Asymmetric Catalysis

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Enantioselective Protonation Catalyzed by a Chiral Bicyclic Guanidine Derivative**

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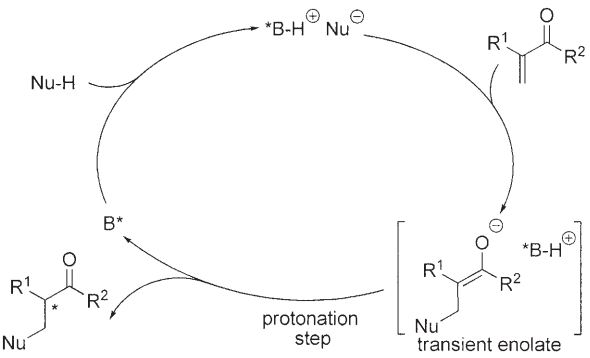
The enantioselective protonation of enolates is a conceptually simple and efficient approach to the preparation of chiral carbonyl compounds with an α stereogenic center.[1] The rate of proton exchange between electronegative atoms is often rapid, which makes discrimination between diastereomeric transition states difficult. Furthermore, *E* and *Z* enolates will exhibit different enantiofacial selectivities. The majority of such reactions have been conducted with preformed enolates and a stoichiometric amount of a chiral proton source.[1,2] Several strategies have been employed for catalytic enantioselective protonation.[1,3] One particularly attractive method is the generation of a transient enolate[4] through a conjugate addition reaction,[5] followed by an in situ enantioselective protonation (Scheme 1). The protonation can occur within the catalyst–enolate ion pair or from a more acidic, achiral proton source, Nu–H.

Seminal research on the tandem conjugate addition–enantioselective protonation strategy was reported by Pracejus et al. in 1977.[5a] *Cinchona* alkaloids and other chiral amines derived from natural products were used to catalyze reactions between methyl 2-phthalimidoacrylate and phenylmethanethiol or diphenylmethanethiol to furnish cysteine esters with moderate enantioselectivities of up to 54% *ee*. This approach, if successful, would be an excellent route to optically active derivatives of cysteine. Some thirty years later, an asymmetric version of the reaction described by Pracejus et al. remained elusive. There were only a few examples of conjugate addition to α-aminoacrylates reported.[5b–d] 2-Phenylacrylates[5e] and unsaturated imides[5f] were protonated in the presence of *Cinchona* alkaloids and bifunctional thiourea, respectively, as catalysts with moderate success. However, an enantioselective conjugate addition followed by the diastereoselective protonation of non-adjacent chiral centers was described recently.[6]



Scheme 1. Chiral Brønsted base (B*) catalyzed addition of nucleophiles (Nu–H) to 1,1-disubstituted alkenes followed by enantioselective protonation.

In contrast, variations of the reaction under the catalysis of transition metals or Lewis acids have found more success. Rhodium complexes were found to catalyze the 1,4-addition of various organometallic reagents, such as organoboranes, to dehydroamino esters,[7a] α-benzyl acrylates,[7b] and diphenylphosphinylallenes.[7c] A chiral Lewis acid derived from $MgBr_2$ and a bisoxazoline was used for radical conjugate addition reactions to α-aminoacrylates[7d] and α-methacrylates.[7e] Secondary phosphines underwent addition to methacrylonitrile under the catalysis of nickel complexes to yield products with high *ee* values.[7f] Heterobimetallic complexes have been shown to catalyze the protonation step in the addition of thiols to α-substituted acrylates.[7g] The diastereoselective addition of a chiral Al–thiol reagent to α-substituted acrylates was also reported.[7h]

We and others have shown previously that chiral guanidines can act as effective catalysts in several highly enantioselective reactions.[8] We reported that chiral bicyclic guanidines are excellent catalysts for Diels–Alder, Michael, and phospha-Michael reactions.[8k–n] Herein, we demonstrate for the first time that a tandem process involving a conjugate addition followed by a highly enantioselective protonation or deuteration can be catalyzed by a Brønsted base, the guanidine derivative **1** (Table 1).

