Double Catalytic Activation with Chiral Lewis Acid and Amine Catalysts

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An effective enantioselective synthetic method based on a new concept of double catalytic activation has been developed, in which both electrophile and nucleophile precursors are activated by use of catalytic amounts of chiral Lewis acid and amine base, respectively. This method has been successfully applied to enantioselective thiol conjugate additions, as well as to Michael reactions of malononitrile, nitromethane, and cyclic 1,3-dicarbonyl compounds in the presence of DBFOX/Ph – nickel(II) aqua complexes with amines. This new method should be a powerful tool, especially when single catalytic activation of either nucleophiles or electrophiles is not sufficient to induce bond formation.

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1. New Concept

Ionic carbon−carbon bond formation involves the nucleophilic attack of nucleophiles on electrophiles. In many cases, nucleophile precursors are used together with base mediators that work to generate nucleophiles through abstraction of acidic hydrogen atoms in nucleophile precursors. This is a general activation pattern of base-mediated carbon−carbon bond-forming reactions. On the other

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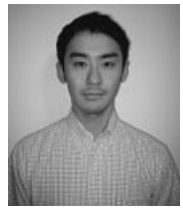

Kennosuke Ito was born in Fukuoka city in 1975. After completing the undergraduate course in Meiji Pharmaceutical University between 1994 and 1998, he moved to Kyushu University as a graduate student (1998−2003). He received the Ph.D. degree in 2003 from Kyushu University under the supervision of Professor Shuji Kanemasa. He is currently pursuing postdoctoral study at North Dakota State University in the research group of Professor Mukund P. Sibi. His research interests are directed toward the development of new synthetic methods and novel catalysis.

MICROREVIEWS: This feature introduces the readers to the author's research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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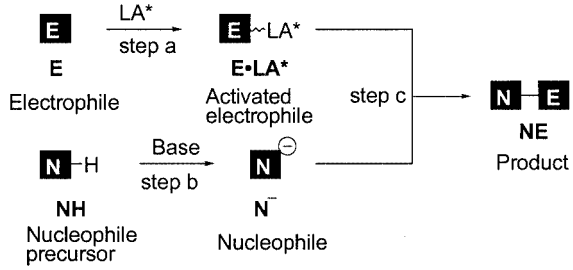
hand, electrophiles can also be activated by coordination of a Lewis acid, through lowering of their LUMO levels, and this is a general activation pattern of Lewis acid-mediated carbon−carbon bond-forming reactions. When a chiral Lewis acid is employed, enantiomers are produced; most catalyzed enantioselective reactions are based on this activation method.

It often happens that reactivity is not high enough to make bond formation possible through the single activation either of nucleophiles or of electrophiles in cases of base- or Lewis acid-mediated carbon−carbon bond-forming reactions. The coordination of a chiral Lewis acid (**LA***) to electrophiles (**E**) as shown in step "a", for example, or the deprotonation of nucleophile precursors (**NH**) with an amine base as shown in step "b" is not always effective to activate the reactions (Scheme 1). One possible solution would be a *double activation* (DA)[1] method in which both electrophiles and nucleophile precursors were activated separately by Lewis acid and base, respectively, as shown in step "c". *A double catalytic activation* (DCA)[2] method using catalytic amounts of both acidic and basic mediators should be economically more useful, especially in the case of enantioselective synthetic reactions under DCA conditions with chiral Lewis acid catalysts.



Scheme 1. Concept of enantioselective double catalytic activation

We have recently reported the successful achievement of a new enantioselective DCA method.[3] In this microreview we describe highly effective enantioselective conjugate addition reactions of thiols, Michael reactions of malononitrile and nitromethane, and enantioselective enol lactone synthesis under the DCA conditions.

2. Selection of Chiral Lewis Acid Catalysts

A serious problem might be expected in reactions under DA or DCA conditions with both a Lewis acid and a base in the same flask. Strong binding of the base to the Lewis acid would be highly likely, causing serious deactivation of both the Lewis acid and the base catalysts. Nevertheless, unusual activation of some Lewis acid catalysts in the presence of some Lewis bases is now known.[4] Selection of appropriate Lewis acid catalysts is therefore of crucial importance for success. Cationic late transition metals or their complexes were our choice.

We were pleased to find unique catalysis by chiral complexes derived from 4,6-dibenzofurandiyl-2,2′-bis(2-phenyloxazoline), designated from now on as DBFOX/Ph, and a variety of late transition metal salts.[5] The cationic nickel(II) aqua complex DBFOX/Ph·NiX_2·nH_2O **A**, where X is a less coordinating anion, such as ClO_4, BF_4, SbF_6, and so on, is a typical example (Figure 1). A variety of DBFOX/Ph cationic complexes derived from magnesium salts and from other transition metal salts (Mn^{II}, Fe^{II}, Co^{II}, Cu^{II}, and Zn^{II}) were found to show high and efficient catalytic activity in Diels-Alder reactions between cyclopentadiene and

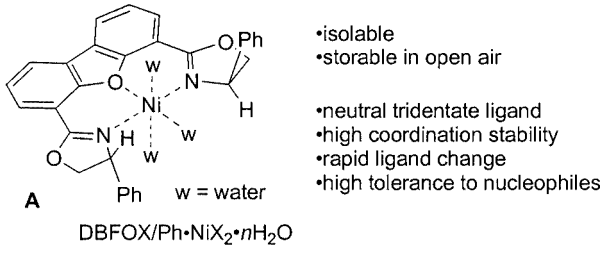
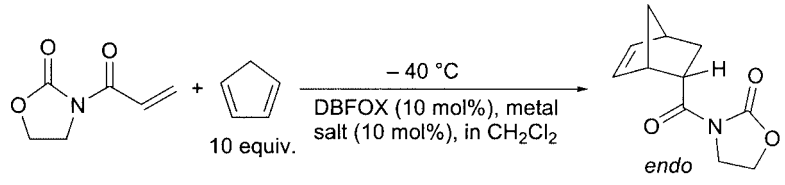


Figure 1. Nickel(II) aqua complex of a DBFOX/Ph ligand

Table 1. DBFOX/Ph complexes of metal salts in asymmetric Diels−Alder reactions − anhydrous complexes vs. aqua complexes



Metal salts	*endo*/*exo*	Yield (%)	*ee* (%)	Metal salts	*endo*/*exo*	Yield (%)	*ee* (%)
$Mg(ClO_4)_2$	97:3	quant.	91 (>99)[a]	$Mg(ClO_4)_2$+$3H_2O$	96:4	68	48
$MnBr_2$+$2AgClO_4$	95:5	95	79	$Mn(ClO_4)_2$·$6H_2O$	97:3	91	83
$FeCl_2$+$2AgClO_4$	99:1	90	98	$Fe(ClO_4)_2$+$3H_2O$	98:2	92	97
$CoBr_2$+$2AgClO_4$	97:3	quant.	93	$Co(ClO_4)_2$·$6H_2O$	97:3	97	99
$NiBr_2$+$2AgClO_4$	95:5	quant.	96	$Ni(ClO_4)_2$·$6H_2O$	97:3	96	>99
$CuCl_2$+$2AgClO_4$	96:4	97	92	$Cu(ClO_4)_2$·$6H_2O$	98:2	95	95
ZnI_2+$2AgClO_4$	98:2	99	97	$Zn(ClO_4)_2$·$6H_2O$	98:2	97	97

[a] One equiv. of DBFOX/Mg $(ClO_4)_2$ was used.

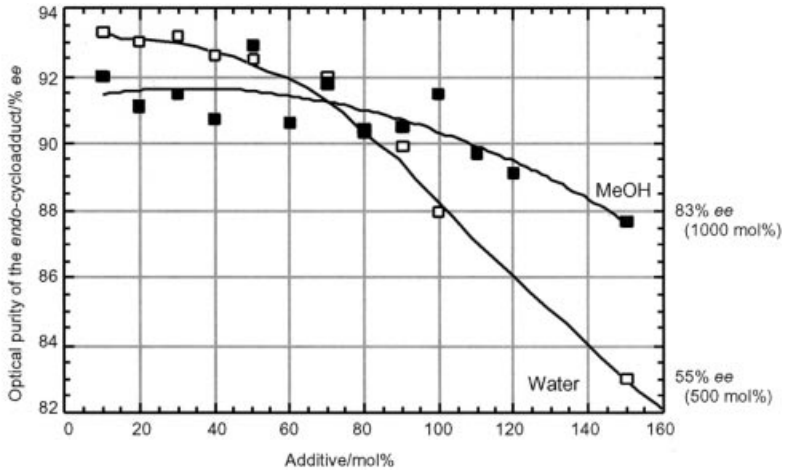


Figure 2. Effect of addition of water and methanol to Diels–Alder reactions catalyzed by DBFOX/Ph·Ni(ClO_4)$_2$ (10 mol %) at room temperature

3-acryloyl-2-oxazolidinone. We were greatly surprised to learn that the aqua complexes often showed catalytic activity similar to that of anhydrous catalysts, and sometimes even better enantioselectivity (Table 1).

In particular, the cationic nickel(II) aqua complexes **A**, bearing highly coordinating water ligands on the metal center, showed high catalytic activity. We therefore examined the tolerance of this nickel(II) aqua complex **A** toward nucleophiles by the addition of some strongly coordinating additives such as water, methanol, carboxylic acids, phenol, and amines.

In the presence of large amounts of water or methanol (15 equivalents or more to catalyst **A**), enantioselectivities were not fatally affected in reactions catalyzed by **A** (X = ClO_4, 10 mol %) at room temperature (Figure 2). Although the selectivity decreased to 55% *ee* when 500 mol % of water was present, the enantioselectivity of 83% *ee* was maintained even in the presence of 1000 mol % of methanol.

Comparable enantioselectivities and diastereoselectivities were recorded even in the presence of amines, albeit not in great excess (Table 2).[5b] The catalyst **A** coordinated strongly to some amines, such as benzylamine and 2,4,6-collidine, to produce the corresponding salts as precipitates. Even so, the Diels–Alder reactions were successfully activated, to provide excellent selectivities with comparable chemical yields. This indicates that the chiral Lewis acid **A** may be effectively utilized together with amines in the same flask, so that enantioselective reactions under DCA conditions would be achieved.

