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Catalytic Enantioselective Aza-Henry Reactions

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Asymmetric aza-Henry reactions provide excellent routes for the synthesis of optically active organic compounds bearing two vicinal different nitrogenated functionalities that can be further transformed into a variety of interesting compounds such as 1,2-diamines or α-amino acids. The catalytic asymmetric version of the reaction (also called the nitro-Mannich reaction) provides highly efficient access to enantiomerically pure compounds. Both metal-based and organic catalysts can be used to promote these reactions in a enantioselective way; in particular, a great variety of different organocatalysts – including thioureas, *N*-oxides, quaternary ammonium salts and chiral Brønsted acids – have demonstrated their efficiency, as has recently been reported by several research groups. In addition, considerable effort is being made in controlling the *syn*/*anti* diastereoselectivities of these reactions when substituted nitroalkanes are used as substrates. In this microreview recent advances, including scope and limitations, are discussed and applications of different catalytic systems for catalytic asymmetric aza-Henry reactions are presented.

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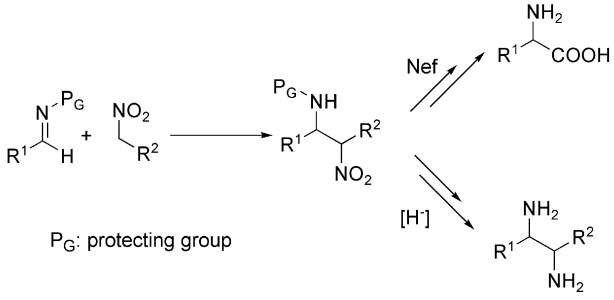
Introduction

The recent growth in high-throughput screening for enantiomerically pure biologically active agents has increased the demand for the development of enantioselective synthetic methods that provide exceptional stereocontrol. In this regard, organic compounds bearing two vicinal nitrogenated functionalities have in recent years been attracting the attention of the synthetic organic chemistry community.[1]

The nucleophilic addition of nitroalkanes to imines and related compounds (aza-Henry or nitro-Mannich reaction; Scheme 1)[2] is a powerful synthetic transformation that allows creation of a carbon–carbon bond with concomitant generation of two vicinal stereogenic centres bearing nitro and amino functional groups. The resulting β-nitroamines represent rather useful synthetic building blocks because the two nitrogenated functions are present in different oxidation states, thus giving access to further transformations with complete chemoselectivity. In addition, the β-nitroamines can easily be converted into α-amino acids and vicinal diamines through Nef reactions[3] and by reduction[4] of the nitro group (Scheme 1).



Scheme 1. Aza-Henry reaction.

Many natural products possessing valuable biological properties contain 1,2-diamino moieties.[5] In recent years several synthetic diamine derivatives have also been employed as medicinal agents, in particular in chemotherapy as antiarrhythmics,[6] antidepressant agents,[7] antihypertensives,[8] analgesics,[9] anticancer and antiviral drugs[10] and as antiparasitic agents.[11] In addition to their applications in medicinal chemistry, the use of vicinal diamines in organic synthesis in the field of catalytic asymmetric synthesis has also increased considerably during the last years, due to their use both as ligands[12] and as organocatalysts.[13]

The biological and synthetic importance of 1,2-diamines has stimulated significant activity in the past,[14] and several conceptually different strategies for their preparation, including enantiomeric resolution,[15] have been developed.[16] Because of the high reactivities of imines with nucleophiles, the development of new chiral non-racemic catalysts to promote the production of enantiomerically pure β-nitroamines has been a challenging task.

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To date, several protocols have been utilized for catalytic enantioselective reactions between imines and nitroalkanes, including both metal-based and metal-free (organocatalytic) approaches. In this account we discuss the scope and applications of these transformations.

Previous Diastereoselective Aza-Henry Reactions

Although nucleophilic additions of nitroalkanes to imines were studied by several groups in the past,[17] all the associated work was devoted to racemic derivatives. The first stereoselective aza-Henry reaction was reported by Anderson and co-workers,[18] who described the addition of the lithium salts of various nitroalkanes **2** to *N*-(*p*-methoxybenzyl)imines **1** (Scheme 2). The additions of the nitroalkane anions to **1** in the presence of acetic acid in most cases gave β-nitroamines **3** with good yields and diastereoselectivities. Both aryl and alkyl imines proved to be compatible with the procedure, affording mixtures of *syn* and *anti* isomers in all cases.[19] In most cases the *anti* isomer was predominant, and only in the case of the bulkier phenylnitromethane was a 15:1 ratio in favour of the *syn* isomer obtained (Scheme 2). Notably, imines derived from enolizable aliphatic aldehydes could be used in this process, in contrast with the strongly basic conditions required for the addition of other α-amino anions to imines.[20]

After studying the reaction illustrated in Scheme 2 in detail, Anderson and co-workers established that the reaction only proceeded in the presence of acetic acid, ruling out the possibility of the addition of a nitronate anion followed by a protonation. The authors stated in their original paper that *"the addition of a nitronate anion to an imine is thermodynamically impossible"* (*sic*), concluding that the reaction should take place either through a nitronic acid or through a protonated imine as a key intermediate. In order to develop a more efficient reaction and in the search for an enantioselective version of the reaction, the authors explored reactions between imines and silyl nitronates promoted by Lewis acids such as $BF_3{\cdot}Et_2O$, $TiCl_2(OiPr)_2$ and lanthanide triflates, which on the basis of previous work with other nucleophiles were seen as highly suitable for

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Pedro Merino was born in Zaragoza in 1962 and graduated with an Honours M.Sc. Degree in Chemistry from the University of Zaragoza, where he also received his Ph.D. with Professor Enrique Melendez in 1989. After two years of a postdoctoral stay in the group of Professor Alessandro Dondoni (University of Ferrara, Italy) working on applications of thiazole chemistry in asymmetric synthesis, he was appointed assistant professor at the University of Zaragoza in 1992. In 1994 he was promoted to Associate Professor and in 2005 he completed his habilitation as Full Professor in Organic Chemistry. In 2006 he was awarded a Chair in Organic Chemistry at the Department of Organic Chemistry of the University of Zaragoza. His research interests include the development of novel synthetic methodologies as well as target-oriented synthesis, the application of heterocycles in synthesis and the use of organic and metal-based catalysts in asymmetric synthesis.

Tomas Tejero was born in Zaragoza, Spain in 1958. He studied Chemistry at the University of Zaragoza, where he received his Ph.D. with honours working with Professor E. Melendez. In 1984 he became Assistant Professor and in 1986 he spent a year as a postdoctoral research associate at the University Pierre et Marie Curie (Paris) under the supervision of Prof. J. Normant. In 1987 he returned to Zaragoza and he achieved his habilitation as Senior Lecturer in 1987. His research interests include asymmetric synthesis including asymmetric catalysis and nuclear magnetic resonance techniques.

Raquel P. Herrera was born in Alicante, Spain in 1977. She received her BS degree from the University of Alicante in 1999 and her MS degree from the same University in 2000. From 1999 to 2003 she completed her Ph.D. under the supervision of Professor Albert Guijarro and Professor Miguel Yus at the University of Alicante. She then took up a European postdoctoral contract with Professor Ricci (Bologna, Italy) in the Industrial Chemistry Faculty until March 2006, at which time she joined Dr. Jose M. Lassaletta's group at the IIQ-CSIC (Seville, Spain). She was appointed to her present position at ICMA (Instituto de Ciencia de Materiales de Aragón) CSIC-University of Zaragoza in January 2008. Her research interests focus on asymmetric organocatalysis and its applications.

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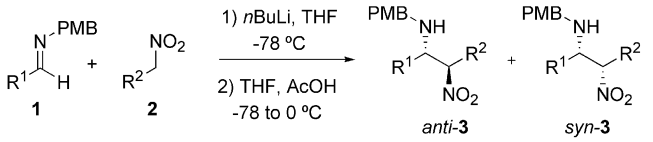
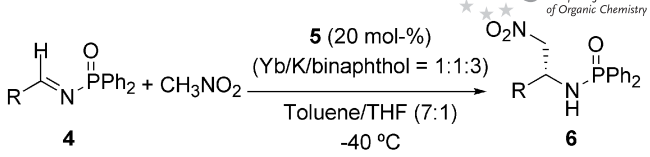


R^1	R^2	Yield (%)	*d.r.* (*anti*/*syn*)
Ph	Et	90	10:1
*n*Pr	Et	95	9:1
*c*Hex	Et	95	2:3
Ph	Ph	74	1:15
$BnOCH_2$	Et	95	3:2
$Ph(CH_2)_3$	Et	95	7:1

Scheme 2. The first diastereoselective aza-Henry reaction.



R	*t* (h)	Yield (%)	*ee* (%)
Ph	60	79	91
p-Cl-C_6H_4	60	93	87
p-Me-C_6H_4	168	85	89
2-furyl	168	57	83
2-thiophenyl	168	41	69

Scheme 3. First catalytic enantioselective aza-Henry reaction.

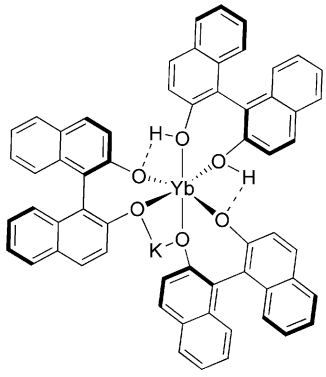
activating imines. The best results were obtained with $Sc(OTf)_3$, which was found to promote the addition of trimethylsilyl nitropropanate ester to imines in good yields and with moderate to good *anti* selectivities with catalyst loadings of 4 mol-%. Dramatic improvements both in yield and in diastereoselectivity were also found when *N*-(*p*-methoxyphenyl)imines were used instead of the corresponding *N*-(*p*-methoxybenzyl)imines **1**.[21]

The effectiveness of lanthanide derivatives as catalysts for aza-Henry reactions was further confirmed by Qian and co-workers, who reported that additions of nitromethane to electron-deficient *N*-tosyl imines were efficiently catalysed even by 1 mol-% of $Yb(OiPr)_3$.[22] Since the Lewis acid employed is the only promoter of the reaction and the reaction proceeds in the absence of any base, it has been proposed that the alkoxide moiety of the catalyst deprotonates the nitromethane, thus transforming the ytterbium derivative into a bifunctional catalyst.

Enantioselective Metal-Catalysed Aza-Henry Reactions

The first examples of catalytic enantioselective aza-Henry reactions, between highly coordinating *N*-phosphinoyl imines **4** and nitromethane (Scheme 3), were reported by Shibasaki and co-workers in 1999.[23] These authors investigated several catalysts prepared from $Yb(OiPr)_3$, $KOtBu$ and (*R*)-binaphthol in different ratios. Interestingly, whereas the complex prepared in a 1:1:2 ratio did not promote the reaction, the same components mixed in 1:1:3 ratio afforded the best results, furnishing nitroamines **6** with good yields and enantioselectivities. No base was needed because the formed complex contained both Brønsted basic and Lewis acid functionalities, capable of activating both the electrophile and the nucleophile.

On the basis of several studies of the LDI-TOF mass spectra of the catalyst solutions, the authors proposed that the active catalyst was a complex formed by [YbK(binaphthoxide)$_2$] and (*R*)-binaphthol, the integrity of which was maintained by hydrogen bonding interactions (Figure 1). Catalysts of this sort, possessing intrinsic helicity, had also been proposed as the active species in other catalytic enantioselective reactions such as the Pudovik reaction.[24]



5

Figure 1. Proposed structure of the heterobimetallic catalyst **5**.