We first investigated the protonation of methyl 2-phthalimidoacrylate, the substrate used by Pracejus et al.[5a] Dehydroamino acids and derivatives were prepared from L-serine in multistep syntheses, during which the chiral center was destroyed to generate the alkene. An improved method in which alkynoates were used was developed by Trost and Dake[9] and made the preparation of 2-phthalimidoacrylates practical and effective. Protonation reactions of various thiols were investigated in the presence of **1** as the catalyst; the products were obtained with moderate *ee* values.

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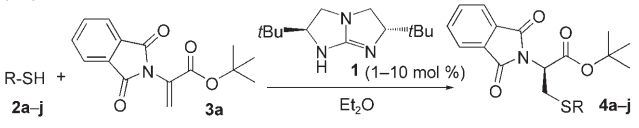
We speculated that the presence of a bulkier ester group would lead to an improvement in the *E*/*Z* enolate ratio, which may translate into an improved enantioselectivity. Indeed, we found that when the guanidine **1** (10 mol%) and thiophenol (**2a**) were added to *tert*-butyl 2-phthalimidoacrylate (**3a**), the adduct **4a** was formed with high enantioselectivity and in high yield (Table 1, entry 1). As a result of noncatalyzed background reactions, a low temperature of −50 °C was necessary for high enantioselectivity. Electron-deficient (Table 1, entries 2–4) and electron-rich aryl thiols (entries 5, 6, 9, and 10) reacted equally well. Bulky aryl thiols (Table 1, entries 5 and 6) and thiols bearing heterocyclic or naphthyl groups (entries 7 and 8) also gave adducts with high *ee* values. Next, we studied thiols containing hydroxy and amino groups (Table 1, entries 9–12). The presence of the acidic phenolic group did not affect the reaction significantly. No oxy- or aza-Michael adducts were observed when thiols **2i** and **2j** were used. The catalyst loading could be further decreased to 5 or even 1 mol% (Table 1, entries 11 and 12). However, to maintain the high *ee* values, the temperature had to be lowered significantly to −116 °C.

Table 1: Enantioselective protonation of *tert*-butyl 2-phthalimidoacrylate (**3a**).



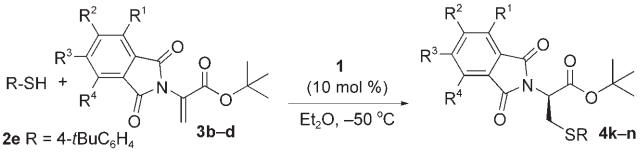
Entry	R	**1** [mol %]	*T* [°C]	*t* [h]	Yield [%][a]	*ee* [%][b]
1	Ph (**2a**)	10	−50	0.5	99	90
2	2-$CF_3C_6H_4$ (**2b**)	10	−50	3	99	93
3	2-$MeO_2CC_6H_4$ (**2c**)	10	−50	2.5	98	90
4	4-BrC_6H_4 (**2d**)	10	−50	4	99	90
5	4-*t*BuC_6H_4 (**2e**)	10	−50	3	92	93
6	3,5-$Me_2C_6H_3$ (**2f**)	10	−50	1	98	94
7	thiophen-2-yl (**2g**)	10	−50	1	99	91
8	naphth-1-yl (**2h**)	10	−50	1	99	89
9	4-HOC_6H_4 (**2i**)	10	−50	0.5	97	84
10[c]	4-$H_2NC_6H_4$ (**2j**)	10	−50	0.5	93	92
11[d]	4-$H_2NC_6H_4$ (**2j**)	5	−116	4.5	88	94
12[d]	4-$H_2NC_6H_4$ (**2j**)	1	−116	6.5	82	90

[a] Yield of the isolated product. [b] Determined by HPLC on a chiral phase. [c] The absolute configuration of **4j** was assigned by X-ray crystallographic analysis (see the Supporting Information for details). [d] The reaction mixture was maintained at −116 °C with a liquid nitrogen–diethyl ether slush bath for 4 h, after which time the temperature was maintained at −78 °C.