Table 2. Effect of other additives (acids and amines); DBFOX/Ph·Ni(ClO_4)$_2$ (10 mol %) at room temp.

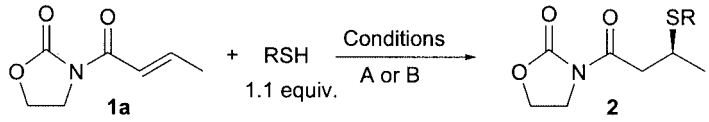
Additive	Mol (%)	Time (h)	Yield (%)	*endo/exo*	*ee* (%)
$PhNH_2$	30	0.7	74	91:9	91
$PhCH_2NH_2$[a]	30	0.7	46	94:6	90
Pyridine	30	0.7	83	95:5	86
2,4,6-Collidine[a]	30	0.7	95	92:8	93
Et_2NH	30	1.2	75	90:10	1
MeCOOH	10	0.7	84	97:3	91
MeCOOH	60	0.7	92	91:9	88
PhCOOH	10	0.7	97	93:7	91
PhCOOH	60	0.7	97	92:8	81
p-$NO_2C_6H_4COOH$	10	0.7	98	93:7	91
PhOH	60	0.7	98	94:6	92

[a] Precipitation appeared.

3. Thiol Conjugate Additions

The nickel(II) aqua complex **A** derived from DBFOX/Ph and Ni(ClO_4)$_2$·6H_2O was found to work well as a chiral catalyst to activate the conjugate addition reactions of thiols to 3-(2-alkenoyl)-2-oxazolidinone (Scheme 2).[3d,5f] It is well known that nickel ions bind strongly with sulfur compounds, especially with thiols, and sulfides have accordingly been known to act as strong poisons for metal catalysts including nickel ions.[6,7] Indeed, precipitation took place when the anhydrous nickel(II) complex **A** (X = ClO_4, n = 0) was used in reactions between benzenethiol and 3-crotonoyl-2-oxazolidinone (**1a**) in dry dichloromethane, causing formation of dark brown precipitates. Such precipitation took place rapidly in the presence of amine additive, and the resulting insoluble material did not show any catalytic activity in the thiol additions. On the other hand, the nickel(II) aqua complex **A** (X = ClO_4, n = 0) was found to be relatively more tolerant than the anhydrous nickel(II) complexes, showing high catalytic activity even in dichloromethane.

Careful examination of the dependence of catalytic activity and selectivity on reaction time indicated that the catalytic activity of **A** was at its maximum in the very early stages of the reaction and gradually decreased with elapsing reaction time. Enantioselectivity also gradually reduced with decreased catalytic activity. These observations indicate that the catalyst slowly changes to a less reactive one under the reaction conditions, probably due to its ready oli-



Condition A: At room temp. in THF
a. DBFOX/Ph + $Ni(ClO_4)_2 \cdot 6H_2O$ (10 mol% each) in THF at r.t. 2 h; b. 3-crotonoyl-2-oxazolidinone (1 equiv.); c. thiol (1.1 equiv.), stirring at r.t. under nitrogen

R	Time (h)	Yield (%)	*ee* (%)
Phenyl	24	quant.	80
o-Tolyl	24	82	89
p-Tolyl	24	82	84
Mesityl	24	84	95
o-Isopropylphenyl	24	96	80
o-*tert*-Butylphenyl	24	quant.	93
p-*tert*-Butylphenyl	24	74	86
1-Naphthyl	24	73	87
2-Naphthyl	24	94	87
Benzyl	48	26	89
o-Methoxyphenyl	48	69	11
p-Methoxyphenyl	72	30	78

Condition B: At 0 °C in CH_2Cl_2/THF (1:1 v/v) with proton sponge (10 mol%)
a. 3-Crotonoyl-2-oxazolidinone (1 equiv.); b. thiol (1.1 equiv.); c. DBFOX/Ph (10 mol%); d. $Ni(ClO_4)_2 \cdot 6H_2O$ (10 mol%); e. proton sponge (10 mol%); f. at 0 °C in CH_2Cl_2/THF = 10:1 v/v; g. under N_2

R	Time (h)	Yield(%)	*ee* (%)
Phenyl	24	84	94
o-Tolyl	96	99	95
p-Tolyl	96	84	91
Mesityl	96	36	96
o-Isopropylphenyl	96	91	97
o-*tert*-Butylphenyl	96	96	94
p-*tert*-Butylphenyl	96	38	69
1-Naphthyl	96	92	55
2-Naphthyl	96	88	91

Scheme 2. Enantioselective conjugate additions of thiols catalyzed by DBFOX/Ph·$Ni(ClO_4)_2 \cdot 3H_2O$

gomerization, reducing its catalytic activity. The solvent of our choice was THF, as a polar solvent in which the thiol conjugate addition reactions proceeded smoothly at room temperature, giving the corresponding adducts **2** in high yields and with high enantioselectivities (under conditions A in Scheme 2).

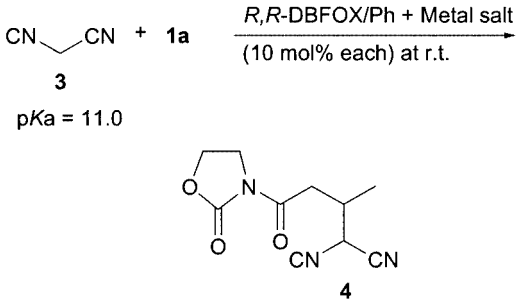
Use of a mixture of catalytic amounts both of the Lewis acid catalyst **A** and of 1,8-bis(dimethylamino)naphthalene, known as proton sponge,[8] in reactions in THF at room temperature was found to provide even better conditions. Thus, under the DCA conditions (conditions B), the reaction was faster, reaching completion in shorter reaction times, so that the reaction temperature could be lowered to 0 °C, resulting in higher enantioselectivities. Thiols become more nucleophilic in the presence of amine base, and the conjugate addition reaction is complete in a shorter reaction time. Although deterioration of the catalyst **A** also takes place more easily in the presence of amine, the relative rate acceleration was much more favorable for the conjugate additions.

4. Malononitrile Michael Additions

Enantioselective conjugate addition reactions of carbon nucleophiles are one of the most powerful transformations in organic synthesis. A number of asymmetric Michael additions to α,β-unsaturated carbonyl acceptors catalyzed by chiral catalysts have been reported.[9−27] However, the development of general and highly enantioselective versions still remains a challenging goal. Here we describe a significant advancement towards the achievement of highly enantioselective Michael addition reactions under the DCA conditions.

Unlike thiol nucleophiles, malononitrile (**3**), with a p*K*a value of 11.0, does not react at a practical reaction rate with α,β-unsaturated carboxylic acid derivatives such as 3-crotonoyl-2-oxazolidinone (**1a**) under uncatalyzed conditions. As shown in Scheme 3, no reaction takes place between **1a** and **3** in THF in the absence of promoters. Even in the presence either of a strong amine such as 2,2,6,6-tetramethylpiperidine (TMP)[28] or of a Lewis acid such as $Ni(ClO_4)_2 \cdot 6H_2O$, no reaction occurs at room temperature in 3 days, indicating that the single activation of malononitrile

either by a base or by a Lewis acid catalyst in THF is totally ineffective. When the solvent was replaced with dichloromethane, however, the same reaction proceeded in the presence of a catalytic amount of nickel(II) aqua complex **A** (X = ClO_4, *n* = 3, 10 mol %), but the rate was slow and enantioselectivity was negligible. Of the catalysts examined, the magnesium complex **B** (X = ClO_4) was the best, and an acceptable enantioselectivity of 86% *ee* was obtained for the adduct **4** (Scheme 3 and Figure 3).[3c]



Metal salt	Solvent	Time (h)	Yield (%)	*ee* (%)
none	THF	72	-	-
TMP	THF	72	-	-
$Ni(ClO_4)_2•6H_2O$	THF	72	-	-
A	CH_2Cl_2	72	40	5
B	CH_2Cl_2	48	45	86
A	THF	72	20	21
C	THF	100	3	10

Scheme 3. Michael additions of malononitrile − survey of catalysis

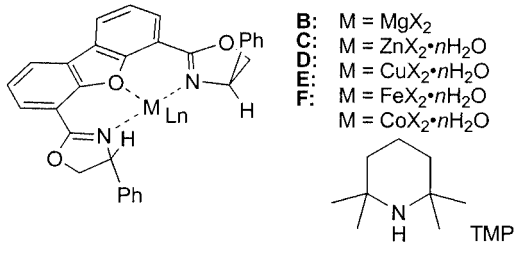
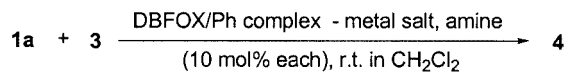


Figure 3. Metal(II) complexes of DBFOX/Ph ligands and 2,2,6,6-tetramethylpiperidine (TMP)

When a catalytic amount of amine was added to **1a** and **3** in dichloromethane in the presence of nickel aqua complex **A** (X = ClO_4, *n* = 3, 10 mol %), the reaction was strongly activated, reaching completion in a much shorter reaction time at room temperature (Scheme 4). A variety of amines, such as DBU, triethylamine, ethyldiisopropylamine, 2,6-lutidine, and TMP, were therefore examined, and it was found that both the reactivity and enantioselectivity were improved. It is interesting to note that selection of the correct combination of amines and Lewis acid catalysts is essential. For the reaction catalyzed by the nickel aqua complex **A**, TMP was found to be the best selection as amine catalyst; with a combination of catalysts **A** and TMP under the DCA conditions the reaction was so rapid that it was complete in only 1 h at room temperature, producing the malononitrile adduct **4** in 91% yield with a moderate enantioselectivity of 77% *ee*.

