]	**3o**	**4ao**	78	90/10	89/11	91

[a] *dr* of **4**.
[b] Reaction time 60 h.
[c] $Ca(NTf_2)_2$ was used as catalyst.
[d] Reaction at −30 °C using $Ca(NTf_2)_2$ as a catalyst with 10 mol% of Bu_4NPF_6 and 10 mol% of [DBUH]OTf.
[e] Reaction at −30 °C using $Ca(NTf_2)_2$ as catalyst for 24 h.
[f] Reaction at −30 °C using $Ca(NTf_2)_2$ as catalyst, 10 mol% [DBUH]OTf as an additive for 24 h.

We next monitored the formation of the chiral calcium catalyst by ^{1}H NMR (Figure 2). The first spectral chart represents ligand **1h** in THF-d_8 and the second ^{1}H NMR chart represents a mixture of **1h** with two equivalents TMG. No change in the chemical shift of the ligand was observed with the exception of a broad



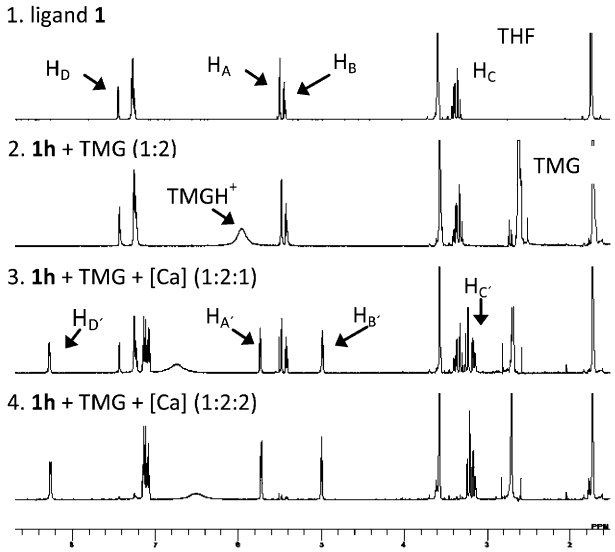


Figure 2. Determination of chiral calcium catalytic species by ^{1}H NMR analysis.

signal at 5.95 ppm that corresponds to the protonated tetramethylguanidine (Figure 1, spectra 1 and 2). Next, following the procedure for the *in situ* preparation of our catalyst, the ligand was stirred with two equivalents of TMG and one equivalent of $CaCl_2 \cdot 2H_2O$ in the presence of MS 4 Å at room temperature for 2 h. Under these conditions, new peaks corresponding to the anticipated catalytic active species were detected (dashed protons in spectrum 3). In the last chart, two equivalents of $CaCl_2 \cdot 2H_2O$ were employed in order to push the complexation of anionic **1h** completely. Under these conditions, almost no peaks corresponding to the free ligand were detected and this indicates that full coordination of **1h** to calcium was achieved (spectrum 4.). These results confirmed the formation of the catalytic active chiral calcium species and the spectral data are comparable to those reported by our group previously.[16c]

We assumed a catalytic cycle and reaction mechanism (Figure 3). The first step involves the deprotonation of the ligand and the formation of the chiral calcium complex **1ha**, which might be in equilibrium with either the binuclear complex **1hb** or **1hc**. All three of these calcium complexes **1ha**–**1hc** could react with a deprotonated Schiff base *via* a counterion exchange to form chiral enolate **1hd** as a key intermediate. The next step is the 1,4-addition of **1hd** to an α,β-unsaturated compound to form enolate **1he**, which, after protonation, provides the desired product **4**. Protonation of **1he** might proceed through pathway A with [TMGH]Cl, in which both TMG and calcium complex are regenerated, or *via* pathway B, where the deprotonation of the Schiff base takes place and chiral enolate **1hd** is regenerated. The [3+2] cycloaddition may proceed through a stepwise mechanism involving enolates **1hd** and **1he**, but in this case, intermediate **1he** undergoes intramolecular Mannich type reaction to furnish amide **1hf** (pathway C). Sequential protonation, which may proceed *via* pathway A or B, affords the corresponding pyrrolidine derivative **5**.