A variety of phthalimidoacrylates, **3b–d** (Table 2, entries 1–3), were developed to enable greater flexibility in the deprotection strategy. For example, the 4,5-dichlorophthalimidoacrylate in **3d** was expected to be cleaved under milder conditions than the other phthalimidoacrylates. Substituents on the *N*-phthalimide protecting group did not affect the enantioselectivities significantly.

Asymmetric conjugate addition reactions of thiols have generally been restricted to aromatic thiols, which are not readily transformed into the free thiol.[10] The uncatalyzed reactions of alkyl thiols are typically more pronounced. Under these newly developed protonation conditions (Table 2), benzyl thiols gave adducts with moderate *ee* values of 40–50%. The enantioselective protonation occurred with high enantioselectivity when the phthalimidoacrylate **3d** was used with an unusual thiol, diphenylmethanethiol **2k** (Table 2, entry 4), which was prepared from benzhydrol and the Lawesson reagent. Reaction rates were higher, and a higher catalyst loading was required to overcome background reactions. When the adduct **4n** was resubjected to the reaction conditions without the addition of the nucleophile **2k**, no retro-Michael reaction was observed. The recovered adduct **4n** showed no loss of enantioselectivity. Thus, the reaction appears to be irreversible.

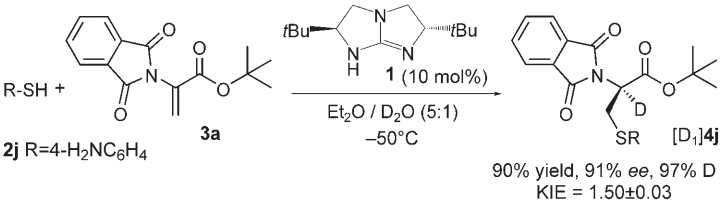
Table 2: Enantioselective protonation of various *tert*-butyl 2-phthalimido acrylates **3**.



Entry	**2**	**3** (R^1, R^2, R^3, R^4)	**4**	*t* [h]	Yield [%][a]	*ee* [%][b]
1	**2e**	**3b** (F, H, H, H)	**4k**	1	99	92
2	**2e**	**3c** (H, Me, H, H)	**4l**	1	98	92
3	**2e**	**3d** (H, Cl, Cl, H)	**4m**	0.5	95	92
4[c]	**2k**	**3d** (H, Cl, Cl, H)	**4n**	2	96	91

[a] Yield of the isolated product. [b] Determined by HPLC on a chiral phase. [c] The reaction was carried out with 20 mol% of **1**. The reaction mixture was maintained at −116 °C for 0.5 h, then at −78 °C.

Chiral α-deuterated carbonyl compounds are often prepared by the deuteration of enolates.[11] The stereospecific replacement of deuterium in amino acids is useful for the effective determination of the 3D structure of proteins by NMR spectroscopy.[12] Deuterated amino acids are also useful for the elucidation of the stereochemical pathways of enzymatic reactions. When deuterium-labeled aryl thiols were prepared separately and deuteration was carried out with the (nondeuterated) guanidine **1**, the level of deuterium incorporation in the products was moderate. The addition of water did not adversely affect the enantioselectivity or yield of the protonation reaction. An alternative protocol was therefore devised in which the aryl thiol, for example, 4-aminobenzenethiol (**2j**) was prestirred in a mixture of diethyl ether and D_2O (5:1) in the presence of **1** (10 mol%; Scheme 2). After half an hour at ambient temperature, the

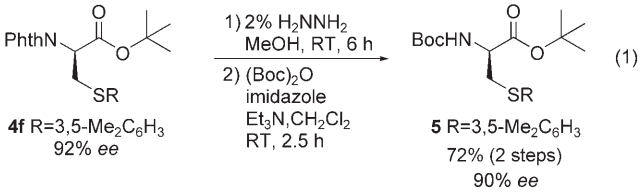


Scheme 2. Enantioselective deuteration of *tert*-butyl 2-phthalimidoacrylate (**3a**).

reaction mixture was cooled to −50 °C, and D_2O was frozen out of the mixture. The phthalimidoacrylate **3a** was added, and the reaction reached completion within an hour to yield [D_1]**4f**, which exhibited a high degree of deuteration, with high enantioselectivity.