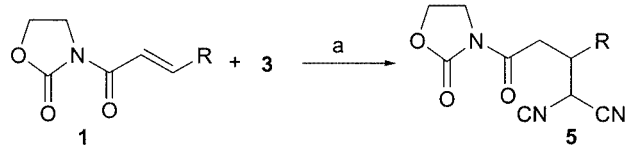


Metal complex[a]	Amine	Time (h)	Yield (%)	*ee* (%)
A	DBU	48	62	80
A	Et_3N	24	96	78
A	iPr_2NEt	4	92	73
A	2,6-Lutidine	4	90	76
A	TMP	1	91	77
B	TMP	168	57	15
C	Et_3N	96	26	26

[a] X = ClO_4 for the complexes **A**, **B**, and **C**.

Scheme 4. Michael additions of malononitrile− role of amine catalysts

However, the magnesium catalyst **B** (X = ClO_4), which displayed the best catalytic activity in the absence of amine catalysts as shown in Scheme 3, was rather deactivated in the presence of a catalytic amount of TMP, showing much lower reactivity and selectivity than in the case of the catalysis of magnesium salt by itself. The reason for the serious deactivation would presumably be strong binding of TMP to the DBFOX/Ph − magnesium complex. This is a typical example of reactions under DCA conditions in which the best combination of a Lewis acid and amine is very important. The authors would like to emphasize that the nickel aqua complex **A** of DBFOX/Ph is one of the best chiral Lewis acid catalysts for reactions under DCA conditions.



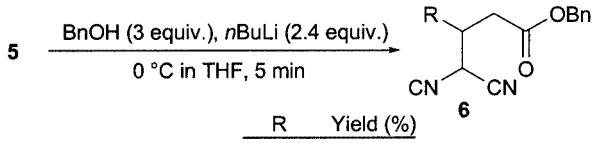
a: Complex **A** (X = $ClO_4•3H_2O$) and TMP (10 mol% each) in CH_2Cl_2

R	Temp. (°C)	Time (h)	Yield (%)	*ee* (%)
Me	− 20	6	90	85
*n*Pr	0	48	quant.	86
*n*Pr	− 20	96	quant.	90
*i*Pr	− 20	48	90	87
*t*Bu	0	168	58	90
*t*Bu	− 20	168	38	94
Ph	r.t.	96	95	75

Scheme 5. Asymmetric Michael additions of malononitrile under double catalytic activation conditions

The enantiopurities of the malononitrile adducts **5** were determined by their derivatization to the UV-visible benzyl esters **6** by treatment with lithiumbenzyl oxide at 0 °C for 5 min, followed by chiral HPLC analysis on Chiralcell CD-H with hexane/2-propyl alcohol as eluent (4:1 v/v,

Scheme 6). No serious racemization took place during this transformation to the corresponding ester derivatives **6**

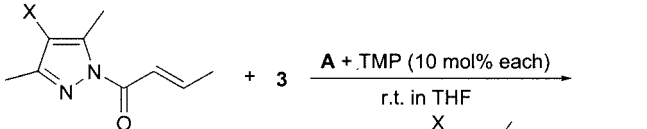


R	Yield (%)
Me	88
*n*Pr	88
*i*Pr	88
*t*Bu	85
Ph	72

Enantioselectivity was determined by chiral HPLC of the esters (Chiralcell OD-H with hexane/2-PrOH = 4:1 v/v).

Scheme 6. Estimation of enantioselectivity

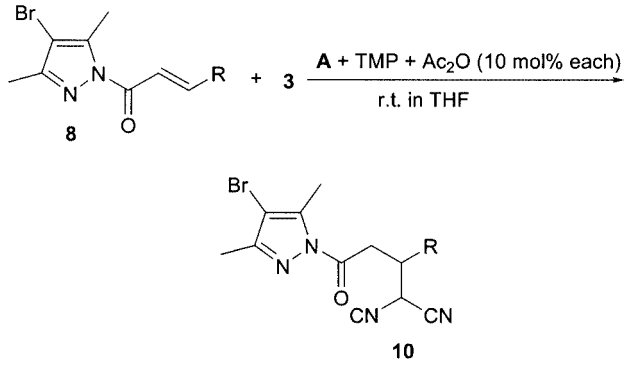
The 2-oxazolidinone chelating auxiliary could be replaced with a 3,5-dimethylpyrazole auxiliary; malononitrile conjugate addition reactions of 1-crotonoyl-3,5-dimethylpyrazole (**7a**) proceeded smoothly at room temperature in THF under the DCA conditions in the presence of the nickel aqua complex **A** (X = ClO_4, n = 3) and TMP, both in catalytic amounts (10 mol %) (Scheme 7). Although the adduct **9a** was obtained in 86% yield, the enantioselectivity was disappointingly low (23% *ee*). We were, however, delighted to observe that enantioselectivity was much improved − as high as 81% *ee* − when an equimolar (with the substrates) amount of acetic anhydride was used as an additive. The amount of acetic anhydride could also be reduced to catalytic levels (10 mol %), giving a comparably satisfactory result. 4-Bromo-1-crotonoyl-3,5-dimethylpyrazole (**8a**) was found to be a better acceptor molecule than **7a**, and the adduct **10a** was produced in a quantitative yield with an enantioselectivity of 88% *ee* in the reaction at room temperature in the presence of a catalytic amount of acetic anhydride.



X	Ac_2O (equiv.)	Time (h)	Yield (%)	*ee* (%)
H	none	5	86	23
H	1	6	89	81
H	0.1	6	82	81
Br	none	5	98	84
Br	0.1	6	92	88

Scheme 7. Use of pyrazole substrates − effect of acetic anhydride

Under the above optimized double catalytic conditions with the nickel(II) perchlorate aqua complex **A**, TMP, and acetic anhydride (10 mol % each) at room temperature in THF, a variety of 1-(2-alkenoyl)-4-bromo-3,5-dimethylpyrazoles **8** could be effectively employed in the Michael additions to malononitrile (**3**), the corresponding adducts being produced with good to high enantioselectivities (Scheme 8). This procedure with bromopyrazole substrates **8** in THF thus has a synthetic advantage that the reactions can be performed at room temperature in shorter reaction times, with comparable enantioselectivities being attained.



R	Time (h)	Yield (%)	*ee* (%)
Me	6	92	88
Me[a]	5	89	86
*i*Pr	7	94	93
cC_6H_{11}	24	88	90
Ph	12	87	88
p-BrC_6H_4	12	94	85
p-MeC_6H_4	24	91	78
2-Furyl	48	78	55

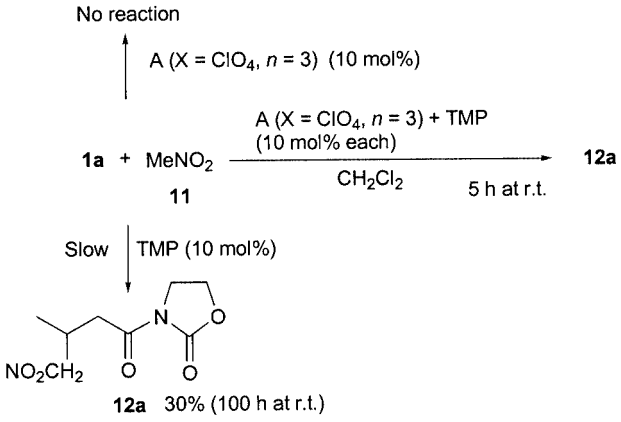
[a] In 2-nitropropane

Scheme 8. Michael additions of malononitrile to the bromopyrazole acceptor − summary

5. Nitromethane Conjugate Additions

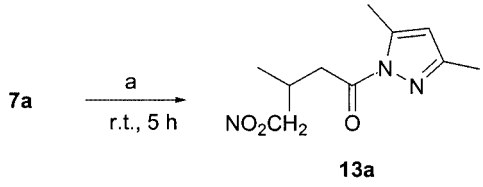
Michael addition reactions of nitromethane to α,β-unsaturated acyl oxazolidinones **1** or pyrazoles **7** and **8** would be expected to result in the formation of γ-nitro acid derivatives.[29−35] These adducts should be important synthetic intermediates, since they can be readily transformed, through reduction of the adducts, into γ-amino acids or pyrrolidinones,[36] which are known as the central skeletons of a variety of biologically active natural products.[37] However, some problems in the synthetic methodology based on the catalyzed enantioselective Michael addition reaction of nitromethane remain unsolved.

No reaction took place between 3-crotonoyl-2-oxazolidinone (**1**) and nitromethane (**11**), which was also used as solvent, either in the absence of any promoters or in the presence of the nickel aqua complex **A** alone (Scheme 9). TMP as amine catalyst promoted the reaction, but even with nitromethane (**11**) as solvent in the reaction, the yield of adduct **12a** was only 30% after 100 h at room temperature. On the other hand, under the DCA conditions with the complex **A** and TMP, the reaction was almost complete in 5 h at room temperature, again pointing to the high synthetic potential of this new activation methodology.



Scheme 9. Nitromethane conjugate additions under double catalytic activation conditions

1-Crotonoyl-3,5-dimethylpyrazole (**7a**) was found to be a much better acceptor than 3-crotonoyl-2-oxazolidinone (**1a**) in the nitromethane conjugate addition reactions. Even the background reaction was promoted by TMP alone (10 mol %) at room temperature, and this reaction in the absence of the nickel(II) complex **A** was complete in 12 h at room temperature. Use of **11** as solvent under the DCA conditions produced a quantitative yield of the corresponding adduct **13a** with an enantioselectivity of 77% *ee* (Scheme 10). It was finally found that a THF/nitromethane mixture (1:1 v/v) was the best choice for the reaction solvent, from the economic standpoint in reactions with other nitroalkanes, providing an improved enantioselectivity of 84% *ee*. These selectivities are acceptably high, since the TMP-catalyzed background reaction was complete in 12 h at room temperature. Thus, the reactions using pyrazole substrates such as **7a** in THF/$MeNO_2$ (1:1, v/v) are essential.