An important drawback of catalyst **5** is that it is not able to promote the aza-Henry reaction with bulkier substituted nitroalkanes at low temperatures. This lack of activity was attributed to the reduced size of the binding pocket of the catalyst, which could have insufficient space to accommodate both the imine and the nitroalkane.

The same group later reported that the combination of (*R*)-ALB {AlLi[(*R*)-binaphthoxide]$_2$} **7** and potassium *tert*-butoxide (Scheme 4) acted as an effective catalyst for a variety of nitroalkanes,[25] thus enhancing the versatility of the BINOL-based system. The *ee* range, however, was not very high, even though the *syn*/*anti* diastereoselectivities of the reactions could be controlled by choosing an appropriate solvent. Whereas the reactions in toluene and THF afforded the corresponding *anti* isomers in only 3:1 and 2:1 ratios, respectively, in dichloromethane the *anti* isomers were obtained in *dr* values of up to 7:1.

The reactions also proceeded smoothly with reduced amounts of the catalyst. In the presence of 10 mol-% of catalyst, for example, the desired products were obtained in good yields, though with slightly lower diastereoselectivities

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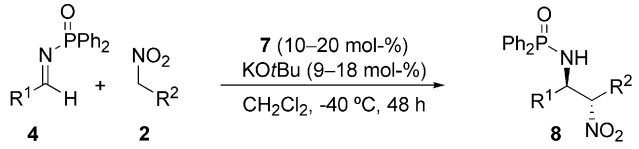

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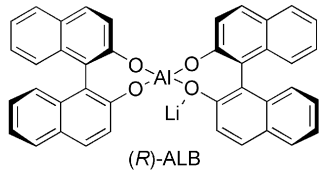


(*R*)-ALB

7

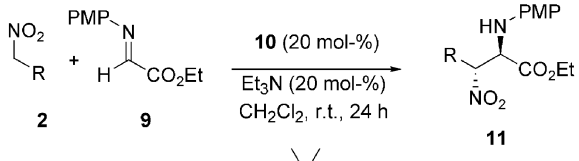
R^1	R^2	**7** (mol-%)	Yield (%)	*d.r.* (*anti/syn*)	*ee* (%)
Ph	Me	20	77	6:1	83
Ph	Et	20	98	6:1	74
Ph	$BnO(CH_2)_2$	20	95	7:1	82
Ph	$BnO(CH_2)_3$	20	75	6:1	77
p-MeO-C_6H_4	Et	20	77	6:1	78
p-Me-C_6H_4	Et	20	68	6:1	77
p-Cl-C_6H_4	Et	20	89	3:1	71
Ph	Me	10	97	5:1	75
Ph	Et	10	87	5:1	71
Ph	$BnO(CH_2)_2$	10	87	5:1	60
Ph	$BnO(CH_2)_3$	10	93	5:1	63
p-MeO-C_6H_4	Et	10	96	5:1	63
p-Me-C_6H_4	Et	10	98	5:1	81
p-Cl-C_6H_4	Et	10	97	3:1	74
Ph	Me	10	78	6:1	76

Scheme 4. Aza-Henry reactions catalysed by (*R*)-ALB **7**.

and/or enantioselectivities. Some limitations of these procedure include the large amount of catalyst needed in the reactions (at least 10 mol-%; i.e., 20 mol-% of BINOL) and the fact that only aromatic imines can be used as substrates.

In that respect, Jørgensen and co-workers achieved notable advances in handling, substrate range and practicability. These authors reported catalytic enantioselective additions of nitroalkanes to the *N*-(*p*-methoxyphenyl)imines **9**, derived from ethyl glyoxylate, in the presence of 20 mol-% of copper(II) catalyst **10**, in which a phenyl bisoxazoline served as a chiral ligand.[26] The reactions could be performed at room temperature, and good to excellent *anti* selectivities and enantioselectivities were observed (Scheme 5). As an additional advantage, the reactions can be carried out with solvents without prior purification or drying and in the absence of any inert atmosphere, thus making the process amenable for technical applications.

The authors made a proposal for the catalytic cycle of the processes, suggested to account for the catalytic activity and for the diastereo- and enantioselectivity (Scheme 6).



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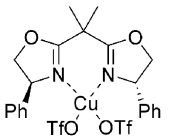

10

R	Yield (%)	*d.r.* (*anti/syn*)	*ee* (%) *anti/syn*
Et	81	95:5	97/87
H	38	-	87
Me	61	70:30	97/95
nC_5H_{11}	52	93:7	95/89
$PhCH_2$	80	95:5	95/88
Ph	59	95:5	74/77

Scheme 5. Aza-Henry reaction catalysed by **10**.

It is important for the outcome of the reaction that catalyst **10** is first mixed with the α-imino ester **9** to give intermediate **12**. Further coordination of the nitro compound should afford intermediate **13**; because this coordination is relatively weak, it has been reported for some BOX-Cu^{II}-catalysed reactions that should be performed in nitromethane as a solvent in order to displace the equilibrium towards the formation of **13**. Deprotonation of the nitro compound in **13** should give complex **14**, the proposed key intermediate in the reaction. In this structure the nitro substituent should occupy the less sterically crowded and more stable equatorial position, which would account for the diastereoselectivity of the reaction. The chiral (*R*)-Ph-BOX ligand in **14** should favour the formation of the (2*R*,3*R*) enantiomer of the product, since the intermediate leading to

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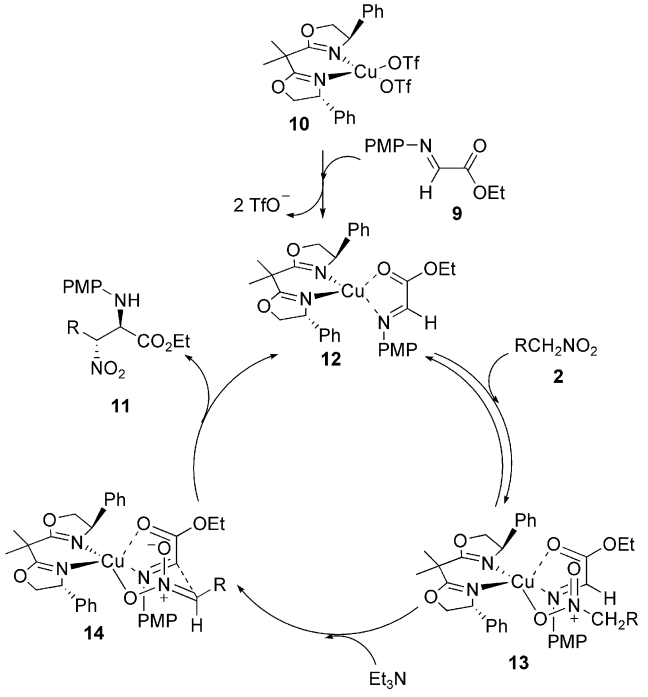
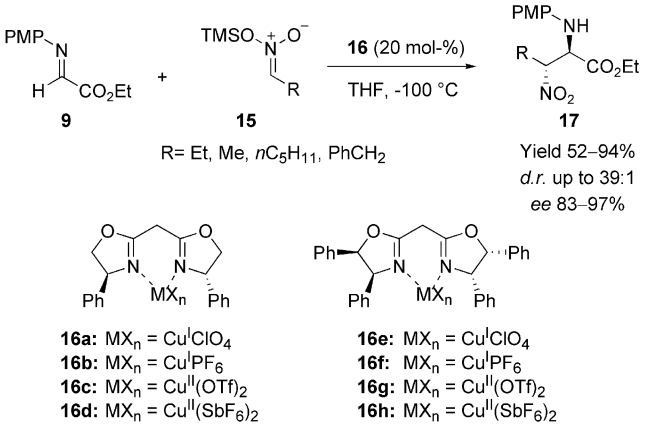


Scheme 6. Proposed catalytic cycle.

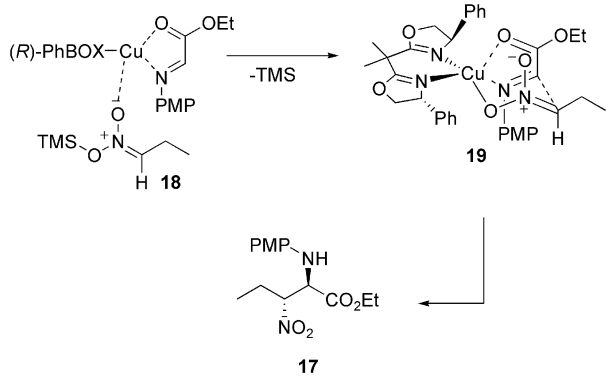
the opposite enantiomer would experience steric repulsion between the bulky *N*-(*p*-methoxyphenyl) substituent of the amino ester and the chiral phenyl substituent of the ligand.

Jørgensen's group also presented the first catalytic highly diastereo- and enantioselective aza-Henry reactions that proceeded in the absence of a base and with lower catalyst loadings. In these reactions, the presence of a base was avoided by using silyl nitronates **15** instead of nitro compounds in reactions with α-imino ester **9** (Scheme 7).[27] The reactions were catalysed by several copper(II) complexes **16** with phenyl bisoxazolines, and good to very good *ee* values and, again, excellent *anti* selectivities were achieved.



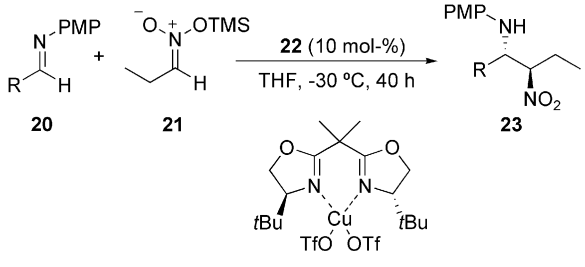
Scheme 7. Asymmetric aza-Henry reactions between imino ester **9** and silylnitronates **15**.

The Danish group proposed the mechanism outlined in Scheme 8 to account for the stereochemical induction of the reactions. In a similar way to that illustrated in Scheme 6, it is postulated that both the α-imino ester **9**, in a bidentate fashion, and the silyl nitronate **15** would be coordinated to the copper centre. When the silyl nitronate **15** interacted with the Lewis acid, forming the starting complex **18**, the TMS group would dissociate from the nitronate to give **19**. This would allow a six-membered cyclic transition state for **19**, with a pentacoordinate copper centre, which would finally lead to **17**. This model can account for the catalytic activity and the diastereo- and enantioselectivity of the reaction.



Scheme 8. Proposed reaction mechanism for the aza-Henry reactions with silylnitronates.

Anderson's group reported a most general and efficient protocol for enantioselective nitro-Mannich coupling between alkyl, aryl and heterocyclic (*p*-methoxyphenyl)imines **20** (instead of the single α-imine ester **9** used by Jørgensen in this process) and trimethylsilyl nitropropanate **21**, catalysed by the chiral *t*Bu-BOX Cu^{II} **22** (Scheme 9).[28]



R	Yield (%)	*d.r.* (*anti*/*syn*)	*ee* (%)
Ph	84	>15:1	94
p-Cl-C_6H_4	84	>15:1	92
o-Cl-C_6H_4	79	8:1	73
2,6-diCl-C_6H_3	<5	n/a	n/a
4-CN-C_6H_4	82	>15:1	92
2-CN-C_6H_4	91	7:1	70
2-furyl	89	11:1	94
*c*Hex	88	>15:1	87
nC_5H_{11}	88	1:1	86

Scheme 9. Aza-Henry reaction catalysed by chiral *t*Bu-BOX Cu^{II} **22**.