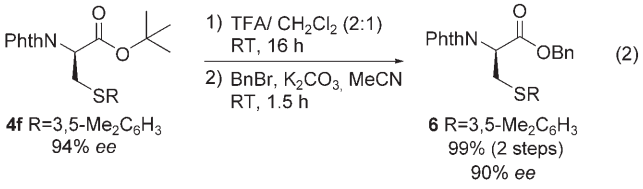
The kinetic isotope effect of the reaction was investigated by carrying out a similar experiment: D_2O was replaced with a 1:1 or 2:1 mixture of D_2O and H_2O. The experiment was repeated three times, and a primary kinetic isotope effect (KIE) of 1.50 ± 0.1 was found. Although no detailed mechanistic studies have yet been conducted, this small but significant KIE shows that the cleavage/formation of a bond containing H (or D) is involved in the rate-determining step.[7f]

We believed that this methodology would allow us to prepare various optically pure analogues of cysteine, in particular those of D-cysteine. Some of these analogues have been shown to be interesting inhibitors of zinc-containing enzymes, such as carboxypeptidase A.[13] This attractive strategy would only be viable if we were able to manipulate the protecting groups without significant racemization of the vulnerable stereogenic center. The phthalimide group of **4f** was cleaved readily by treatment with hydrazine in methanol [Eq. (1); PhthN = phthalimido]. To determine the *ee* value by



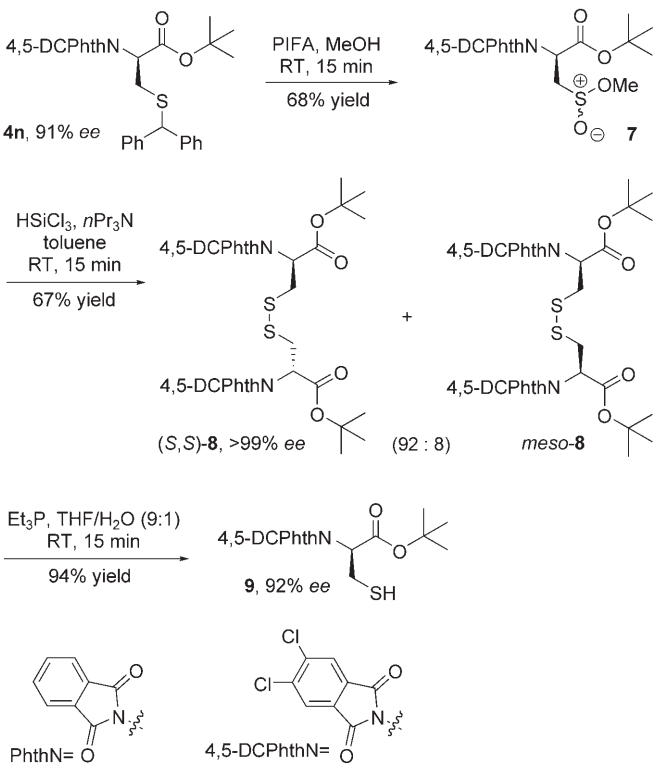
(1)

HPLC analysis on a chiral phase, reprotection of the resulting amino group was necessary. Without purification of the intermediate, the Boc-protected amine **5** (Boc = *tert*-butoxycarbonyl) was prepared in good yield over two steps. Similarly, the *tert*-butyl ester **4f** was cleaved with trifluoroacetic acid (TFA) and converted into the benzyl ester **6** [Eq. (2); Bn = benzyl]. In both cases, a slight decrease in the *ee* value was observed.