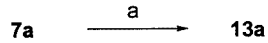
a: Complex **A** (X = ClO_4, n = 3) + TMP (10 mol% each)

Conditions	Result
In $MeNO_2$ (0.1 M)	95% (77% *ee*)
In THF / $MeNO_2$ (1:1 v/v, 0.1 M)	97% (84% *ee*)

1. $MeNO_2$ / THF (1:1 v/v) is the best solvent
2. Pyrazole substrate is essential
3. Background reaction at r.t. for 12 h: 91%

Scheme 10. Nitromethane Michael addition

As shown in Scheme 11, the cationic nickel(II) salt DBFOX/Ph aqua complex **A** (X = ClO_4, n = 3) was much more active as a Lewis acid catalyst than the anhydrous complex **A** (X = SbF_6, n = 0), providing the adduct **13a** in a quantitative yield and with an enantioselectivity of 84% *ee* in the reaction in THF/**11** (1:1 v/v) (Scheme 11). Although the cobalt(II) aqua complex **F** (X = ClO_4) was also an active catalyst, providing a selectivity of 86% *ee* for **13a**, the reactivity was rather poor, giving **13a** in only 36% yield after a long reaction time of 144 h at room temperature. The DBFOX/magnesium complexes **B** of perchlorate and trifluoromethanesulfonate salts, the zinc(II) complexes **C**, and the copper(II) complexes **D** were found to be totally inactive.



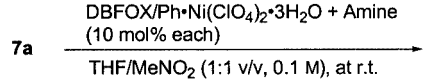
a. DBFOX/Ph + MX_2•nH_2O + TMP (10 mol% each) in THF / **11** (1:1 v/v, 0.1 M) at r.t.

MX_2•nH_2O	Time (h)	Yield (%)	*ee* (%)[b]
$Ni(ClO_4)_2$•6H_2O	5	97	84
$Ni(SbF_6)_2$	48	19	31
$Co(ClO_4)_2$•6H_2O	144	36	86
$Zn(ClO_4)_2$•6H_2O	24	nr[c]	-
$Cu(ClO_4)_2$•6H_2O	24	nr[c]	-
$Mg(ClO_4)_2$	24	trace[c]	-
$Zn(OTf)_2$	24	nr[c]	-
$Cu(OTf)_2$	24	nr[c]	-
$Mg(OTf)_2$	24	trace	-

[b]Determined by chiralcell AD, [c]nr: no reaction.

Scheme 11. Survey of DBFOX/Ph metal complex catalysts

TMP was one of the most active amine catalysts, so this amine was selected for further work on nitromethane Michael additions (Scheme 12). DBU, dicyclohexylamine, 1,1,3,3-tetramethylguanidine, *N*,*N*-diisopropylethylamine, and 1,8-bis(dimethylamino)naphthalene were also equally effective (Scheme 12). *N*,*N*′-Diisopropylethylenediamine, piperidine, and pyrrolidine, however, were less active, and so TMP, as a bulky piperidine, thus worked much better than piperidine itself. Catalytic circulation was ineffective for monoethanolamine, 2,6-lutidine, 1,1,3,3-hexamethyldi-



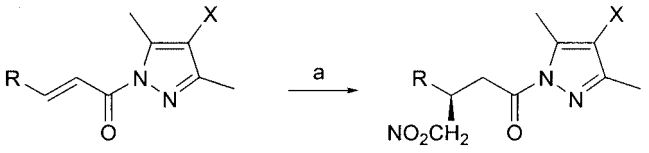
Amine	Time (h)	Yield (%)	*ee* (%)[a]
TMP	5	97	84
DBU	5	97	72
Dicyclohexylamine	5	quant	74
1,1,3,3-Tetramethylguanidine	6	94	71
N,*N*-Diisopropylethylamine	6	79	74
1,8-Bis(dimethylamino)naphthalene	12	96	74
N,*N*′-Diisopropylethylenediamine	48	78	69
Triton B	96	44	88
Piperidine	96	54	67
Pyrrolidine	96	31	70
Monoethanolamine	96	20	64
2,6-Lutidine	96	17	51
1,1,3,3-Hexamethyldisilazane	96	12	69
Tris(trimethylsilyl)amine	96	11	69
2,2,4,4,6,6-Hexamethylcyclotrisilazane	96	18	76

[a]Determined by Chiralcell AD.

Scheme 12. Survey of amine catalysts

silazane, tris(trimethylsilyl)amine, and 2,2,4,4,6,6-hexamethylcyclotrisilazane.

Reactions between nitromethane and 1-(2-alkenoyl)-3,5-dimethylpyrazoles **7**, **8**, and **14**, bearing a variety of β-substituents, were examined under the DCA conditions in 1:1 v/v THF/nitromethane (Scheme 13). When the reaction temperature was lowered to −20 °C, enantioselectivities were improved, but the reactions became much slower, and yields of the adducts **13**, **15**, and **16** were decreased.



7: X = H
8: X = Br
14: X = I

13: X = H
15: X = Br
16: X = I

a. **A** (X = ClO_4, *n* = 3), TMP (10 mol% each) in THF/$MeNO_2$ = 1:1 v/v at –20 °C

R	X	Time (h)	Yield (%)	*ee* (%)
Me	H	96	85	94
Me	Br	96	97	95
Me	I	96	62	96
Et	H	120	84	95
*n*Pr	H	96	96	91
*i*Pr	H	168	74	97
cC_6H_{11}	H	168	90	91
*t*Bu	H	168	39	95
(*E*)-MeCH=CH-	H	96	49	77
MeOOC	H	96	53	84
Ph	H	168	90	93
p-ClC_6H_4	H	24	quant.	97
3,4-$(OCH_2O)C_6H_3$	H	168	77	98
2-Furyl	H	96	75	97
2-Thienyl	H	168	83	97

Scheme 13. Nitromethane Michael additions

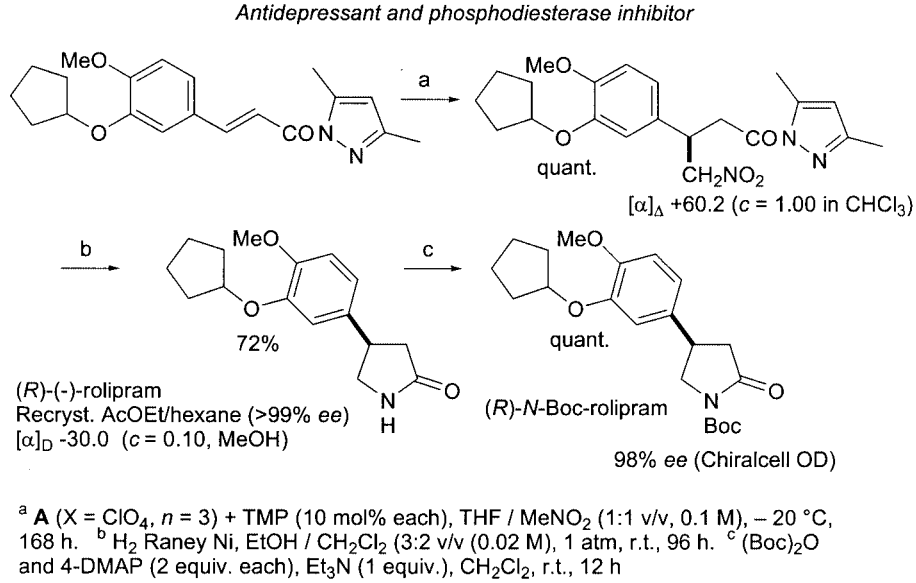
When the 4-positions in the pyrazole auxiliaries of 1-crotonoyl-substituted substrates were halogenated, as shown with **7a**, **8a**, and **14a** (R = Me, X = halo), higher enantioselectivities were observed for the bromo- and iodo-substituted adducts **15a** and **16a** (R = Me, X = Br or I, Scheme 13). The bromo-substituted substrate **8a** was more reactive than the other two (**7a** and **14a**). Acceptors **7** with β-substituents of any simple alkyl types such as methyl, ethyl, propyl, isopropyl, cyclohexyl, and *tert*-butyl worked well for enantioselectivities, although the *tert*-butyl substrate was less reactive. Acceptors functionalized with alkenyl and ester substituents showed rather decreased selectivities, while those with phenyl, substituted phenyl, and heteroaryl substituents provided excellent selectivities and chemical yields. Thus, the nitromethane conjugate addition reactions of alkenoyl pyrazole substrates, under the DCA conditions with catalytic amounts both of the nickel(II) aqua complex **A** and of TMP, provide an extremely effective synthetic method for the construction of enantiomers of γ-nitro acid derivatives, and further γ-amino acids.

Our new synthetic methodology for effective enantiomer production, based on these nitromethane conjugate additions under the DCA conditions, was successfully applied to the synthesis of (*R*)-rolipram, (*R*)-4-(3-cyclopentyloxy-4-methoxy)phenyl-2-pyrrolidinone, known as a potent antidepressant and phosphodiesterase inhibitor (Scheme 14).[38] The first step is the synthesis of 1-[(3-cyclopentyloxy-4-methoxy)cinnamoyl]-3,5-dimethylpyrazole. The enantioselective nitromethane conjugate addition to the resulting pyrazole derivative was performed under the DCA conditions, producing the nitromethane adduct in a quantitative yield. The nitro group was reduced to an amine with Raney nickel, followed by cyclization to afford rolipram in 72% yield. The rolipram synthesized was transformed into *N*-Boc derivative with an enantiomeric purity determined as 98% *ee*. (*R*)-Rolipram was thus synthesized in two steps starting from the readily available cinnamoyl amide of 3,5-dimethylpyrazole in 72% yield.