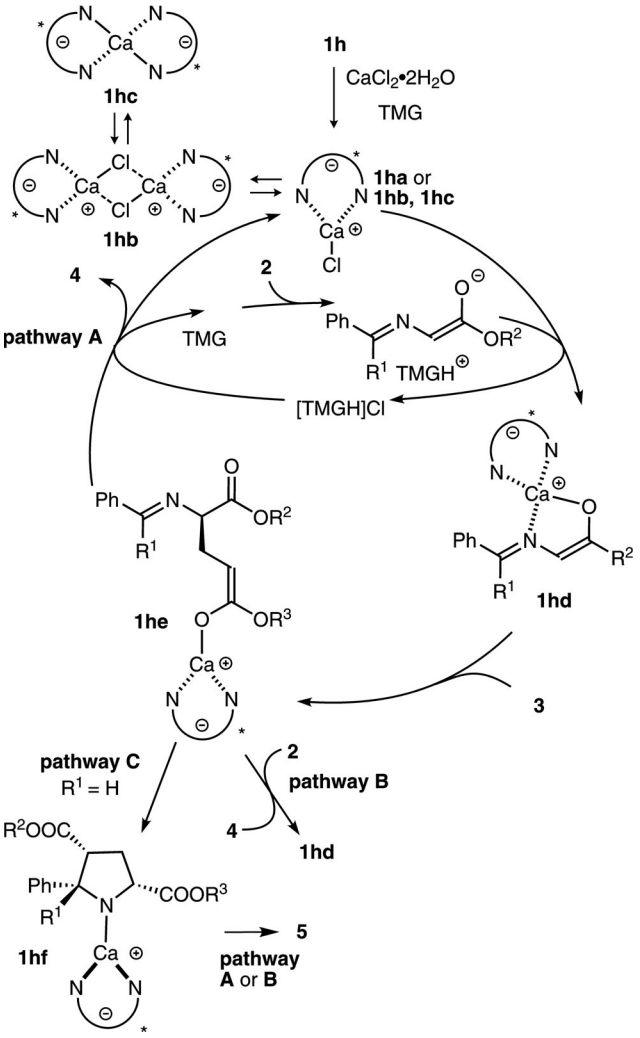
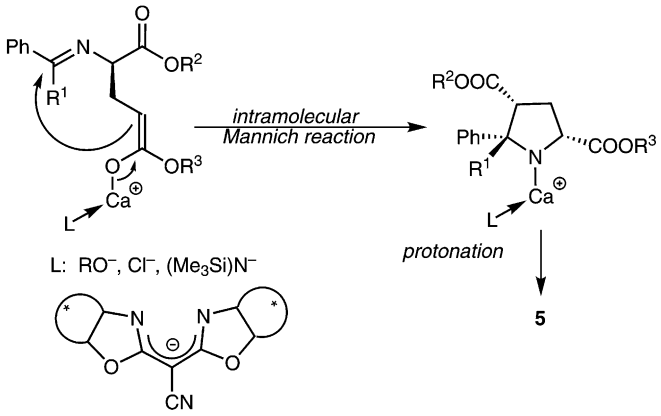
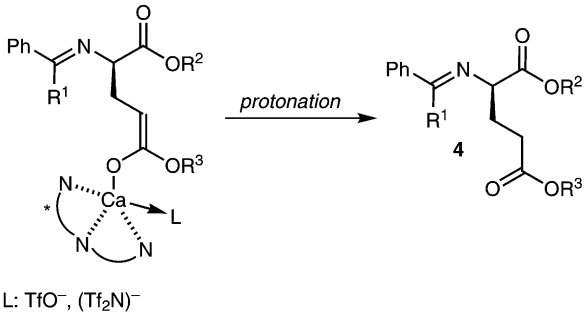


Figure 3. Assumed reaction mechanism for 1,4-addition and [3+2] cycloaddition reactions of glycine Schiff bases with α,β-unsaturated carbonyl compounds.