(2)

Trifluoroacetic acid (TFA) is the typical reagent used for the deprotection of *S*-diphenylmethyl thioethers; however, as it might also cleave the *tert*-butyl ester, an alternative approach had to be developed. Hydrogenolysis with Pd/C and H_2 was unsuccessful. Finally, selective oxidative cleavage with (bis(trifluoroacetoxy)iodo)benzene (PIFA) in the presence of MeOH gave methyl sulfinate **7** (Scheme 3). (Di-

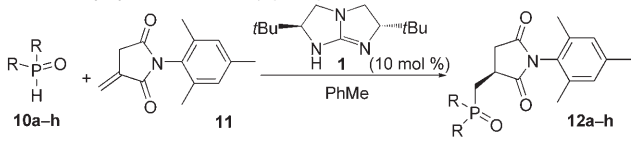


Scheme 3. Cleavage of the thioether.

acetoxyiodo)benzene (PIDA), with a lower oxidizing power, did not effect the cleavage reaction. Although the oxidation of a sulfide to a sulfoxide with a hypervalent iodine oxidant has been described previously,[14] such a cleavage reaction has not. Reduction with trichlorosilane resulted in the fully protected cystine (*S*,*S*)-**8** with an improved *ee* value of > 99 %. This improvement in the *ee* value was probably due to the formation of a small amount of *meso*-**8**, which locked up the other enantiomer. The disulfide bond was cleaved with Et_3P to give the cysteine analogue **9**. All three reactions were mild and rapid, each complete within 15 min.

N-Substituted itaconimides are highly useful four-carbon-atom synthons. We showed previously that these cyclic imides are tuneable and can be adapted for use with the guanidine catalyst system through modifications of the imide protecting group.[8l] With these imides, only transient *Z* enolates would be formed. The guanidine derivative **1** catalyzed the enantioselective protonation of adducts formed from aryl or alkyl thiols and *N*-substituted itaconimides, such as **11**. For example, the reaction between *tert*-butylthiol and itaconimide **11** gave an adduct with 78 % *ee* (optimization is ongoing). We also found that the addition of the secondary phosphine oxides **10a–h** to *N*-substituted itaconimides proceeded smoothly. Reactions with *N*-phenylitaconimide proceeded with good to moderate levels of enantioselectivity. *N*-Substituted itaconimides, including *N*-alkyl, *N*-benzyl, and various *N*-aryl itaconimides, were used to investigate the effect of substituents. Eventually, we concluded that substituents at the 2- and 6-positions were crucial for high enantioselectivity, with the highest *ee* values observed with *N*-(2,4,6-trimethylphenyl)itaconimide (**11**; Table 3). Reactions between itaco-

Table 3: Enantioselective protonation of *N*-(2,4,6-trimethylphenyl)itaconimide (**11**) with secondary phosphine oxides.



10a–h **11** **12a–h**

Entry	R	*T* [°C]	*t* [h]	Yield [%][a]	*ee* [%][b]
1[c]	naphth-1-yl (**10a**)	0	2	95	98
2	2-Me-naphth-1-yl (**10b**)	0	1	93	87
3	2-EtC_6H_4 (**10c**)	0	8	94	92
4	4-FC_6H_4 (**10d**)	0	6	79	91
5	3-ClC_6H_4 (**10e**)	0	1.5	95	92
6	2-$CF_3C_6H_4$ (**10f**)	−20	3	89	96
7	3-$CF_3C_6H_4$ (**10g**)	−50	6	93	94
8	3-FC_6H_4 (**10h**)	−50	10	88	94

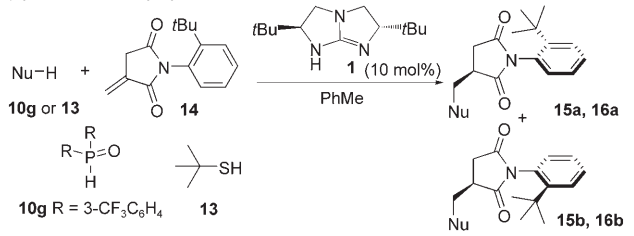
[a] Yield of the isolated product. [b] Determined by HPLC on a chiral phase. [c] The absolute configuration of **12a** was assigned by X-ray crystallographic analysis (see the Supporting Information for details).