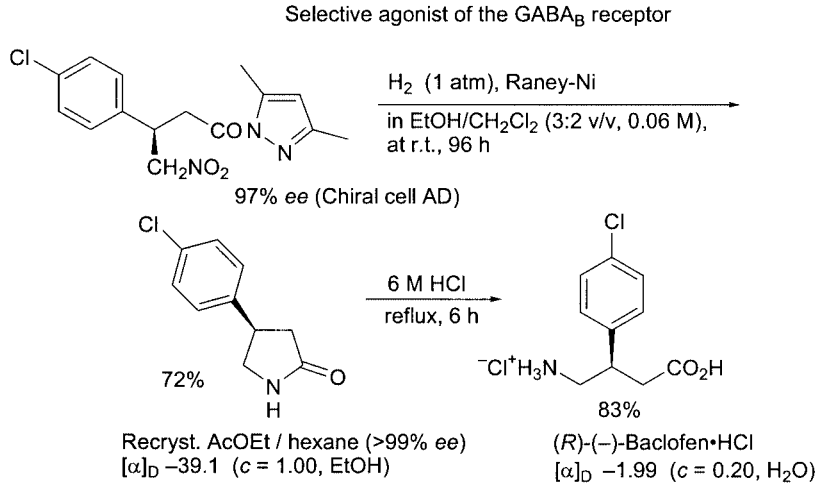
A similar synthetic application is shown in Scheme 15, in which a three-step synthesis of (*R*)-baclofen hydrochloride, known as a selective agonist of the $GABA_B$ receptor,[39] was achieved through a key step involving the catalyzed enantioselective Michael addition of nitromethane under the DCA conditions. The Michael adduct (97% *ee*) was similarly transformed through a Raney nickel reduction/cyclization sequence to give enantiopure (*R*)-4-(*p*-chlorophenyl)-2-pyrrolidinone, which was then hydrolyzed to give (*R*)-baclofen hydrochloride.

6. Enol Lactone Synthesis

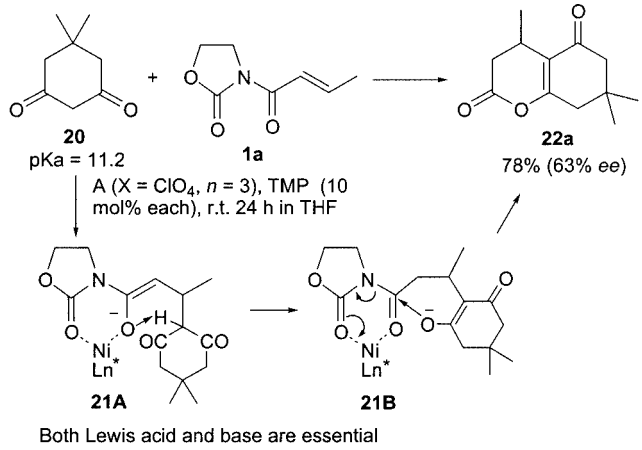
Use of 1,3-dicarbonyl compounds as nucleophile precursors in catalyzed enantioselective Michael additions is quite rare.[40] Accordingly, 5,5-dimethyl-1,3-cyclohexanedione (**20**) was applied as a nucleophile precursor in enantioselective Michael additions to the oxazolidinone substrate **1a** under the DCA conditions in the presence of nickel(II) complex **A** (X = ClO_4, *n* = 3) and TMP (Scheme 16). The reaction took 24 h at room temperature, and the product, obtained in 78% yield (63% *ee*), was not the corresponding Michael adduct but the enol lactone **22a** produced through the elimination of the oxazolidinone auxiliary. The formation of **22a** could easily be understood in terms of a reaction mechanism including the initial conjugate addition of **20** to **1a** to form the adduct anion **21A**, which then underwent intramolecular protonation of the enolate to give the enol anion **21B**, followed by lactonization of **21B** to produce enol lactone **22a**. Although it is well known that 3-acyl-2-oxazolidinone substrates hardly undergo acyl substitution reactions, the transformation observed above is a special case. Both the electrophilicity of the amide carbonyl group and the elimination of the oxazolidinone auxiliary of **21B** were powerfully activated through the coordination of the nickel(II) ion catalyst. Since enol lactones have been synthesized under harsh conditions,[41−43] this enantioselective reaction catalyzed by a chiral catalyst at room temperature should offer a highly significant synthetic method for biologically active coumarins, flavonoids, neoflavonoids, and enol lactones.[44]



Scheme 14. Synthesis of (*R*)-(−)-rolipram



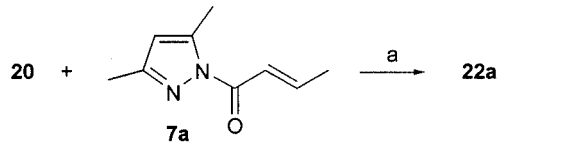
Scheme 15. Synthesis of (*R*)-(−)-baclofen·HCl



Scheme 16. Enol lactone formation under CDA conditions

When 3-crotonoyl-2-oxazolidinone **1a** was replaced with 1-acryloyl-3,5-dimethylpyrazole **7a** in the above enol lactone synthesis in THF at room temperature, the yield of the enol lactone **22a** was much decreased (Scheme 17). 3,5-Dimethylpyrazole is a stronger leaving group than oxazolidin-2-one and, in addition, 3,5-dimethylpyrazole is a strong nucleophile toward the pyrazole acceptor **7a**, so that the starting alkene **7a** was rapidly consumed to give the pyrazole adduct **23**. As a result, the yield of **22a** was much decreased, although the enantioselectivity of this reaction was as high as 91% *ee*.

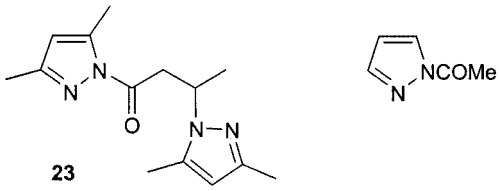
To our delight, however, the undesired pyrazole addition was mostly inhibited in the presence of acetic anhydride, the 3,5-dimethylpyrazole, formed by substitution in the cyclization step, being scavenged by *N*-acetylation with acetic anhydride. In particular, the reaction between **20** and **7a** under the DCA conditions in the presence of **A** (X =



[a]A (X = ClO_4, *n* = 3), TMP (10 mol% each), Ac_2O (1.1 equiv.), r.t.

Solvent	Ac_2O (equiv.)	Time (h)	Yield (%)	*ee* (%)
THF	–	24	38	91
CH_2Cl_2	1.1	144	90	52
THF	1.1	12	99	96

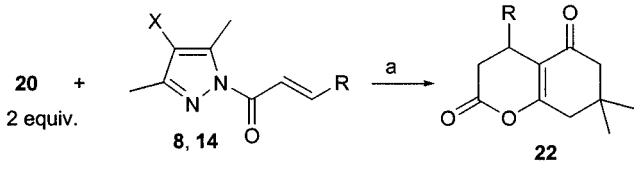
THF is essential as reaction solvent



Scheme 17. Effect of acetic anhydride and solvent

ClO_4, *n* = 3) in THF at room temperature, together with 1.1 equivalent of acetic anhydride, was complete in 12 h, producing a quantitative yield of the enol lactone **22a** with an excellent enantioselectivity of 96% *ee*. On the other hand, the same reaction in dichloromethane was much slower, so that it took 144 h for the reaction to reach completion, giving **22a** in 90% yield and with an enantioselectivity of 52% *ee*. Reactions between 5,5-dimethyl-1,3-cyclohexanedione (**20**) and 1-(2-alkenoyl)-3,5-dimethypyrazoles (**7**) should thus be performed at room temperature in THF in the presence of acetic anhydride.

4-Bromo-1-crotonoyl-3,5-dimethylpyrazole (**8a**) was found to be even more reactive than the pyrazole derivative **7a**. The reaction was complete in 5 h at room temperature in the presence of acetic anhydride, producing enol lactone **22a** in 93% yield with an enantioselectivity of 96% *ee* (Scheme 18). Under these optimized reaction conditions, the bromopyrazole acceptors **8**, with a variety of substituents at the β-position, were successfully applied. All the results are summarized in Scheme 18. The bromopyrazole substrates **8** with small methyl and ethyl substituents or a electron-withdrawing methoxycarbonyl group are highly reactive, so the reactions are complete in under 10 h at room temperature. Substitution with bulky alkyl groups such as isopropyl and cyclohexyl, however, makes the reactions much slower, and it takes a long time to reach completion of the reactions with acceptors **8** with 1-alkenyl and heteroaryl substituents such as 1-propenyl and 2-furyl at the β-position. The best enantioselectivity observed was up to 99% *ee*.



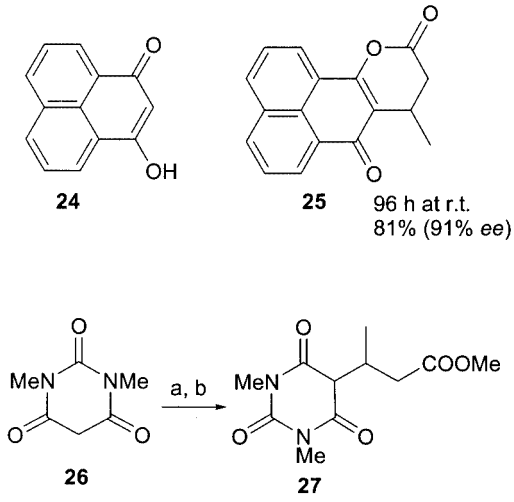
[a]A (X = ClO_4, *n* = 3), TMP (10 mol% each), Ac_2O (2 equiv.), r.t., THF (0.1 M)

R	X	Time (h)	Yield (%)	*ee* (%)[a]
Me	Br	5	93	96
Me	I	6	62	98
Et	Br	8	73	93
*n*Pr	Br	24	94	92
*i*Pr	Br	96	71	96
cC_6H_{11}	Br	96	53	95
1-Propenyl	Br	48	85	90
2-Furyl	Br	168	73	89
CO_2Me	Br	3	77	nd[b]
Ph	Br	12	94	99

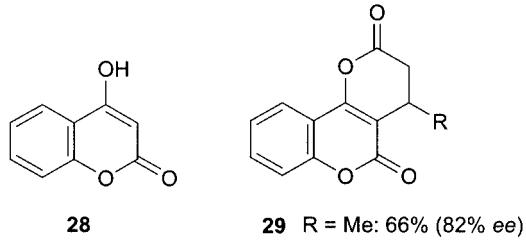
[a]Determined by chiral HPLC. [b] nd: not determined.