Although this protocol, based on the use of silyl nitronate derivatives, requires prior derivatization of the nitro species, it uses the lowest reported loading of commercially

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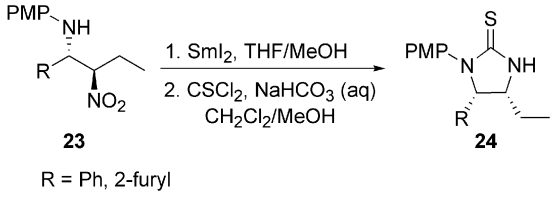
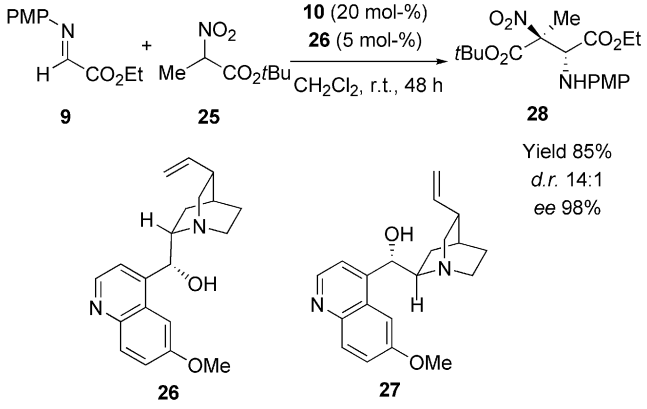
available metal catalyst and chiral ligand, giving rise to the highest yields and selectivities for such a broad substrate range, including aliphatic aldimines.

Determination of the absolute configurations was particularly difficult. To solve the problem, the authors converted two of the β-nitroamine products **23** into the corresponding thioimidazolidinones **24** by SmI_2 reduction[29] and treatment with thiophosgene (Scheme 10). The absolute configurations were determined by single-crystal X-ray analysis, with use of the sulfur as the heavy atom needed for accurate calculation of the Flack parameters.



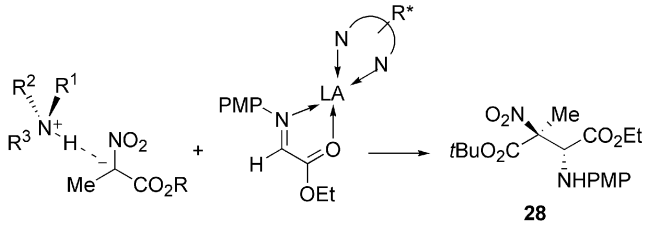
Scheme 10. Determination of absolute configurations.

More recently, Jørgensen and co-workers reported an approach to the formation of optically active quaternary centres by use of combinations of the chiral Lewis acid **10** and a series of cinchona alkaloids, including hydroquinine, quinidine, cinchonidine, quinine and the dimeric cinchona alkaloids $(DHQ)_2PHAL$ and $(DHQD)_2PHAL$. The best results with lower amounts (5 mol-%) of alkaloid were obtained with quinine **26** (Scheme 11).[30] This procedure led to compound **28** with *ee*s of up to 98% and a diastereomeric ratio of 14:1, in excellent yields. A mismatching effect was found between the previously used (*R*)-Ph-BOX ligand (catalyst **10**) and quinidine **27**, the pseudoenantiomer of quinine, which reduced the diastereomeric ratio to 8.5:1, although with a high enantioselectivity (96%) being maintained. In the presence of quinidine **27** and the enantiomeric ligand (*S*)-Ph-BOX (catalyst *ent*-**10**), on the other hand, the reaction afforded the opposite enantiomer – *ent*-**28** – in 8.5:1 ratio (–91% *ee*), thus demonstrating that the enantioselectivity of the process is governed solely by the chiral Lewis acid ligand.



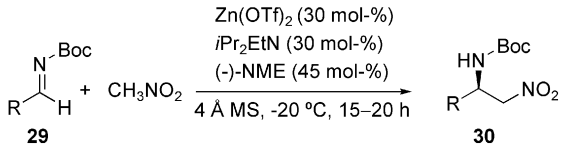
Scheme 11. Formation of optically active quaternary centres in aza-Henry reactions.

The authors envisioned a strategy for controlling the assembly of tertiary nucleophiles with electrophiles, in which a chiral Lewis acid catalyst activates the electrophile and organocatalytic activation of the nucleophile thereby generates a diastereomeric pair, which adds to the formed complex (Scheme 12).



Scheme 12. Dual chiral activation.

Palomo and co-workers have reported enantioselective aza-Henry reactions between nitromethane and *N*-Boc arylimines in the presence of the combination of $Zn(OTf)_2$, (–)-*N*-methylephedrine (NME) and Hünig's base, all commercially available, as an activating system for the reactions (Scheme 13).[31,32] It was observed that the presence of traces of moisture or protic contaminants in the reaction mixture were detrimental to the enantioselectivity. In this regard, the addition of molecular sieves (4 Å) was beneficial and gave the highest enantioselectivity in these aza-Henry reactions. A practical aspect of the method, although restricted to aromatic imines, is that a single recrystallization of the crude nitroamine from hexane and/or mixtures of ethyl acetate and hexane could provide products of increased enantiomeric purity.



R	Yield (%)	*ee* (%)
Ph	81	97
o-Me-C_6H_4	75	99
p-Me-C_6H_4	90	92
m-MeO-C_6H_4	80	90
p-MeO-C_6H_4	73	91
p-Cl-C_6H_4	97	96
p-F_3C-C_6H_4	98	92
m-NO_2-C_6H_4	59	90
p-NO_2-C_6H_4	65	87
p-MeO_2C-C_6H_4	78	94
1-Naphthyl	95	94
2-Naphthyl	70	93
3,5-diCl-4-MeO-C_6H_2	66	87

Scheme 13. Aza-Henry reactions catalysed by $Zn(OTf)_2$ and NME.

The elaboration of the obtained aza-Henry products into 1,2-diamines or into amino acids could be performed by known procedures.[32] Reduction of the nitro group in **30** led to the known monoprotected diamine **31**,[33] whereas Nef oxidation under the conditions described by Mioskow-

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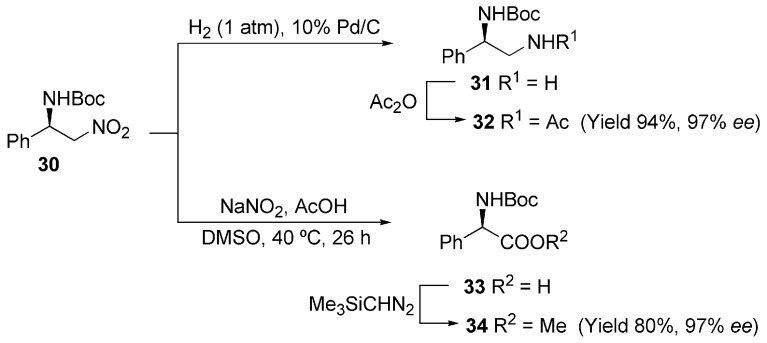
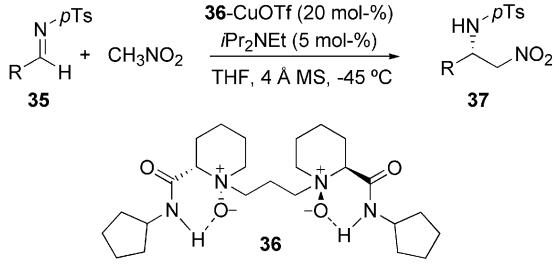


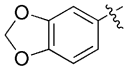
Scheme 14. Some transformations and determination of absolute configurations.

ski and co-workers[34] followed by methylation afforded the corresponding *N*-Boc-protected (*R*)-phenylglycine methyl ester **34** (Scheme 14).

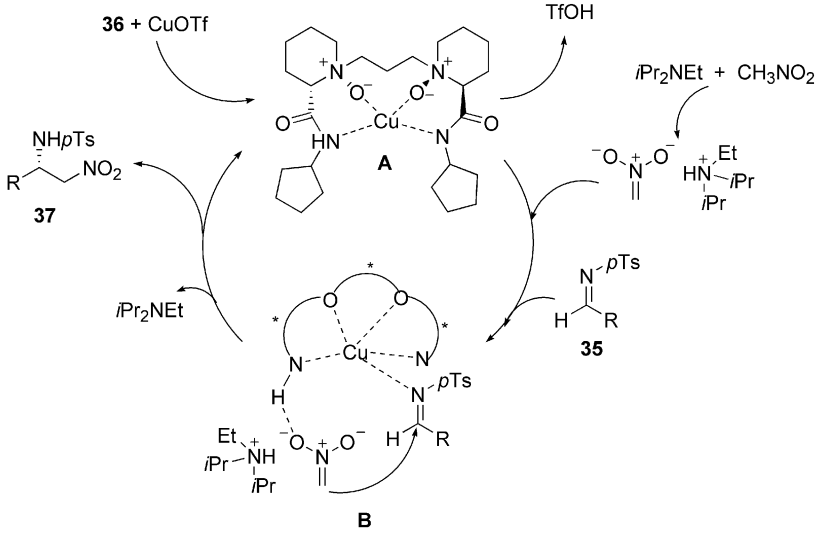
In 2007, Feng and co-workers found that the complex formed between copper(I) triflate and *N*,*N*-dioxide **36** functioned as an efficient catalyst for the addition of nitromethane to *N*-tosyl aldimines **35**. Aza-Henry reactions proceeded smoothly in the presence of catalytic amounts of Hünig's base to afford the corresponding nitroamines **37** in good yields and with high enantioselectivities (Scheme 15).[35] The catalytic system **36**·Cu^{I} was applied to various *N*-tosyl arylimines **35**, containing either an electron-donating substituent or an electron-withdrawing substituent, as well as heteroaryl imines, to afford the corresponding products in good yields and with high enantioselectivities.

The authors proposed a feasible reaction mechanism for this process. According to some experimental results and previous studies,[36] they assumed that complex **A**, generated in situ from the mixture of **36** and CuOTf, would be the active species.[37] After deprotonation of nitromethane by Hünig's base, both the imine and the nitronate should interact with the Cu complex, thus generating the complex **B**, in which the chiral catalyst would position the nitronate



R	*t* (h)	Yield (%)	*ee* (%)
Ph	57	90	91
1-naphthyl	22	88	86
2-naphthyl	57	80	93
p-Me-C_6H_4	70	81	93
m-Me-C_6H_4	64	96	92
o-Me-C_6H_4	87	79	89
p-MeO-C_6H_4	70	64	90
	87	63	89
2-furyl	32	89	84
p-Cl-C_6H_4	64	99	84

Scheme 15. Aza-Henry reactions catalysed by **36**·CuOTf.



Scheme 16. The catalytic cycle proposed for the **36**·CuOTf-catalysed reaction.

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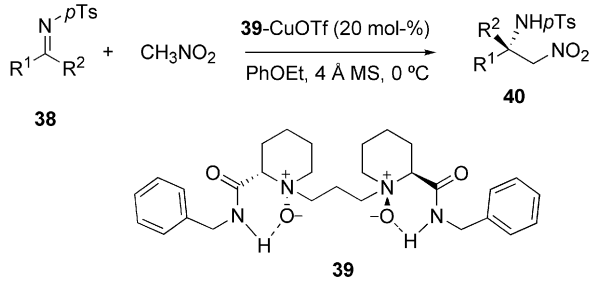
on the *Re* face of the imine, consistently with steric and electronic considerations. Addition of the nitronate to the imine followed by protonation should afford the product **37** and regenerate the catalyst as illustrated in the catalytic cycle depicted in Scheme 16.

The same catalytic system based on the chiral *N*,*N*′-dioxide copper complex formed between compound **39** and copper(I) triflate also catalysed the addition of nitromethane to ketimines **38** (Scheme 17).[38] Although the yields of the reaction were moderate, high values of enantioselectivity were obtained in the only reported catalytic asymmetric aza-Henry reactions with ketimines. In addition, the reactions could be performed with a range of substrates including aryl alkyl ketones and one dialkyl ketone.