The formation of the cycloadduct may be determined by the nature of catalysts, as well as the structure of both substrates. In the case of calcium complexes bearing electron-donating ligands such as anionic **1h** or alkoxides, a more electron rich enolate **1he** is formed and this intermediate may be a stronger nucleophile that can readily undergo intramolecular Mannich reaction (Figure 4, A). On the other hand, in the catalytic system consisting of more Lewis acidic $Ca(OTf)_2$ [or $Ca(NTf_2)_2$] and **1i**, the neutral coordinative ligand may not affect electron properties of **1ie** significantly and the main contribution is probably derived from the triflate [or bis(trifluoromethanesulfonyl)amide] anion (Figure 4, B). In this scenario, the corresponding enolate is less nucleophilic, rather basic, and protonation is therefore preferred (Figure 4, B). Equally, steric factors may play an important role. Less steric hindered Schiff bases **2b** and **2c** afforded exclusively the [3+2] cycloadducts (Table 2, entries 8–14). However, in reactions of amides **3d** and **3e** with (diphenylmethylene)amino-Schiff base **2a**, the corresponding pyrrolidines were obtained in high yields (Table 2, entries 6 and 7). Due to the greater stability of amide enolates (compared with esters enolates) and significantly higher nucleophilicity,[30] cyclization of enolates **1he** derived from the mentioned substrates proceeds smoothly despite of higher steric demand of **2a**. Additionally, protonation of enolate **1he** may be kinetically favored, while the [3+2] cycloaddition may lead to the more stable pyrrolidine derivatives and may be thermodynamically controlled (especially in the reactions of β-branched α,β-unsaturated compounds).



A: *more nucleophilic enolate* ***1he***



B: *less nucleophilic, basic enolate* ***1ie***

Figure 4. 1, 4-Addition *vs.* [3+2] cycloaddition.

Conclusions

In conclusion, highly efficient 1,4-addition and [3+2] cycloaddition reactions of glycine Schiff bases with α,β-unsaturated carbonyl compounds using a simple $CaCl_2 \cdot 2H_2O$-based catalyst have been developed. The reactions proceeded smoothly at −20 °C, and high enantioselectivities of the corresponding products were achieved with Box-type ligand **1h** bearing a chiral indane scaffold. The introduced methodology was successfully applied to a broad range of substrates by employing 5 mol% of the catalyst. Additionally, modification of the catalytic system by using more Lewis acidic calcium salts and neutral coordinative ligand **1i** allows for the tuning of the chemoselectivity of the reaction and to extend its application for β-substituted α,β-unsaturated carbonyl compounds. From a practical viewpoint, further investigations and applications of calcium-based catalysts in asymmetric transformations is a challenging topic, which is currently underway in our laboratory.

Experimental Section

Typical Procedure for $CaCl_2 \cdot 2H_2O$-Box-Catalyzed 1,4-Addition and [3+2] Cycloaddition Reactions of Glycine Schiff Bases with α,β-Unsaturated Carbonyl Compounds

A typical procedure for 1,4-addition is represented by the reaction of glycine Schiff base **2a** with methyl acrylate (**3a**). In the glovebox, $CaCl_2 \cdot 2H_2O$ (2 mg, 0.0135 mmol), ligand **1h** (4.9 mg, 0.0135 mmol) and MS 4 Å (90 mg) were added into 30-mL flame-dried flask. THF (0.5 mL) was added and after 5 min, TMG (3.4 μL, 0.027 mmol) in THF (0.5 mL) was added. The resulting mixture was stirred under an argon atmosphere for 2 h and then cooled to −20 °C. **2a** (95.7 mg, 0.324 mmol) in THF (0.5 mL) was slowly added, followed by dropwise addition of **3a** (24.1 μL, 0.27 mmol) in THF (0.5 mL). After the mixture had been stirred at the same temperature for 24 h, saturated NH_4Cl (10 mL) was added to quench the reaction. Dichloromethane (10 mL) was added, the organic layer was separated and the aqueous layer was extracted with dichloromethane (2×15 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and, after filtration, the solvent was evaporated under reduced pressure. The crude product was purified by preparative thin layer chromatography (hexane-ethyl acetate = 4:1) to afford 1,4-adduct **4aa**; yield: 90 mg (87%). The enantioselectivity of the product was determined by HPLC.