Scheme 18. Use of a variety of acceptors in dimedone reactions

Not only 5,5-dimethyl-1,3-cyclohexanedione (**20**) but also other cyclic 1,3-dicarbonyl compounds such as 3-hydroxy-1-phenalenone (**24**), 1,3-dimethylbarbituric acid (**26**), and 4-hydroxycoumarin (**28**) also underwent the smooth enol lactone synthesis under the DCA conditions at room temperature, producing the corresponding enol lactone derivatives **25**, **27**, and **29**, respectively (Scheme 19). The enol lactone product formed from the cyclic diamide **26** was so un-



[a] *R,R*-DBFOX/Ph•Ni$(ClO_4)_2$•3H_2O (10 mol%), TMP (10 mol%), Ac_2O (1.1 equiv.), THF (0.1 M), r.t., 96 h.
[b] MeONa (cat.) in MeOH (excess), r.t., 24 h.



Scheme 19. Enol lactone synthesis with a variety of active methylene compounds

stable that it was easily decomposed, so isolation of the resulting enol lactone was difficult. Subsequent treatment with sodium methoxide in methanol at room temperature gave the crotonate adduct **27** in a high yield. In the reaction of cyclic keto ester **28**, the enol lactone **29** was obtained regioselectively. This product **29** corresponds to the enol lactone produced through the cyclization of enol form of the ketone functionality, not the ester one.

7. Conclusions

We have therefore developed an effective enantioselective synthetic method based on a new concept of double catalytic activation, in which both electrophile and nucleophile precursors are activated by catalytic amounts of chiral Lewis acid and amine base, respectively. This method has been successfully applied to enantioselective thiol conjugate additions and Michael reactions of malononitrile, nitromethane, and cyclic 1,3-dicarbonyl compounds, producing enantiomers of a variety of adducts in high chemical yields with excellent enantioselectivities. This new methodology should represent a powerful tool, especially when single catalytic activation of either nucleophiles or electrophiles is not sufficient to accelerate bond formation between substrates,. In order to achieve successful high activation of substrates, selection of the correct chiral Lewis acid and amine catalysts is important. In our case, combinations of the DBFOX/Ph/nickel(II) aqua complexes with 2,2,6,6-tetramethylpiperidine were found to be especially effective. Use of polar reaction solvents such as tetrahydrofuran and strongly chelating auxiliaries such as 3,5-dimethylpyrazole was also essential to provide high reactivity and enantioselectivity.

[1] [1a] B. M. Trost, G. K. Mikhail, *J. Am. Chem. Soc.* **1987**, *109*, 4124−4127. [1b] M. Wada, H. Aiura, K. Akiba, *Tetrahedron Lett.* **1987**, *29*, 3377−3380. [1c] H. L. Maanen, H. Kleijn, J. T. B. H. Jastrzebski, J. Verweij, A. P. G. Kieboom, G. Van Koten, *J. Org. Chem.* **1995**, *60*, 4331−4338. [1d] B. Lecea, A. Arrieta, I. Arrastia, F. P. Cossío, *J. Org. Chem.* **1998**, *63*, 5216−5227. [1e] S. Saito, S. Yamazaki, H. Yamamoto, *Angew. Chem. Int. Ed.* **2001**, *40*, 3613−3617.

[2] [2a] N. End, L. Macko, M. Zehnder, A. Pfaltz, *Chem. Eur. J.* **1998**, *4*, 818−824. [2b] N. Nishiwaki, K. R. Knudsen, K. V. Gothelf, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2001**, *40*, 2992−2995. [2c] M. Shibasaki, N. Yoshikawa, *Chem. Rev.* **2002**, *102*, 2187−2209. [2d] F. Chen, X. Feng, B. Qin, G. Zhang, Y. Jiang, *Org. Lett.* **2003**, *5*, 949−952. [2e] B. M. Trost, A. Fettes, B. T. Shireman, *J. Am. Chem. Soc.* **2004**, *126*, 2660−2661.

[3] [3a] K. Itoh, S. Kanemasa, *J. Am. Chem. Soc.* **2002**, *124*, 13394−13395. [3b] K. Itoh, Y. Oderaotoshi, S. Kanemasa, *Tetrahedron: Asymmetry* **2003**, *14*, 635−639. [3c] K. Itoh, S. Kanemasa, *Tetrahedron Lett.* **2003**, *44*, 1799−1802. [3d] S. Kanemasa, *Syn. Org. Chem. Jpn.* **2003**, *61*, 1073−1080.

[4] [4a] S. E. Denmark, T. Wynn, *J. Am. Chem. Soc.* **2001**, *123*, 6199−6200. [4b] S. E. Denmark, T. Wynn, G. L. Beutner, *J. Am. Chem. Soc.* **2002**, *124*, 13405−13407.

[5] [5a] S. Kanemasa, Y. Oderaotoshi, H. Yamamoto, J. Tanaka, E. Wada, D. P. Curran, *J. Org. Chem.* **1997**, *62*, 6454−6455. [5b] S. Kanemasa, Y. Oderaotoshi, S. Sakaguchi, H. Yamamoto, J. Tanaka, E. Wada, *J. Am. Chem. Soc.* **1998**, *120*, 3074−3088. [5c] S. Kanemasa, Y. Oderaotoshi, E. Wada, *Syn. Org. Chem. Jpn.* **1998**, *56*, 368−376. [5d] S. Kanemasa, Y. Oderaotoshi, J. Tanaka, E. Wada, *Tetrahedron Lett.* **1998**, *39*, 7521−7524. [5e] S. Kanemasa, Y. Oderaotoshi, J. Tanaka, E. Wada, *J. Am. Chem. Soc.* **1998**, *120*, 12355−12356. [5f] S. Kanemasa, Y. Oderaotoshi, J. Tanaka, E. Wada, *J. Am. Chem. Soc.* **1999**, *121*, 8675−8676. [5g] S. Kanemasa, T. Yoshimiya, E. Wada, *Tetrahedron Lett.* **1998**, *39*, 8869−8872. [5h] S. Kanemasa, T. Kanai, *J. Am. Chem. Soc.* **2000**, *122*, 10710−10711. [5i] M. Shirahase, S. Kanemasa, Y. Oderaotoshi, *Org. Lett.* **2004**, *6*, 675−678.

[6] Catalytic poison by sulfur compounds: [6a] R. G. Pearson, *J. Am. Chem. Soc.* **1963**, *85*, 3533−3539. [6b] T.-L. Ho, *Chem. Rev.* **1975**, *75*, 1−20. [6c] P. Marécot, E. Paraiso, J. M. Dumas, J. Barbier, *Appl. Cat., A: General* **1992**, *80*, 79−88. [6d] L. S. Liebeskind, J. Srogl, C. Savarin, C. Polanco, *Pure Appl. Chem.* **2002**, *74*, 115−122. [6e] C. M. Yam, J. Cho, C. Cai, *Langmuir* **2003**, *19*, 6862−6868.

[7] Thiol conjugate additions: [7a] H. Hiemstra, N. Wynberg, *J. Am. Chem. Soc.* **1981**, *103*, 417−430. [7b] K. Suzuki, A. Ikegawa, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3277−3282. [7c] H. Yamashita, T. Mukaiyama, *Chem. Lett.* **1985**, 363−366. [7d] E. Emori, T. Arai, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1998**, *120*, 4043−4044. [7e] M. Saito, M. Nakajima, S. Hashimoto, *Tetrahedron* **2000**, *56*, 9589−9594. [7f] S. Kobayashi, C. Ogawa, M. Kawamura, S. Masaharu, *Synlett* **2001**, 983−985. [7g] K. Nishimura, K. Tomioka, *J. Org. Chem.* **2002**, *67*, 431−434. [7h] P. McDaid, Y. Chen, L. Deng, *Angew. Chem. Int. Ed.* **2002**, *41*, 338−340.

[8] Effective use of proton sponge in synthesis: [8a] I. Rodríguez, G. Sastre, A. Corma, S. Iborra, *J. Catal.* **1999**, *183*, 14−23. [8b] M. Darabantu, T. Lequeux, J.-C. Pommelet, N. Plé, A. Turck, *Tetrahedron* **2001**, *57*, 739−750. [8c] A. Corma, S. Iborra, I. Rodríguez, F. Sánchez, *J. Catal.* **2002**, *211*, 208−215. [8d] A. E. Taggi, A. M. Hafez, H. Wack, B. Young, D. Ferraris, T. Lectka, *J. Am. Chem. Soc.* **2002**, *124*, 6626−6635. [8e] T. Dudding, A. M. Hafez, A. E. Taggi, T. R. Wagerle, T. Lectka, *Org. Lett.* **2002**, *4*, 387−390. [8f] A. M. Hafez, T. Dudding, T. R. Wagerle, M. H. Shah, A. E. Taggi, T. Lectka, *J. Org. Chem.* **2003**, *68*, 5819−5825.

[9] Enantioselective Michael addition reactions, review: [9a] M. P. Sibi, S. Manyem, *Tetrahedron* **2000**, *56*, 8033−8061. [9b] J. Christoffers, A. Mann, *Angew. Chem. Int. Ed.* **2001**, *40*, 4591−4597. [9c] N. Krause, A. Hoffmann-Röder, *Synthesis* **2001**, 171−196. [9d] E. R. Jarvo, S. J. Miller, *Tetrahedron Lett.* **2002**, *58*, 2481−2495.

[10] Chiral crown ethers, azacrown ethers: [10a] D. J. Cram, G. D. Y. Sogah, *J. Chem. Soc., Chem. Commn.* **1981**, 625−628. [10b] H. Brunner, B. Hammer, *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 312−313. [10c] D. J. Cram, Y. Sogah, *J. Am. Chem. Soc.* **1985**, *107*, 8301−8302. [10d] M. Takasu, H. Wakabayashi, K. Furuta, N. Yamamoto, *Tetrahedron Lett.* **1988**, *29*, 6943−6946. [10e] E. V. Dehmlow, C. Sauerbier, *Liebigs Ann. Chem.* **1989**, 181−185. [10f] J. Crosby, J. F. Stoddart, X. Sun, M. R. W. Venner, *Synthesis* **1993**, 141−145. [10g] E. Brunet, A. M. Poveda, D. Rabasco, E. Oreja, L. M. Font, M. S. Batra, J. C. Rodriguez-Ubis, *Tetrahedron: Asymmetry* **1994**, *5*, 935−948. [10h] L. Tõke, L. Fenichel, M. Albert, *Terahedron Lett.* **1995**, *36*, 5951−5954. [10i] L. Tõke, P. Bakó, G. M. Keserü, M. Albert, L. Fenichel, *Tetrahedron* **1998**, *54*, 213−222.