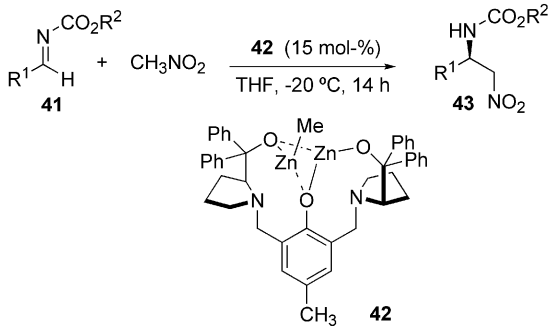
R^1	R^2	*t* (d)	Yield (%)	*ee* (%)
Ph	Me	5	39	88
o-F-C_6H_4	Me	5	50	91
p-F-C_6H_4	Me	5	48	92
p-Cl-C_6H_4	Me	5	58	93
m-Cl-C_6H_4	Me	5	70	96
p-Br-C_6H_4	Me	5	61	92
p-Me-C_6H_4	Me	5	21	90
p-MeO-C_6H_4	Me	10	30	88
o-MeO-C_6H_4	Me	10	44	87
m-MeO-C_6H_4	Me	10	49	85
Ph	Et	10	36	92
2-naphthyl	Me	10	47	88
2-furyl	Me	5	51	91
2-thienyl	Me	10	43	78
$PhCH_2CH_2$	Me	5	47	71
*c*Hex	Me	10	35	83

Scheme 17. Catalytic enantioselective aza-Henry reactions of ketimines.

Trost and co-workers reported the dinuclear zinc catalyst **42** as a catalyst for additions of nitroalkanes to carbamate-protected imines **41** (Scheme 18).[39] This catalyst had previously been used by Qian and co-workers in catalytic asymmetric aza-Henry reactions of *N*-tosyl imines.[40]

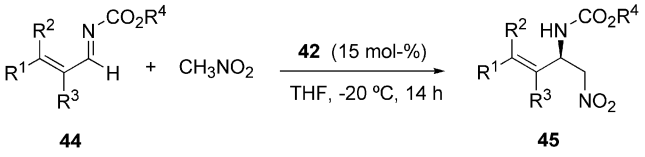
More interesting are the results obtained in the same work with α,β-unsaturated imines **44**, which proved to be a particularly useful class of substrate giving rise to the α-nitroamine products **45** in high enantiomeric excesses under the best reaction conditions (Scheme 19).

Although attempts to detail the reaction mechanism have not been undertaken, a useful cycle that explains the absolute stereochemistry of the products can be proposed



R^1	R^2	**42** (mol-%)	*T* (°C)	Yield (%)	*ee* (%)
Ph	*t*Bu	30	r.t.	67	91
Ph	Bn	30	r.t.	52	76
Ph	Me	30	r.t.	65	91
p-Me-C_6H_4	Me	30	r.t.	65	96
p-MeO-C_6H_4	*t*Bu	30	-20	65	75
2-furyl	*t*Bu	15	-20	82	92
2-thienyl	*t*Bu	30	-20	48	82
*t*Bu	Me	15	r.t.	58	89
$TBSOCH_2(CH_3)_2C$	Me	30	r.t.	66	91

Scheme 18. Aza-Henry reactions of aryl and alkyl imines **41**.



R^1	R^2	R^3	R^4	Yield (%)	*ee* (%)
Ph	H	H	Me	60	93
Ph	H	H	Bn	65	81
p-MeO-C_6H_4	H	H	Me	44	97
2-furyl	H	H	Me	58	93
Ph	Ph	H	Me	56	94
Ph	H	Me	Me	69	82

Scheme 19. Aza-Henry reactions of α,β-unsaturated imines **44**.

(Scheme 20). The initial step of this cycle involves deprotonation of nitromethane by catalyst **42** to give the zinc nitronate intermediate **A**. Binding of the imine in the orientation indicated then gives structure **B**, which can be attacked by the nitronate to give intermediate **C**. Although this scenario is consistent with the absolute stereochemistry of the product, an alternate scenario in which the nitronate adds directly to the unbound imine to give intermediate **C** is also plausible. Association of nitromethane followed by proton transfer then returns intermediate **A**, via a structure such as **D**, regenerating the active species and leading to the product of the reaction.

Very recently, Shibasaki and co-workers reported the utility of the homodinuclear Ni_2-Schiff base complex **47** in the preparation of α-quaternary *anti*-α-nitro-β-amino esters **48** through condensations between *N*-Boc imines **29** and *tert*-butyl nitroacetates (Scheme 21).[41] Very good to excellent *anti* selectivities were obtained with high enantiomeric

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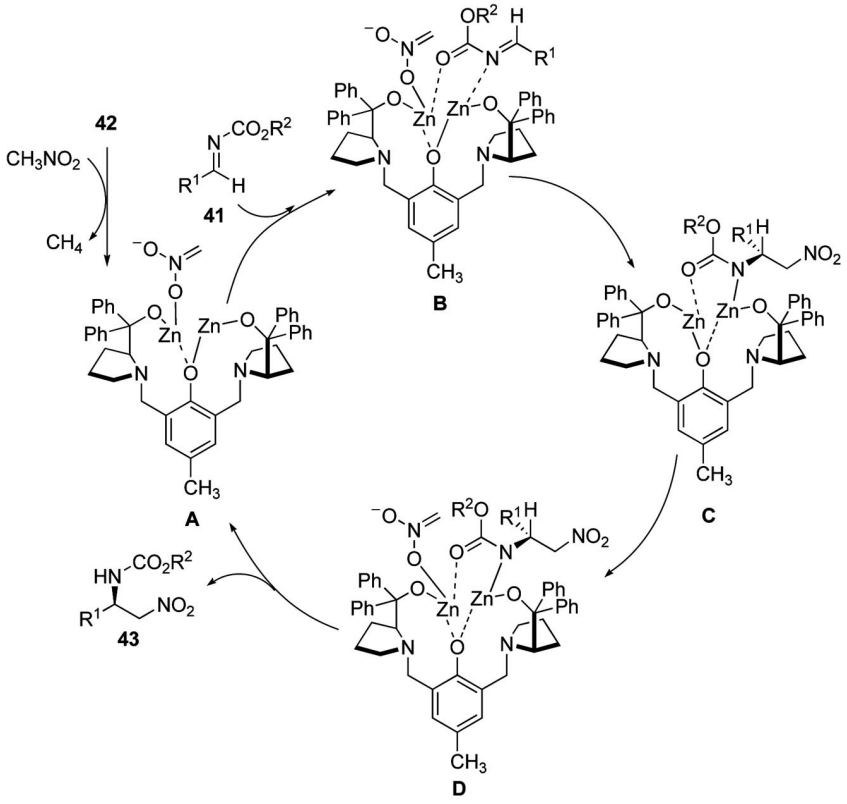
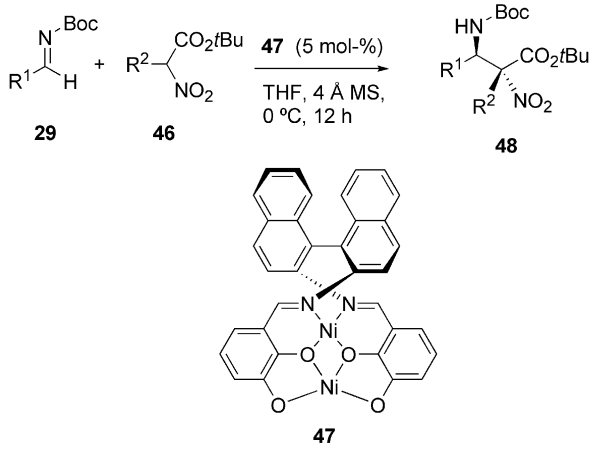
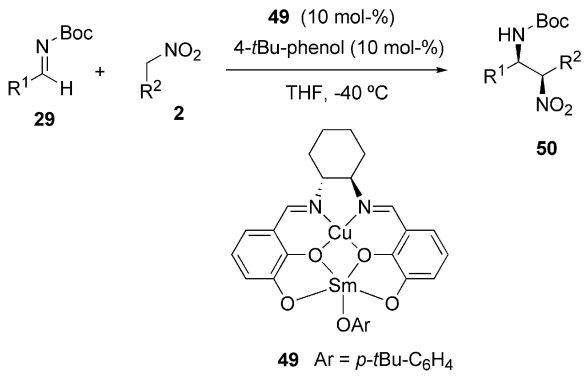


Scheme 20. Possible mechanism for aza-Henry reactions catalysed by **42**.



R^1	R^2	Yield (%)	*d.r.* (*anti/syn*)	*ee* (%)
Ph	Me	95	91:9	98
p-MeO-C_6H_4	Me	92	87:13	98
p-Me-C_6H_4	Me	90	89:11	97
p-Cl-C_6H_4	Me	87	86:14	97
p-F-C_6H_4	Me	91	90:10	91
3-thienyl	Me	96	91:9	99
Ph	Et	91	94:6	99
Ph	*n*Pr	92	92:8	>99
Ph	Bn	94	88:12	94

Scheme 21. Catalytic asymmetric aza-Henry reactions between nitroacetates **46** and *N*-Boc imines **29**.



R^1	R^2	*t* (h)	Yield (%)	*d.r.* (*anti/syn*)	*ee* (%)
Ph	Me	23	96	>20:1	94
2-naphthyl	Me	48	87	>20:1	93
p-Me-C_6H_4	Me	48	90	>20:1	98
m-Me-C_6H_4	Me	48	77	>20:1	96
p-MeO-C_6H_4	Me	48	87	>20:1	94
p-Cl-C_6H_4	Me	48	81	>20:1	90
2-furyl	Me	48	71	>20:1	91
$PhCH_2CH_2$	Me	48	62	>20:1	83
Ph	Et	44	84	>20:1	88
p-Me-C_6H_4	Et	48	68	>20:1	95
p-MeO-C_6H_4	Et	48	64	>20:1	91

Scheme 22. *syn*-Selective catalytic asymmetric aza-Henry reactions with *N*-Boc imines.

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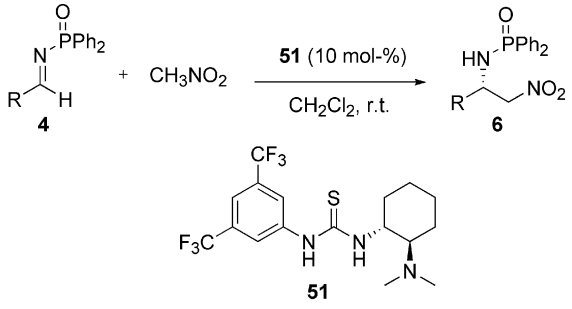
excesses for the *anti* adducts. Preliminary studies on the mechanism of the reaction suggested the importance of the two metal centres in the catalyst.

Shibasaki's group utilized the heterobimetallic Cu-Sn-Schiff base complex **49** with the same *N*-Boc imines **29** to obtain *syn* adducts **50** (Scheme 22). The reactions proceeded with good chemical yields and excellent *syn* selectivities and enantioselectivities when 4-*tert*-butylphenol (10 mol-%) was added as an additive. This work represented an important milestone in the field of the aza-Henry reactions because it was the first catalytic asymmetric approach in which *syn* adducts were obtained not only predominantly but as the only observed products.[42]

Organocatalytic Enantioselective Aza-Henry Reactions

Organocatalysis is an expanding area of research in asymmetric organic synthesis.[43] Catalysts of organic origin are an appealing option in comparison with the metal catalysts often used to achieve high enantio- and diastereoselectivities. In this sense, asymmetric nitro-Mannich reactions in the presence of organocatalysts have only recently begun to receive much attention.