nimide **11** and the secondary phosphine oxides **10a–e** in the presence of catalyst **1** (10 mol%) at 0°C were complete within several hours to give the chiral cyclic imides **12a–e** in high yields and with high *ee* values (Table 3, entries 1–5). When phosphine oxides with electron-withdrawing substituents were used, the reaction rates were typically higher, and a lower reaction temperature was required for high enantioselectivity (Table 3, entries 6–8). The unique structures of cyclic imides **10a–h** promise access with this reaction to a range of interesting chiral α,γ-aminophosphine oxides and α,γ-aminophosphines.

N-Phenylitaconimides with a large *ortho* substitutent, such as a *tert*-butyl group, have a significant barrier to rotation about the C–N axis and exist as racemic atropisomers at ambient temperature. The synthesis and application of such axially chiral imides in asymmetric synthesis has generated much interest; however, these compounds are still not widely used.[15] We found that the guanidine **1** could catalyze the addition of phosphine oxide **10g** to *N*-(2-*tert*-butylphenyl)-itaconimide (**14**) to give a mixture of the diastereoisomers **15a** and **15b** (Table 4, entry 1). A higher *ee* value (>99%) was observed for the *anti* diastereoisomer **15a** than for the *syn* diastereoisomer **15b**. Similar observations were made when *tert*-butylthiol (**13**) was used as the nucleophile to obtain imides **16a** and **16b** (Table 4, entry 2). When a 1:1 mixture of **15a** and **15b** was heated at reflux in toluene for 12 h, the two diastereoisomers were obtained in a 2:1 ratio in favor of the *anti* diastereoisomer; the *ee* values equilibrated to 88–86% *ee* for both diastereoisomers.

In summary, the chiral bicyclic guanidine derivative **1** was found to catalyze protonation and deuteration reactions with high enantioselectivity. Both linear and cyclic substrates can be used in this highly successful Brønsted base catalyzed tandem conjugate addition–enantioselective protonation reaction, and the protonation was shown to be rapid, selective, and irreversible. The small but significant kinetic isotope effect indicates that the cleavage/formation of a bond containing H (or D) is involved in the rate-determining step. We are currently studying the mechanism of the reaction.

Table 4: Enantioselective protonation of axially chiral *N*-(2-*tert*-butylphenyl)itaconimide (**14**).



Entry	NuH	*T* [°C]	*t* [h]	Yield [%][a]	d.r.	*ee* [%][b]
1[c]	**10g**	−50	2	92	1:1	**15a**: >99, **15b**: 79
2[c]	**13**	−50	30	97	1:1	**16a**: 90, **16b**: 74

[a] Combined yield of the two isolated diastereoisomers. [b] Determined by HPLC on a chiral phase. [c] The relative configurations of the products were determined by NOE analysis (see the Supporting Information for details).

Experimental Section

Representative procedure: The thiophenol **2j** (13.8 mg, 0.110 mmol, 1.10 equiv) and **1** (0.22 mg, 0.0010 mmol, 0.010 equiv) were stirred in Et_2O (1.00 mL) in a 4 mL sample vial at −116°C (Et_2O/liquid N_2 slush bath) for 10 min. The phthalimidoacrylate **3a** (27.3 mg, 0.100 mmol, 1.00 equiv) was then added as a solid, and the reaction mixture was stirred for 4 h at −116°C. (A conversion of 80% was determined by TLC after 4 h.) Dry ice was then added to the ether bath, and the temperature was allowed to warm gradually to −78°C. The mixture was stirred at −78°C for a further 2.5 h, by which time the reaction was complete. Flash chromatography afforded **4j** (32.5 mg, 82%) as bright-yellow crystals.

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