[3+2] Cycloaddition reactions involve the same experimental procedure. A typical reaction of glycine Schiff base **2c** (71 mg, 0.324 mmol) with methyl crotonate (**3f**) (29 μL, 0.27 mmol) gave the corresponding [3+2] adduct **5cf**; yield: 74 mg (85%). The enantioselectivity of the product was determined by HPLC.

Experimental Procedure for Ca-Pybox-Catalyzed Asymmetric 1,4-Addition Reactions of Glycine Schiff Base (3a) with β-Substituted Acrylates

A typical experimental procedure is described for the reaction of glycine Schiff base **2a** with methyl crotonate (**3f**). In the glovebox, calcium triflate (6.8 mg, 0.02 mmol), ligand **1i** (7.9 mg, 0.02 mmol) and MS 4 Å (50 mg) were added to a 10-mL vial and 1,2-diethoxyethane (0.25 mL) was then added. The resulting mixture was stirred at room temperature in the glovebox for 1 h and sequentially *tert*-butyl 2-[(diphenylmethylene)amino]acetate (**2a**) (59 mg, 0.2 mmol, neat), DBU (3.2 μL, 0.02 mmol, neat) and 1,2-diethoxyethane (0.75 mL) were added in this order. The reaction vial was then transferred out of the glovebox and cooled to −20 °C. After 10 min., methyl crotonate (**3f**) (25.5 μL, 0.24 mmol, neat) was added dropwise and mixture was stirred at the same temperature for 24 h. The reaction was then quenched by addition of saturated NH_4Cl (5 mL) and extracted with dichloromethane (3×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and, after filtration, the solvent was evaporated. The crude product was purified by preparative thin layer chromatography (hexane-ethyl acetate = 4:1) to afford 1,4-adduct **4af**; yield: 71 mg (89%). Diastereoselectivity and the ratio of 1,4-adduct/[3+2] cycloadduct were determined from crude

^{1}H NMR. The enantioselectivity of the product was determined by HPLC.

Ca-Pybox-Catalyzed Asymmetric 1,4-Addition of *tert*-Butyl 2-[(diphenylmethylene)amino]acetate to (*E*)-Methyl 5-Phenylpent-2-enoate (Gram Scale)

In a 30-mL flask, calcium bis(trifluoromethanesulfonyl)imide (223.6 mg, 0.372 mmol), ligand **1i** (146.5 mg, 0.372 mmol), Bu_4NPF_6 (144.3 mg, 0.372 mmol) and MS 4 Å (934 mg) were combined in 1,2-diethoxyethane (4.75 mL). The resulting mixture was stirred at room temperature for 2 h, and sequentially *tert*-butyl 2-[(diphenylmethylene)amino]acetate (**2a**) (1.1 g, 3.72 mmol, neat), DBU (56.0 μL, 0.372 mmol, neat) and 1,2-diethoxyethane (14.25 mL) were added successively. The flask was then cooled to −30 °C. After 10 min, (*E*)-methyl 5-phenylpent-2-enoate (**3n**) (850.0 mg, 4.47 mmol, neat) was added dropwise followed by the addition of [DBUH]OTf (112 mg, 0.372 mmol) in 3 mL of anhydrous THF. The resulting mixture was stirred at the same temperature for 48 h. The reaction was then quenched by addition of saturated NH_4Cl (10 mL) and extracted with dichloromethane (3×50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and, after filtration, the solvent was evaporated. The crude product was purified by column chromatography (hexane-ethyl acetate = 10:1 to 5:1) to afford (*2S,3S*)-1-*tert*-butyl 5-methyl-2-[(diphenylmethylene)amino]-3-phenethylpentanedioate (**4an**); yield: 1.56 g (86%). Diastereoselectivity and the ratio of 1,4-adduct/[3+2] cycloadduct were determined by ^{1}H NMR analysis of the crude product (1,4-adduct/[3+2] = 86/14, *dr* = 86/14). HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 100/1, flow rate = 0.2 mL min^{-1}, detection wavelength = 254 nm): t_R = 43.2 min. (*minor*), t_R = 47.8 min. (*major*) (83% *ee*).

A complete Experimental Section is provided in the Supporting Information.

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