The first organocatalytic aza-Henry reaction was reported by Takemoto and co-workers, who used the thiourea **51** as a bifunctional catalyst in the reactions of *N*-diphenylphosphinoyl imines **4** with an excess of nitromethane (Scheme 23).[44] The reactions were restricted to aromatic *N*-phosphinoyl imines; good yields and moderate enantioselectivities were obtained.



R	Yield (%)	*ee* (%)
Ph	87	67
p-Me-C_6H_4	72	63
p-Cl-C_6H_4	76	67
2-naphthyl	78	70
2-furyl	85	76
2-pyridyl	91	68
2-thienyl	57	64
cinnamyl	68	65

Scheme 23. Aza-Henry reactions catalysed by bifunctional thiourea **51**.

It has been reported that urea and thiourea moieties can interact with a variety of polar compounds such as nitro and related compounds through hydrogen bond interactions as illustrated in Figure 2.[45] This concept has already been applied to a variety of organic reactions,[46] in particular to asymmetric additions of malonates to nitroolefins, in the presence of the same bifunctional thiourea organocatalyst **51**, capable of acting as a base with a tertiary amino moiety and as a mild Brønsted acid with the two protons of the thiourea group.[47]

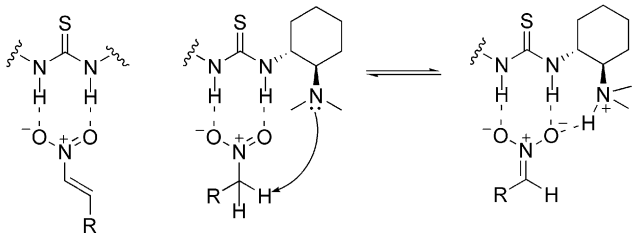


Figure 2. Working hypothesis for thiourea-based organocatalysis.

These authors envisioned that the same catalyst might also be exploited for the activation of a nitroalkane, through the initial coordination of the nitro group to the thiourea moiety and further intramolecular deprotonation through the dimethylamino functionality.

The enantiomeric excesses reported in Scheme 23 were considerably increased by the same Japanese group through the use of *N*-Boc aryl aldimines **29**. Moreover, not only nitromethane added with good chemical yields and enantioselectivities but so did several nitroalkanes bearing aryl, alcohol, ether and ester groups, thus demonstrating the versatility of the reactions. With substituted nitroalkanes the corresponding nitroamines were obtained with moderate to high *anti* selectivities and excellent enantioselectivities (Scheme 24).[48] The synthetic utility of this reaction was demonstrated by further preparation of substituted piperidines of biological interest from the obtained β-nitroamines.

An explanation of the high selectivities observed in the reaction might be provided by the formation of a ternary complex **C** of catalyst, imine and nitronate supported by hydrogen bonding interactions. The formation of this complex could be accounted for through two different routes as depicted in Scheme 25. In route *a* the thiourea catalyst would first activate the nitroalkane to form complex **A**, which after intra- or intermolecular deprotonation would generate the nitronate complex **B**. Further coordination of the imine would produce complex **C**. In route *b* the thiourea would coordinate to the imine to form complex **D**, which after coordination and deprotonation would give rise to **C**. Given the predominant formation of **C**, the corresponding *anti*-nitroamine should be obtained enantioselectively through an oriented attack of the nitronate moiety on the imine carbon.

Almost simultaneously with Takemoto's work, Johnston and co-workers reported the application of the chiral bisamidine triflate salt **53** as a catalyst for aza-Henry reactions of activated *N*-Boc imines **29** (Scheme 26).[49] The corresponding nitroamines **52** were obtained with moderate yields, very good *anti* selectivities and good enantioselectivities for both nitromethane and nitroethane.

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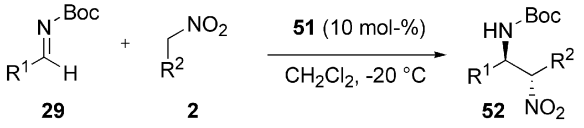
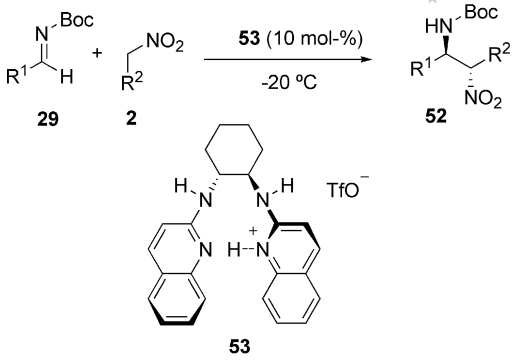


R^1	R^2	*t* (h)	Yield (%)	*d.r.* (*anti/syn*)	*ee* (%)
p-F-C_6H_4	H	24	80	-	98
p-Me-C_6H_4	H	24	82	-	93
p-MeO-C_6H_4	H	60	71	-	95
1-naphthyl	H	24	85	-	95
2-naphthyl	H	48	85	-	85
2-furyl	H	60	81	-	91
3-pyridyl	H	24	89	-	98
2-thienyl	H	24	83	-	83
p-F-C_6H_4	$PhCH_2$	24	94	97:3	95
p-Me-C_6H_4	$PhCH_2$	24	90	93:7	92
3-pyridyl	$PhCH_2$	24	93	83:17	93
2-furyl	Me	24	92	90:10	93
2-furyl	nC_5H_{11}	24	82	93:7	99
2-furyl	$PhCH_2$	24	84	83:17	97
2-furyl	$HOCH_2$	24	75	75:25	90
2-furyl	$BnOCH_2$	24	80	86:14	95
2-furyl	$BnO(CH_2)_2$	24	86	93:7	94
2-furyl	$BnO(CH_2)_3$	24	80	91:9	92
2-furyl	$HO(CH_2)_3$	24	80	92:8	89
2-furyl	$TfO(CH_2)_3$	24	78	93:7	90

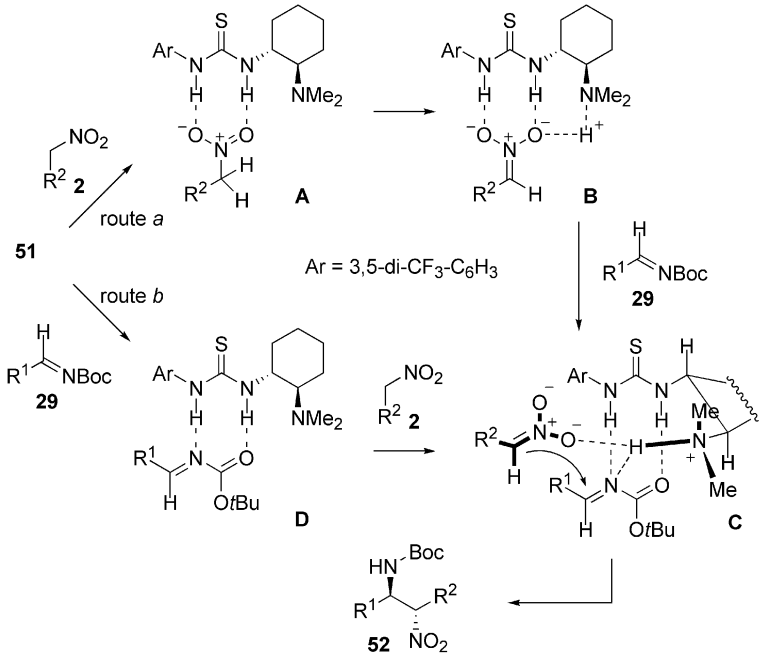
Scheme 24. Extended aza-Henry reactions catalysed by bifunctional thiourea **51**.



R^1	R^2	Yield (%)	*d.r.* (*anti/syn*)	*ee* (%)
Ph	H	57	-	60
p-NO_2-C_6H_4	H	61	-	82
m-NO_2-C_6H_4	Me	65	-	95
Ph	Me	69	14:1	59
p-CF_3O-C_6H_4	Me	53	19:1	81
p-Cl-C_6H_4	Me	59	17:1	82
m-NO_2-C_6H_4	Me	51	11:1	89
o-NO_2-C_6H_4	Me	62	7:1	82
p-CF_3-C_6H_4	Me	50	19:1	84
p-NO_2-C_6H_4	Me	60	7:1	90

Scheme 26. Chiral proton-catalysed aza-Henry reaction.

The similar catalyst **55a** was employed for the direct synthesis of α-quaternary *syn*-α-nitro-β-amino esters **56** through the enantioselective addition of α-alkyl-α-nitroesters to *N*-Boc aldimines **29** (Scheme 27).[50] Important structural differences were included in **55a** in order to ensure high *ee* values. Thus, the presence of the methoxy group in **55a** was crucial for the obtention of a more active bifunctional catalyst. The synergistic effect of catalyst and hindered nitroesters for providing high *syn*/*anti* stereoselectivity was demonstrated by achiral catalysis with Hünig's base, which proceeded with lower diastereoselectivity (<2:1 *dr*).



Scheme 25. Proposed mechanism for the aza-Henry reaction catalysed by thiourea **51**.

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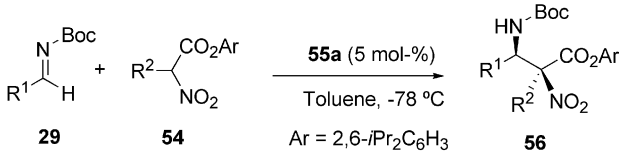
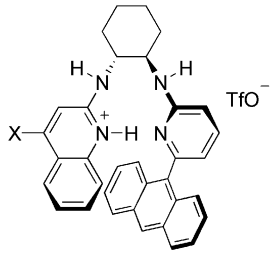


29 54 56



55a X = OMe
55b X = H

R^1	R^2	Yield (%)	*d.r.* (*syn*/*anti*)	*ee* (%)
p-Cl-C_6H_4	Et	83	>20:1	98
2-naphthyl	Et	80	>20:1	96
p-MeS-C_6H_4	Et	81	13:1	98
p-PhS-C_6H_4	Et	59	10:1	96
p-PhS-C_6H_4	Et	83	8:1	96
p-Me-C_6H_4	Et	61	>20:1	97
p-Me-C_6H_4	Et	80	>20:1	96
p-MeO-C_6H_4	Et	73	12:1	95
2-furyl	Et	86	5:1	94
p-Cl-C_6H_4	Me	82	12:1	99
p-Cl-C_6H_4	*n*Pr	82	15:1	97
p-Cl-C_6H_4	*n*Bu	88	16:1	97

Scheme 27. Chiral proton-catalysed additions of α-alkyl-α-nitroesters to *N*-Boc imines.

Catalyst **55b** was used for enantioselective additions of α-nitroesters to *N*-Boc arylaldimines followed by in situ reductive denitration, thus providing a convenient enantioselective approach to β-amino acids. The developed methodology was used for the asymmetric synthesis of the β-amino acid (+)-chaenorhine.[51]

The reaction illustrated in Scheme 27 was also catalysed by chiral ammonium betaine **57**, which acts as a bifunctional catalyst in the aza-Henry reaction. Both aromatic and aliphatic aldimines are suitable substrates for the reactions, which proceed with moderate *syn* selectivities but excellent enantioselectivities for both *syn* and *anti* adducts (Scheme 28).[52] Notably, catalyst **57** afforded the opposite enantioselectivity to catalyst **55a** and only 1 mol-% was necessary for achieving high enantiomeric excesses.