[11] Chiral tripodal oxazoline-*t*BuOK complexes: S.-G. Kim, K. H. Ahn, *Tetrahedron Lett.* **2001**, *42*, 4175−4177.

[12] Chiral phase-transfer catalysts: [12a] H. Wynberg, B. Greijdanut, *J. Chem. Soc., Chem. Commn.* **1978**, 427−428. [12b] A. Kawara, T. Taguchi, *Tetrahedron Lett.* **1994**, *35*, 8805−8808. [12c] R. S. E. Conn, A. V. Lovell, S. Karady, L. M. Weinstock, *J. Org. Chem.* **1986**, *51*, 4710−4711. [12d] A. Sera, K. Takagi, H. Katayama, N. Yamada, *J. Org. Chem.* **1988**, *53*, 1157−1161. [12e] A. Loupy, J. Sansoulet, A. Zaparucha, C. Merienne, *Tetrahedron Lett.* **1989**, *30*, 333−336. [12f] A. Kawara, T. Taguchi, *Tetrahedron Lett.* **1994**, *35*, 8805−8808. [12g] E. J. Corey, M. C. Noe, F. Xu, *Tetrahedron Lett.* **1998**, *39*, 5347−5350. [12h] F-Y. Zhang, E. J. Corey, *Org. Lett.* **2000**, *2*, 1097−1100. [12i] D. Y.

Kim, S. C. Huh, S. M. Kim, *Tetrahedron Lett.* **2001**, *42*, 6299−6301. [12j] E. Diez-Barra, A. de la Hoz, S. Merino, A. Rodriguez, P. Sánchez-Verdú, *Tetrahedron* **1998**, *54*, 1835−1844. [12k] R. T. Dere, R. R. Pal, P. S. Patil, M. M. Salunkhe, *Tetrahedron Lett.* **2003**, *44*, 5351−5353.

[13] Metal L-prolinate catalysts: [13a] M. Yamaguchi, N. Yokota, T. Minami, *J. Chem. Soc., Chem. Commn.* **1991**, 1088−1089. [13b] E. Juaristi, A. K. Beck, J. Hansen, T. Matt, T. Mukhopadhyay, M. Simson, D. Seebach, *Synthesis* **1993**, 1271−1290. [13c] M. Yamaguchi, T. Shiraishi, M. Hirama, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1176−1178. [13d] T. Kumamoto, S. Aoki, M. Nakajima, K. Koga, *Tetrahedron: Asymmetry* **1994**, *5*, 1431−1432. [13e] M. Yamaguchi, T. Shiraishi, M. Hirama, *J. Org. Chem.* **1996**, *61*, 3520−3530.

[14] Chiral magnesium catalyst: [14a] J. Ji, D. M. Barnes, J. Zhang, S. A. King, S. J. Wittenberger, H. E. Morton, *J. Am. Chem. Soc.* **1999**, *121*, 10215−10216. [14b] D. M. Barnes, J. Ji, M. G. Frickes, M. A. Fitzgerald, S. A. King, H. E. Morton, F. A. Plagge, M. Preskill, S. H. Wagaw, S. J. Wittenberger, Ji Zhang, *J. Am. Chem. Soc.* **2002**, *124*, 13097−13105.

[15] Chiral aluminum catalysts: [15a] E. N. Jacobsen, M. S. Taylor, *J. Am. Chem. Soc.* **2003**, *125*, 11204−11205. [15b] I. T. Raheem, S. N. Goodman, E. N. Jacobsen, *J. Am. Chem. Soc.* **2004**, *126*, 706−707.

[16] Chiral scandium catalyst: [16a] M. Nakajima, Y. Yamaguchi, S. Hashimoto, *J. Chem. Soc., Chem. Commn.* **2001**, 1596−1597. [16b] M. Nakajima, S. Yamamoto, Y. Yamaguchi, S. Nakamura, S. Hashimoto, *Tetrahedron* **2003**, *59*, 7307−7313.

[17] Chiral europium catalyst: F. Bonadies, A. Lattanzi, L. R. Orelli, S. Pesci, A. Scettri, *Tetrahedron Lett.* **1993**, *34*, 7649−7650.

[18] Chiral nickel catalyst: J. Christoffers, U. Rößler, T. Werner, *Eur. J. Org. Chem.* **2000**, 701−705.

[19] Chiral copper catalysts: [19a] G. Desimoni, P. Quadrelli, P. P. Righetti, *Tetrahedron* **1990**, *46*, 2927−2934. [19b] G. Desimoni, G. Dusi, G. Faita, P. Quadrelli, P. P. Righetti, *Tetrahedron* **1995**, *51*, 4131−4144.

[20] Chiral rhodium catalyst: [20a] M. Sawamura, H. Hamashima, Y. Ito, *J. Am. Chem. Soc.* **1992**, *114*, 8295−8296. [20b] M. Sawamura, H. Hamashima, Y. Ito, *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2559−2562.

[21] Chiral platinum catalyst: A. J. Blacker, M. L. Clarke, M. S. Loft, M. F. Mahon, J. M. Williams, *Organometallics* **1999**, *18*, 2867−2873.

[22] Chiral ruthenium catalyst: M. Watanabe, K. Murata, T. Ikariya, *J. Am. Chem. Soc.* **2003**, *125*, 7508−7509.

[23] Chiral heterobimetallic catalysts: [23a] H. Sasai, T. Arai, M. Shibasaki, *J. Am. Chem. Soc.* **1994**, *116*, 1571−1572. [23b] H. Sasai, T. Arai, Y. Satow, K. N. Houk, M. Shibasaki, *J. Am. Chem. Soc.* **1995**, *117*, 6194−6198. [23c] T. Arai, H. Sasai, K. Aoe, K. Okamura, T. Date, M. Shibasaki, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 104−106. [23d] M. Shibasaki, H. Sasai, T. Arai, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1236−1256. [23e] G. Manickam, G. Sundararajan, *Tetrahedron: Asymmetry* **1997**, *8*, 2271−2278. [23f] T. Arai, H. Sasai, K. Yamaguchi, M. Shibasaki, *J. Am. Chem. Soc.* **1998**, *120*, 441−442. [23g] Y. S. Kim, S. Matsunaga, J. Das, A. Sekine, T. Ohshima, M. Shibasaki, *J. Am. Chem. Soc.* **2000**, *122*, 6506−6507. [23h] G. Kumaraswamy, M. N. V. Sastry, N. Jene, *Tetrahedron Lett.* **2001**, *42*, 8515−8517. [23i] S. C. Jha, N. N. Joshi, *Tetrahedron: Asymmetry* **2001**, *12*, 2463−2466. [23j] T. Ohshima, Y. Xu, R. Takita, S. Shimizu, D. Zhong, M. Shibasaki, *J. Am. Chem. Soc.* **2002**, *124*, 14546−14547. [23k] R. Takita, T. Ohshima, M. Shibasaki, *Tetrahedron Lett.* **2002**, *43*, 4661−4665. [23l] S. Narasimhan, S. Velmathi, *Synth. Commun.* **2002**, *32*, 3791−3795. [23m] E. F. DiMauro, M. C. Kozlowski, *Organometallics* **2002**, *21*, 1454−1461. [23n] N. Prabagaran, G. Sundararajan, *Tetrahedron: Asymmetry* **2001**, *13*, 1053−1058. [23o] S. Velmathi, S. Swarnalakshmi, S. Narasimhan, *Tetrahedron: Asymmetryetry* **2003**, *14*, 113−117. [23p] S. Harada, N. Kumagami, T. Kinoshita, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 2582−2690. [23q] N. Kumagai, S. Matsunaga, M. Shibasaki, *Org. Lett.* **2001**, *3*, 4251−4254. [23r] K. Majima, A. Okada, T. Ohshima, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 15837−15845. [23s] Ref. [2a].

[24] Chiral palladium catalysts: [24a] Y. Hamashima, D. Hotta, M. Sodeoka, *J. Am. Chem. Soc.* **2002**, *124*, 11240−11241. [24b] Y. Hamashima, H. Takano, D. Hotta, M. Sodeoka, *Org. Lett.* **2003**, *5*, 3225−3228.

[25] Chiral organocatalysts: [25a] J. M. Betancort, K. Sakthivel, R. Thayumanavan, C. F. Barbas III, *Tetrahedron: Asymmetry* **2001**, *42*, 4441−4444. [25b] J. M. Betancort, C. F. Barbas III, *Org. Lett.* **2001**, *3*, 3737−3740. [25c] A. Alexakis, O. Andrey, *Org. Lett.* **2002**, *4*, 3611−3614. [25d] O. Andrey, A. Alexakis, G. Bernardinelli, *Org. Lett.* **2003**, *5*, 2559−2561. [25e] P. Melchiorre, K. A. Jørgensen, *J. Org. Chem.* **2003**, *68*, 4151−4157. [25f] N. Halland, P. S. Aburel, K. A. Jørgensen, *Angew. Chem. Int. Eng. Ed.* **2003**, *42*, 661−665.

[26] Chiral amine catalysts: [26a] A. Corma, S. Iborra, I. Rodriguez, M. Iglesias, F. Sánchez, *Catalysis Lett.* **2002**, *82*, 237−242. [26b] D. Ma, K. Cheng, *Tetrahedron: Asymmetry* **1999**, *10*, 713−719. [26c] M. Ostendorf, S. van der Neut, F. P. J. T. Rutjes, N. Hiemstra, *Eur. J. Org. Chem.* **2000**, 105−113.