Jacobsen and co-workers found that thiourea **58** promoted stereoselective additions of nitroethane to aromatic *N*-Boc aldimines **29** to afford *anti*-nitroamines **59** with very good diastereoselectivities and excellent enantioselectivities (Scheme 29).[53] High enantioselectivities were obtained with a series of substituted benzaldimine derivatives bearing both electron-donating and electron-withdrawing substituents. Aromatic heterocyclic *N*-imines and 2-naphthaldehyde-derived imine underwent reactions with excellent enantioselectivities and provided products with synthetically useful levels of diastereoselectivity. When the reactions were extended to more sterically challenging secondary nitroalkanes, such as 2-nitropropane, it was necessary to add 2.0 equiv. of Hünig's base to promote the reaction. Under these conditions the corresponding adduct was obtained in 87% yield and 92% *ee*.

The bis-thiourea/BINAM-based catalyst **60** catalysed additions of nitroalkanes to *N*-Boc imines **29** (Scheme 30).[54] Moderate chemical yields and good enantioselectivities were obtained in the reactions, for which a model with catalyst **60** activating both the imine and the anion of the nitroalkane through hydrogen bonding was proposed.

Despite the remarkable levels of selectivity so far reported, these methods were restricted to non-enolizable aldehyde-derived imines. The isolation of *N*-carbamoyl imines derived from aliphatic enolizable aldehydes, for instance, had not been reported, because they readily tautomerize to the corresponding ene carbamates,[55] thus resulting in a considerable limitation to the generality of their applications. A possible way to overcome these drawbacks was the generation of the imine in situ through the use of a carbamate with a good leaving group at the carbon atom α to the nitrogen atom, as in the α-amido sulfones **61**. In this sense, Herrera, Bernardi and co-workers reported the first asymmetric aza-Henry reaction using *N*-carbamoyl imines generated in situ from α-amido sulfones **61** under phase-transfer conditions, using the commercially available *N*-benzyl quininium chloride **62** (Scheme 31).[56]

Several α-amido sulfones **61** derived from aromatic and heteroaromatic aldehydes were treated with nitromethane under optimized reaction conditions to furnish the corresponding optically active *N*-Boc β-nitroamines **63** with fairly good yields and enantiomeric excesses. The reactions also proved possible with enolizable linear and branched aldehyde-derived azomethine substrates; in all cases the corresponding β-nitroamines were obtained with very good yields and enantioselectivities. Finally, variation of the protecting group on the nitrogen atom was also briefly investigated with imines bearing Cbz moieties, thus demonstrating that this method is not restricted to *N*-Boc-protected β-nitroamines.

Simultaneously, Palomo and co-workers reported the same reaction with the same catalyst **62** but with a different base, extending the protocol to nitroethane (Scheme 32).[57]

In a more recent work, the same authors studied the reaction mechanism for this process using a combination of experimental observations and quantum calculations. The proposed catalytic cycle is outlined in Scheme 33.[58] The initially generated nitronate anion **64** is the actual base that promotes elimination of sulfinic acid from α-amido sulfones to provide the intermediate *N*-acyl imines (slow step), at which point a second molecule of nitonate anion **64** adds to the performed (in situ) imine (fast step) to provide the final product after protonation. In the same work, the authors achieved an important generalization of the phase-transfer-catalysed enantioselective aza-Henry reaction for a variety of nitroalkanes, thus allowing the preparation of γ-amino-α,β-unsaturated esters.

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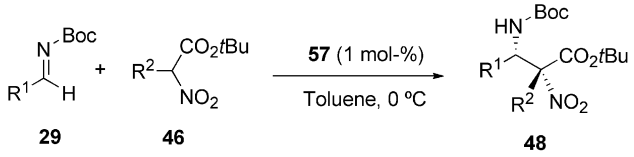
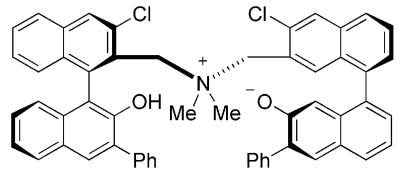
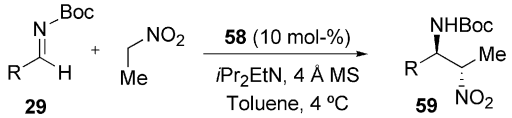
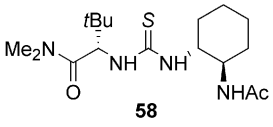




R^1	R^2	*t* (h)	Yield (%)	*d.r.* (*syn/anti*)	*ee* (%) *syn/anti*
p-Cl-C_6H_4	Me	8	>99	3.6:1	99/91
p-Br-C_6H_4	Me	6	96	3.8:1	99/92
p-MeO-C_6H_4	Me	9	96	5.0:1	99/72
p-MeO_2C-C_6H_4	Me	3	95	4.4:1	99/92
o-Me-C_6H_4	Me	10	91	5.2:1	98/93
2-furyl	Me	6	>99	4.4:1	99/96
1-naphthyl	Me	15	96	3.8:1	98/91
$PhCH_2CH_2$	Me	10	91	2.0:1	97/92
$CH_3(CH_2)_7$	Me	11	97	2.2:1	99/91
Ph	Et	24	93	3.2:1	99/87

Scheme 28. Chiral ammonium betaine-catalysed aza-Henry reactions.





R	Yield (%)	*d.r.* (*anti/syn*)	*ee* (%)
Ph	96	15:1	92
p-Cl-C_6H_4	98	7:1	95
m-Cl-C_6H_4	85	7:1	96
m-Cl-C_6H_4	99	2:1	93
p-Me-C_6H_4	90	12:1	96
m-Me-C_6H_4	99	9:1	95
p-(MeO)-C_6H_4	95	16:1	96
3-pyridyl	79	7:1	97
2-furyl	95	6:1	93
2-naphthyl	91	5:1	97

Scheme 29. Enantioselective organocatalytic additions of nitroethane to imines **29**.

Ricci and co-workers screened a variety of cinchona-based thiourea organocatalysts to promote additions of nitromethane to a variety of aromatic and heteroaromatic protected imines. Out of the several catalysts screened, thiourea **66** proved to be the most efficient. Several protecting groups on the nitrogen atom were tested, including *N*-Boc, *N*-Cbz and *N*-Fmoc groups. The corresponding products were obtained with good yields and enantioselectivities (Scheme 34).[59] The reaction appears to be tolerant with respect to the nature of the imine, and the benefits of catalyst **66** extend over a wide range of substrates. The good results obtained with the Cbz- and Fmoc-protected imines further confirm the tolerance of this catalytic reaction to different *N*-carbamoyl protecting groups.

Using the same kind of cinchona catalysts, Schaus and co-workers reported that hydroquinine-derived thiourea catalyst **69** promoted aza-Henry reactions between nitroalkanes and *N*-carbamoyl imines, affording β-nitroamines in good yields and with very good enantioselectivities (Scheme 35).[60] The reactions were found to be successful with both electron-rich and electron-poor carbamoyl imines; as a major innovation nitroethane was used, resulting in excellent diastereo- and enantioselectivities.

Recently, Ellman and co-workers have reported the *N*-sulfinyl urea **71** as a new class of organocatalyst, the effectiveness of which was demonstrated by performing aza-Henry reactions with high selectivities, including the first example of enantioselective H-bonding-catalysed additions to aliphatic *N*-Boc imines **29** (Scheme 36).[61] Excellent enantioselectivities were observed with imines bearing both electron-rich and electron-poor aromatic substituents. More significantly, aliphatic *N*-Boc imines were found to be effective substrates yielding hitherto unreported compounds. High diastereoselectivities and enantioselectivities were also achieved in the additions to unbranched and β-branched imine substrates. Notably, the obtained products were the enantiomers of those obtained from α-amido sulfones upon catalysis with **62**.

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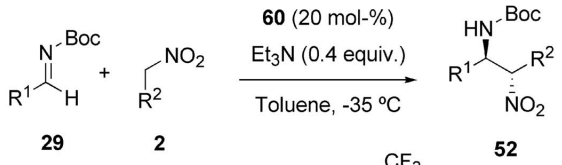
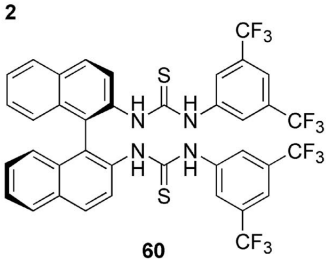
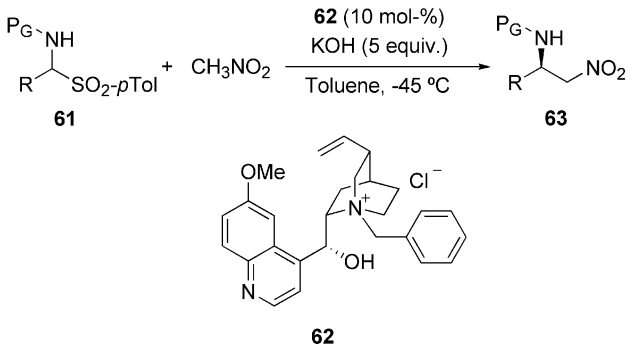




R^1	R^2	*t* (h)	Yield (%)	*ee* (%) (*syn*/*anti*)
Ph	H	36	55	86
p-Cl-C_6H_4	H	15	62	85
m-Cl-C_6H_4	H	15	53	91
o-Cl-C_6H_4	H	15	61	74
p-Br-C_6H_4	H	24	50	78
p-MeO-C_6H_4	H	36	50	89
o-MeO-C_6H_4	H	36	40	65
p-Me-C_6H_4	H	36	48	86
1-naphthyl	H	36	65	85
3-pirydyl	H	22	63	81
Ph	Me	36	59	70 (77:23)
Ph	Et	36	63	80 (80:20)

Scheme 30. Aza-Henry reactions of *N*-Boc imines **29** catalysed by bis-thiourea **60**.



R	P_G	*t* (h)	Yield (%)	*ee* (%)[a]
Ph	Boc	40	95	84 (>99)
o-Br-C_6H_4	Boc	64	70	76
p-(MeO)-C_6H_4	Boc	60	75	88 (>99)
1-naphthyl	Boc	44	95	84
2-furyl	Boc	25	81	75
$PhCH_2CH_2$	Boc	40	98	95
*c*Hex	Boc	42	84	98
*i*Pr	Boc	40	95	95
Et	Boc	40	92	94
Me	Boc	43	86	92
Ph	Cbz	44	53	73
*c*Hex	Cbz	40	96	93

[a] The number in parentheses refers to the product after a single recrystallization.

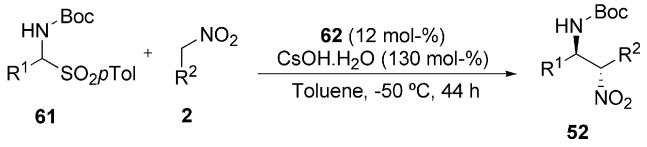
Scheme 31. Aza-Henry reactions with *N*-carbamoyl imines generated in situ.

Chang and co-workers developed a new class of bifunctional oxazoline-derived thioureas **72**, which served as efficient organocatalysts for asymmetric aza-Henry reactions between nitroalkanes and *N*-Boc aryl aldimines (Scheme 37).[62]

The authors envisaged that the combination of the oxazoline moiety with the thiourea may promote the asymmetric aza-Henry reactions as a bifunctional catalyst, because after the classical activation of the nitronate by the thiourea unit the neighbouring endocyclic oxazoline nitrogen atom might induce deprotonation in a way similar to that exerted by the dimethylamino group in the thiourea developed by Takemoto and co-workers (Figure 3).

The results showed that, in general, the reactions took place efficiently (68–97% yields) with high levels of enantioselectivity (74–92% *ee*s) for *N*-Boc phenyl imines bearing either electron-donating or electron-withdrawing substituents.

A different chiral bifunctional thiourea organocatalyst bearing a glycosyl scaffold and a tertiary amino group was reported by Zhou and co-workers (Scheme 38).[63] As shown in Scheme 38, the bifunctional thiourea **73** proved to be an effective organocatalyst for asymmetric aza-Henry reactions between *N*-Boc imines and nitromethane, afford-



R^1	R^2	Yield (%)	*ee* (%)
$PhCH_2CH_2$	H	83	96
Et	H	80	96
*n*Pr	H	78	94
*n*Hex	H	78	98
$(CH_3)_2CHCH_2$	H	75	97
*i*Pr	H	81	95
*c*Hex	H	77	98
Ph	H	79	91
p-MeO-C_6H_4	H	82	91
p-Cl-C_6H_4	H	79	80 (96)[a]
p-F_3C-C_6H_4	H	80	82 (90)[a]
m-NO_2-C_6H_4	H	72	83 (90)[a]
1-naphthyl	H	81	90 (94)[a]
2-furyl	H	72	84
$PhCH_2CH_2$	Me	85	91 (90:10)[b]
Ph	Me	88	94 (93:7)[b]
p-MeO-C_6H_4	Me	87	90 (95:5)[b]
p-Cl-C_6H_4	Me	88	98 (75:25)[b]

[a] The number in parentheses refers to the product after a single crystallization from hexane. [b] Diastereoselective ratio.

Scheme 32. Asymmetric aza-Henry reactions under phase-transfer catalysis conditions.

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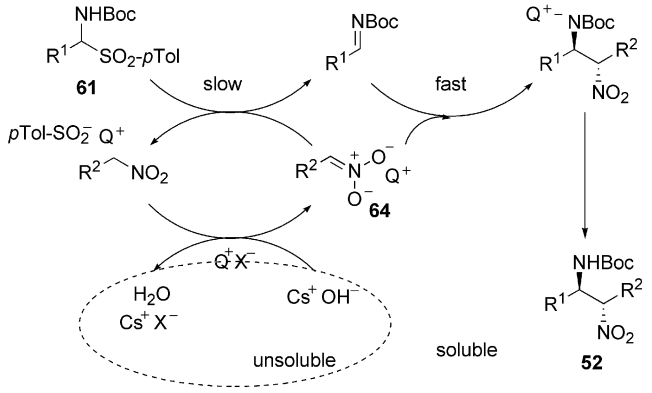
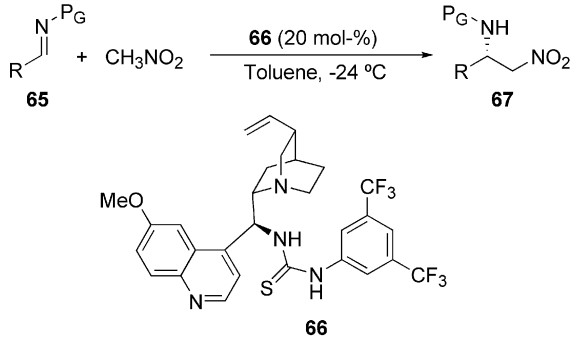


Scheme 33. General mechanism for the aza-Henry reaction involving α-amido sulfones under phase-transfer conditions.

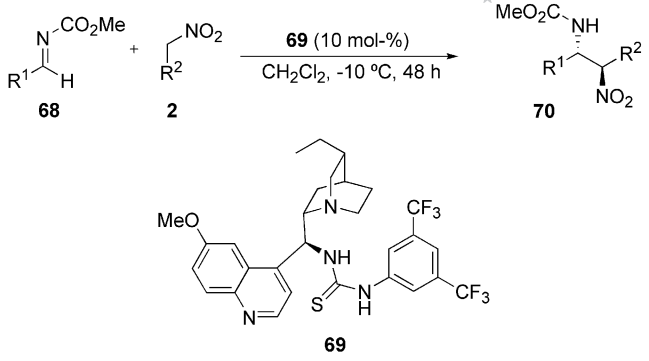


R	P_G	*t* (h)	Yield (%)	*ee* (%)
Ph	Cbz	22	64	84
Ph	Fmoc	43	60	90
Ph	Boc	18	72	88
1-naphthyl	Boc	20	87	88
2-naphthyl	Boc	23	95	85
p-Cl-C_6H_4	Boc	68	77	94
p-Cl-C_6H_4	Cbz	45	58	90
m-Br-C_6H_4	Boc	24	66	80
p-MeO-C_6H_4	Boc	45	65	82
2-thienyl	Boc	40	50	82
2-furyl	Boc	40	70	42

Scheme 34. Asymmetric aza-Henry reactions catalysed by thiourea **66**.

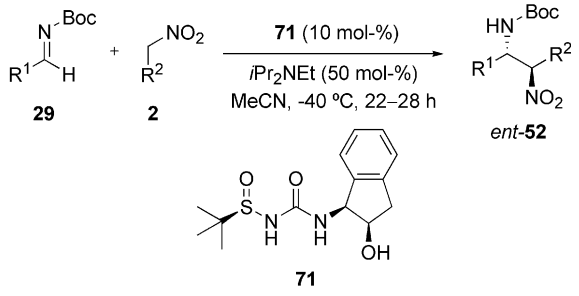
ing the corresponding adducts in good to excellent yields and with excellent enantioselectivities in acceptable reaction times. Excellent enantioselectivities were obtained and in most cases almost perfect enantiocontrol was achieved. In addition, reactions of nitroethane, not shown in the scheme, also proceeded smoothly with excellent enantioselectivities, albeit with low to good diastereoselectivities.

Simple aza-Henry reactions between *N*-Boc imines **29** and α-nitroesters **74**, catalysed by bifunctional thiourea **75**, have been reported very recently by Li, Chen and co-workers. Good diastereomeric ratios in favour of *anti* isomers and excellent enantioselectivities were obtained with the addition of 10 mol-% of catalyst (Scheme 39).[64] Al-



R^1	R^2	Yield (%)	*d.r.* (*anti*/*syn*)	*e.r.* (%)
Ph	H	91	93:7	---
m-Me-C_6H_4	H	98	91:9	---
m-F-C_6H_4	H	98	98:2	---
cinnamyl	H	80	90:10	---
2-furyl	H	60	92:8	---
2-furyl-propenyl	H	97	98:2	---
Ph	Me	96	94:6	100:0
m-Me-C_6H_4	Me	98	97:3	90:10
m-F-C_6H_4	Me	98	91:9	97:3
cinnamyl	Me	80	90:10	92:8
2-furyl	Me	73	97:3	82:18
2-furyl-propenyl	Me	90	97:3	83:17

Scheme 35. Asymmetric nitro-Mannich reactions catalysed by thiourea **69**.



R^1	R^2	Yield (%)	*d.r.* (*anti*/*syn*)	*ee* (%)
Ph	Me	84	85:15	95
p-MeO-C_6H_4	Me	64	90:10	95
p-Me-C_6H_4	Me	68	79:21	95
p-CF_3-C_6H_4	Me	92	77:23	92
o-Cl-C_6H_4	Me	88	80:10	94
2-naphthyl	Me	80	84:16	93
*n*Bu	Me	80	92:8	96
*i*Bu	Me	76	93:7	96
*i*Bu	Bn	62	88:12	96
*i*Bu	H	64	-	95

Scheme 36. Aza-Henry reactions catalysed by sulfinyl urea **71**.

though the reactions showed a good scope, hindered substrates afforded lower yields or even no reaction, as in the case of $R^1 = R^2 = Ph$.

The similar bifunctional thiourea **77** has been reported by Wang and co-workers to catalyse aza-Henry reactions between *N*-Boc imines and nitroalkanes. In the case of sub-

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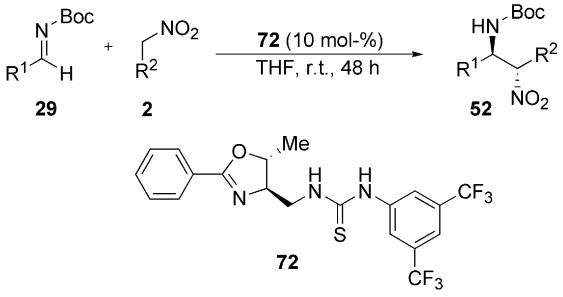


R^1	R^2	Yield (%)	*ee* (%)
Ph	H	93	88
o-Me-C_6H_4	H	84	90
p-Me-C_6H_4	H	93	74
m-MeO-C_6H_4	H	86	78
p-MeO-C_6H_4	H	92	88
p-Cl-C_6H_4	H	95	92
p-CF_3-C_6H_4	H	97	83
m-NO_2-C_6H_4	H	75	89
p-NO_2-C_6H_4	H	68	80
Ph	Me	94	87 (2.5:1)[a]
Ph	Et	93	90 (3.2:1)[a]

[a] Values in parentheses indicate *anti/syn* ratio.

Scheme 37. Aza-Henry reactions of *N*-Boc imines **29** catalysed by **72**.

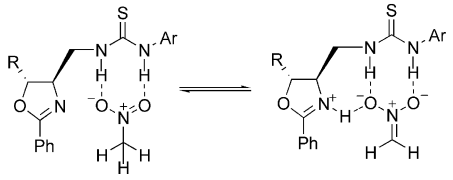
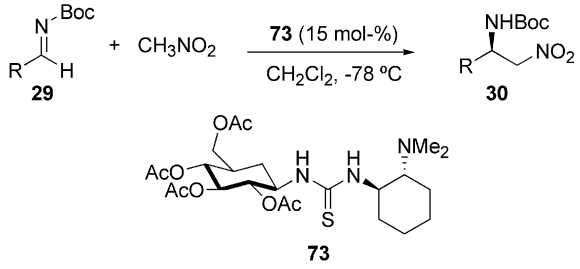
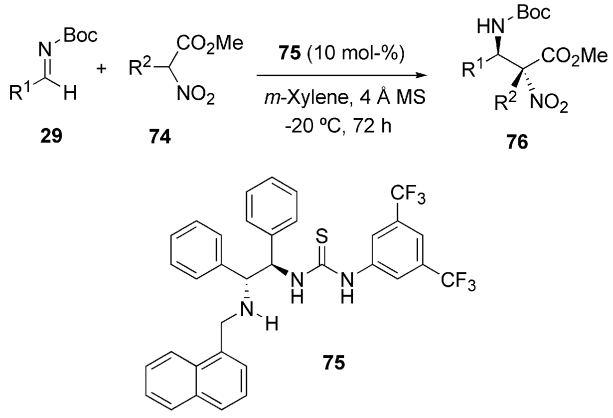


Figure 3. Catalytic activation of nitroalkanes by thiourea **72**.



R	*t* (h)	Yield (%)	*ee* (%)
Ph	60	86	>99
p-MeO-C_6H_4	66	94	94
p-Me-C_6H_4	68	93	83
p-Cl-C_6H_4	60	93	>99
m-F-C_6H_4	39	87	>99
p-F-C_6H_4	65	91	>99
o-Cl-C_6H_4	42	85	92
1-naphthyl	65	95	>99
2-furyl	62	86	90
p-CF_3-C_6H_4	64	85	94
o-CF_3-C_6H_4	61	84	96

Scheme 38. Thiourea **73** catalyses asymmetric additions of nitromethane to *N*-Boc imines **29**.



R^1	R^2	Yield (%)	*d.r.* (*anti/syn*)	*ee* (%)
Ph	Me	86	17.2:1	96
p-F-C_6H_4	Me	78	9.8:1	96
m-Cl-C_6H_4	Me	83	10.4:1	95
o-Cl-C_6H_4	Me	79	7.9:1	91
p-Me-C_6H_4	Me	86	14.3:1	96
m-Me-C_6H_4	Me	85	17:1	94
2-furyl	Me	85	8.5:1	95
2-thienyl	Me	75	3.8:1	91
Ph	$PhCH_2$	68	7.6:1	93
Ph	*i*Pr	38	5.4:1	96
Ph	Ph	----	------	-----

Scheme 39. Aza-Henry reactions between α-substituted nitroacetates **74** and *N*-Boc imines.

stituted nitro compounds, excellent *anti* selectivities were observed. In all cases, very high enantioselectivities were also obtained. The reaction showed a broad scope for a variety of aromatic aldimines; additionally, an isobutyl imine gave rise to the expected adduct with an excellent yield and *ee* (Scheme 40).[65]

Rueping and co-workers have reported for the first time the development of new direct Brønsted-acid-catalysed diastereo- and enantioselective nitro-Mannich reactions between α-imino esters and diverse nitroalkanes, providing valuable β-nitro-α-amino esters (Scheme 41).[66] This process represents the first example of direct enantioselective Brønsted-acid-catalysed activation of nitroalkanes and allows the desired amino acid esters to be isolated in good yields and with excellent enantioselectivities with the widest substrate scope of nitroalkanes to date.

The authors postulated a plausible reaction mechanism in which they assume that the chiral Brønsted acid **79** plays a bifunctional role (Scheme 42). On the one hand, the α-imino ester **78** would be activated by protonation, resulting in the formation of the chiral ion pair **A**. It can be assumed that the adjustment of the nitroalkane/nitronate equilibrium should also be accelerated by **79**. The addition of the nitronate **81** to the activated imino ester **A** could then occur via the intermediate **B**, in which the chiral bifunctional BINOL-phosphate would act simultaneously as a Brønsted acid and as a Lewis base, resulting in regeneration of catalyst **79** and formation of the desired amino ester **80**.

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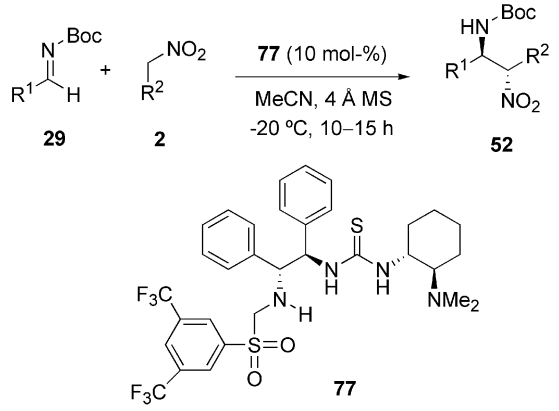
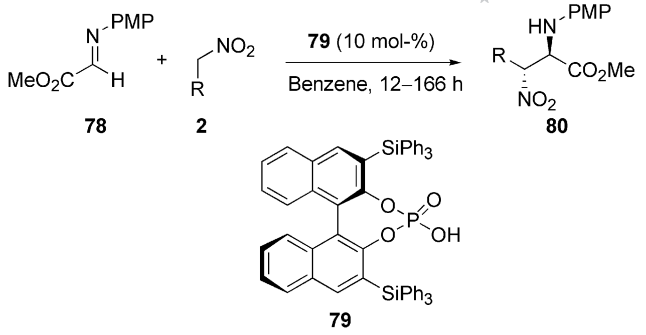


R^1	R^2	Yield (%)	*d.r.* (*anti/syn*)	*ee* (%)
Ph	H	97	-----	99
p-Me-C_6H_4	H	88	-----	99
p-MeO-C_6H_4	H	85	-----	99
o-MeO-C_6H_4	H	94	-----	99
p-Cl-C_6H_4	H	93	-----	99
o-Cl-C_6H_4	H	90	-----	99
p-F-C_6H_4	H	91	-----	99
p-CF_3-C_6H_4	H	96	-----	99
2-naphthyl	H	89	-----	97
1-naphthyl	H	98	-----	99
2-furyl	H	99	-----	96
3-pyridyl	H	91	-----	99
*i*Bu	H	99	-----	98
Ph	Me	92	97:3	99
p-Me-C_6H_4	Me	90	96:4	98
p-MeO-C_6H_4	Me	95	98:2	98
o-MeO-C_6H_4	Me	88	97:3	99
p-Cl-C_6H_4	Me	93	96:4	96
o-Cl-C_6H_4	Me	97	97:3	99
2-naphthyl	Me	91	97:3	97
2-furyl	Me	93	94:6	96
3-pyridyl	Me	88	96:4	99
Ph	Et	94	99:1	99
p-Me-C_6H_4	Et	99	97:3	99
p-MeO-C_6H_4	Et	93	99:1	98
Ph	Bn	95	99:1	99
*i*Bu	Me	93	93:7	97

Scheme 40. Additions of nitroalkanes to *N*-Boc imines.

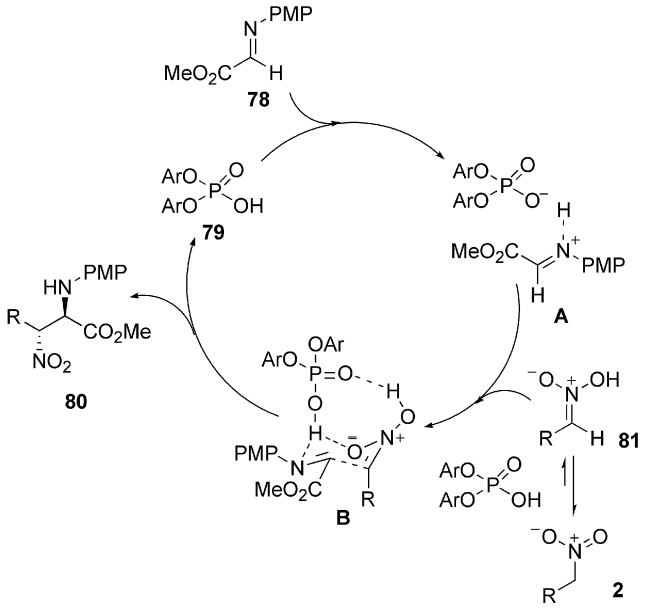
Wulff and co-workers reported that the novel BINAM-based thiourea catalyst **60** was an effective catalyst for promoting reactions between *N*-Boc aromatic aldimines **29** and nitroalkanes **2** (Scheme 43).[67] The corresponding β-nitroamines **52** were obtained in moderate yields and with good enantioselectivities.

The authors proposed a model for the catalyst action in which both components of the reaction – imine and nitronate anion – are activated simultaneously by hydrogen bonding interactions. According to this model, illustrated in Figure 4, one of the thiourea units interacts with the imine through two hydrogen bonds while the other thiourea group interacts simultaneously with the anion of nitromethane through hydrogen bonds to each of the oxygen atoms of the nitronate anion.



R	Yield (%)	*d.r.* (*anti/syn*)	*e.r.*
Et	64	9:1	96:4
Me	61	10:1	96:4
nC_5H_{11}	65	9:1	96:4
$PhCH_2$	93	13:1	94:6
p-Br-$C_6H_4CH_2$	84	11:1	93:7
p-MeO-$C_6H_4CH_2$	73	13:1	94:6
2-thienyl-CH_2	69	13:1	92:8
$PhCH_2CH_2CH_2$	57	7:1	96:4
p-Me-C_6H_4	64	2:1	92:8

Scheme 41. Scope of the enantioselective aza-Henry reactions catalysed by **79**.



Scheme 42. Proposed reaction mechanism for aza-Henry reactions catalysed by **79**.

Conclusions

Enantioselective aza-Henry reactions represent a powerful and direct method for preparing enantiomerically pure organic compounds containing two vicinal nitrogenated functionalities. The reactions form carbon–carbon bonds both stereo- and enantioselectively, with good to excellent yields and enantioselectivities when appropriate catalysts are used. The factors that determine the courses of the reac-

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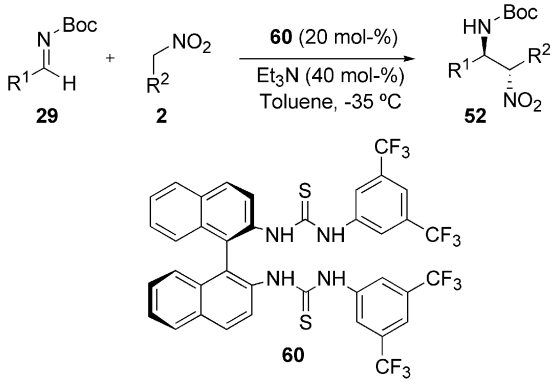

R^1	R^2	*t* (h)	Yield (%)	*ee* (%)
Ph	H	36	55	86
p-Cl-C_6H_4	H	15	62	85
m-Cl-C_6H_4	H	15	53	91
o-Cl-C_6H_4	H	15	61	74
p-Br-C_6H_4	H	24	50	78
p-MeO-C_6H_4	H	36	50	89
o-MeO-C_6H_4	H	36	40	65
p-Me-C_6H_4	H	36	48	86
1-naphthyl	H	36	65	85
3-pyridyl	H	22	63	81
Ph	Me	36	59	70
Ph	Et	36	63	80

Scheme 43. Aza-Henry reactions catalysed by bis-thiourea **60**.

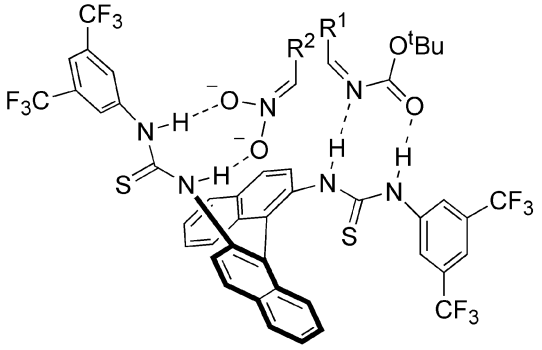

Figure 4. Proposed activation model for catalyst **60**.

tions and the structures of the obtained β-nitroamines are well understood. The reactions are equally facile when aryl and alkyl aldimines are used, and *anti* β-nitroamines were obtained predominantly when substituted nitroalkanes were used, even though recent reports by Shibasaki[42] and Johnston[50] have shown that it is also possible to obtain *syn* adducts. Several protecting groups at the nitrogen atom are also usable, thus facilitating further chemoselective transformations. The reactions utilize several types of catalyst with equal effectiveness. The directness of the reactions, the generality of the catalysts that can be used, which permits great flexibility in selection of ligands, and the versatility of the reactions, which provide for a variety of substrates, are enormous and impressive advantages that should facilitate access both to α-amino acids and to 1,2-diamines for biological studies and synthetic applications. In spite of these advantages the bulk of reported aza-Henry reactions involve aldimines. Only the work of Feng and co-workers, illustrated in Scheme 17,[38] refers to the catalytic enantioselective approach with ketimines. In addition, there are, to the best of our knowledge, only two reports concerning catalytic non-asymmetric aza-Henry reactions with ketimines. The first one involved the acetic acid-promoted addition of lithium propanate or the Lewis acid-catalysed addition of trimethylsilyl nitropropanate to the ketimine derived from acetone;[68] the second one reported sodium carbonate-catalysed additions of nitromethane to aldimines derived from arylmethyl ketones.[69] In addition, two excellent enantioselective approaches based on the use of chiral nonracemic *N*-sulfinylimines were reported by García-Ruano and co-workers[70] and by Terada and co-workers.[71] It is obvious that the use of ketimines should give access to a number of interesting compounds bearing quaternary centres, which would increase their importance if they could be prepared in a more efficient way by catalytic enantioselective approaches.

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