[27] Chiral bifunctional organocatalysts: T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672−12673.

[28] [28a] L. A. Flippin, J. M. Muchowski, D. S. Carter, *J. Org. Chem.* **1993**, *58*, 2463−2467. [28b] J. F. Remenar, B. L. Lucht, D. Kruglyak, F. E. Romesberg, J. H. Gilchirst, D. B. Collum, *J. Org. Chem.* **1997**, *62*, 5748−5754. [28c] S. H. Wiedemann, A. Ramírez, D. B. Collum, *J. Am. Chem. Soc.* **2003**, *125*, 15893−15901. [28d] L. M. Pratt, A. Newman, J. St. Cyr, H. Johnson, B. Miles, A. Lattier, E. Austin, S. Henderson, B. Hershey, M. Lin, Y. Balamraju, L. Sammonds, J. Cheramie, J. Karnes, E. Hymel, B. Woodford, C. Carter, *J. Org. Chem.* **2003**, *68*, 6387−6391.

[29] Chiral crown ethers, azacrown ethers: [29a] P. Bakó, Á. SzFllősy, P. Bombicz, L. Tőke, *Synlett* **1997**, 291−292. [29b] P.B. Bakó, T. Kiss, L. Tőke, *Tetrahedron Lett.* **1997**, *38*, 7259−7262. [29c] T. Novák, K. Ludányi, B. Pete, P. Bombicz, L. Tőke, G. Keglevich, *Tetrahedron: Asymmetry* **1999**, *10*, 2373−2380. [29d] P. Bakó, Z. Bajor, L. Tőke, *J. Chem. Soc., Perkin. Trans. 1* **1999**, 3651−3655. [29e] T. Bakó, P. Bakó, Á. SzFllősy, M. Czugler, G. Keglevich, L. Tőke, *Tetrahedron: Asymmetry* **2002**, *13*, 203−209. [29f] T. Bakó, P. Bakó, G. Keglevich, N. Báthori, M. Czugler, J. Tatai, T. Novák, G. Parlagh, L. Tőke, *Tetrahedron: Asymmetry* **2003**, *14*, 1917−1923.

[30] Chiral alkaloids (chiral amines): [30a] T. Uchida, K. Matsumoto, *Chem. Lett.* **1981**, 1673. [30b] A. Sera, K. Takagi, H. Katayama, N. Yamada, *J. Org. Chem.* **1988**, *53*, 1157−1161. [30c] D. Y. Kim, S. C. Huh, *Tetrahedron* **2001**, *57*, 8933−8938.

[31] Chiral phase-transfer catalysts: [31a] S. Colonna, H. Hiemstra, H. Wynberg, *Chem. Commun.* **1978**, 238−239. [31b] S. Colonna, A. Re, *J. Chem. Soc., Perkin. Trans. 1* **1981**, 547−552. [31c] E. J. Corey, F.-Y. Zhang, *Org. Lett.* **2000**, *2*, 4257−4259. [31d] T. Ooi, K. Doda, K. Maruoka, *J. Am. Chem. Soc.* **2003**, *125*, 9022−9023. [31e] T. Ooi, T. Miki, M. Taniguchi, M. Shiraishi, M. Takeuchi, K. Maruoka, *Angew. Chem. Int. Ed.* **2003**, *42*, 3796−3798.

[32] Metal L-prolinate catalysts: [32a] M. Yamaguchi, T. Shiraishi, Y. Igarashi, M. Hirama, *Tetrahedron. Lett.* **1994**, *35*, 8233−8236. [32b] M. Yamaguchi, Y. Igarashi, R. S. Reddy, T. Shiraishi, M. Hirama, *Tetrahedron.* **1997**, *53*, 11223−11236. [32c] See ref. [12e].

[33] L-Proline catalysts: V. Pham, S. Hanessian, *Org. Lett.* **2000**, *2*, 2975−2978.

[34] Nickel catalysts: A. Schionato, S. Paganelli, C. Botteghi, *J. Mol. Cat.* **1991**, *66*, 7−21.

[35] Heterobimetallic catalysts: [35a] E. Keller, A. L. Spek, B. L. Feringa, *Tetrahedron: Asymmetry* **1997**, *8*, 3403−3413. [35b] K. Funabashi, Y. Saida, M. Kanai, T. Arai, H. Sasai, M. Shibasaki, *Tetrahedron Lett.* **1998**, *39*, 7557−7558.

[36] Examples of γ-amino acids or pyrrolidinones: [36a] W. Hartwig, L. Born, *J. Org. Chem.* **1987**, *52*, 4352−4358. [36b] D.-F. Huang, L. Huang, *Tetrahedron* **1990**, *46*, 3135−3142. [36c] S. Kanemasa,

A. Tatsukawa, E. Wada, *J. Org. Chem.* **1991**, *56*, 2875−2883. [36d] E. Caudert, F. Acher, R. Azerad, *Synthesis* **1997**, 863−865. [36e] M. Seki, K. Kondo, *Synthesis* **1999**, 745−747. [36f] A. R. Katrizky, S. Mehta, H.Y. He, X. Cui, *J. Org. Chem.* **2000**, *65*, 4364−4369. [36g] B. B. Snider, Y. Gu, *Org. Lett.* **2001**, *3*, 1761−1763. [36h] M. Oba, S. Koguchi, K. Nishiyama, *Tetrahedron* **2002**, *58*, 9359−9363. [36i] Y. Hayashi, M. Shoji, S. Yamaguchi, T. Mukaiyama, J. Yamaguchi, H. Kakeya, H. Osada, *Org. Lett.* **2003**, *5*, 2287−2290. [36j] J. S. Bryans, N. E. A. Chessum, N. Huther, A. F. Parsons, F. Chelfi, *Tetrahedron* **2003**, *59*, 6221−6231. [36k] M. Oba, N. Nishiyama, K. Nishiyama, *J. Chem. Soc., Chem. Commn.* **2003**, 776−777. [36l] Z. Yan, J. Wang, W. Tian, *Tetrahedron Lett.* **2003**, *44*, 9383−9384. [36m] B. Alcaide, P. Almendros, J. M. Alonso, *J. Org. Chem.* **2004**, *69*, 993−996. [36n] G. Blay, I. Fernández, B. Monje, J. R. Pedro, *Tetrahedron* **2004**, *60*, 165−170.

[37] Examples of synthetic applications for biologically active products: [37a] J. S. Plummer, L. A. Emery, M. A. Stier, M. J. Suto, *Tetrahedron Lett.* **1993**, *34*, 7529−7532. [37b] V. L. Patorocinio, P. R. R. Costa, C. R. D. Correia, *Synthesis* **1994**, 474−476. [37c] Z. J. Witczak, Y. Li, *Tetrahedron Lett.* **1995**, *36*, 2595−2598. [37d] A. Bartels, P. G. Jones, J. Liebscher, *Tetrahedron: Asymmetry* **1997**, *8*, 1545−1549. [37e] J. S. Costa, A. G. Dias, A. L. Anholeto, M. D. Monteiro, V. L. Patrocinio, P. R. R. Costa, *J. Org. Chem.* **1997**, *62*, 4002−4006. [37f] A. C. Pinto, C. B. L. Freitas, A. G. Dias, V. L. P. Pereira, B. Tinant, J.-P. Declercq, P. R. R. Costa, *Tetrahedron: Asymmetry* **2002**, *13*, 1025−1031. [37g] A. G. Moglioni, B. N. Brousse, A. Álvarez-Larena, G. Y. Moltrasio, R. M. Ortuno, *Tetrahedron: Asymmetry* **2002**, *13*, 451−454.

[38] [38a] J. Mulzer, R. Zuhse, R. Schmiechen, *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 870−872. [38b] P. W. Baures, D. S. Eggleston, K. F. Erhard, L. B. Cieslinski, T. J. Torphy, S. B. Christensen, *J. Med. Chem.* **1993**, *36*, 3274−3277. [38c] A. I. Meyers, L. Snyder, *J. Org. Chem.* **1993**, *58*, 36−42. [38d] M. Braun, K. Oppenbusch, C. Unger, *Synlett* **1995**, 1174−1176. [38e] A. Diaz, J. G. Saro, J. L. Grancía-Navío, J. J. Vaquero, J. Alvarez-Builla, *Synthesis* **1997**, 559−562. [38f] T. Honda, F. Ishikawa, K. Kanai, S. Sato, D. Kato, H. Tominaga, *Heterocycles* **1996**, *42*, 109−111. [38g] M. Anada, O. Mita, H. Watanabe, S. Kitagaki, S. Hashimoto, *Synlett* **1999**, 1775−1777. [38h] M.-Y. Chang, P.-P. Sun, N.-C. Chang, *Heterocycles* **2003**, *60*, 1865−1872.

[39] [39a] C. Herdeis, H. P. Hubmann, *Tetrahedron: Asymmetry* **1992**, *3*, 1213−1221. [39b] N. Langlois, N. Dahuron, H.-S. Wang, *Tetrahedron.* **1996**, *52*, 15117−15126. [39c] M. Anada, S. Hashimoto, *Tetrahedron Lett.* **1998**, *39*, 79−82. [39d] C. Baldoli, S. Maiorana, E. Licandro, D. Perdicchia, B. Vandoni, *Tetrahedron: Asymmetry* **2000**, *11*, 2007−2014. [39e] M.-Y. Chang, P.-P. Sun, S.-T. Chen, N.-C. Chang, *Tetrahedron Lett.* **2003**, *44*, 5271−5273. [39f] Ref.[31c]

[40] Enantioselective Michael additions of 1,3-dicarbonyl compounds: [40a] N. Halland, T. Velgaard, K. A. Jørgensen, *J. Org. Chem.* **2003**, *68*, 5068−5074. [40b] N. Halland, T. Hansen, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2003**, *42*, 4955−4957.

[41] Base or acid anhydride catalyzed enol lactone synthesis: [41a] K. Kato, Y. Shizuri, Y. Hirata, *Chem. Commun.* **1968**, 324−325. [41b] K. Shizuri, K. Kato, Y. Hirata, A. Murobushi, S. Yamamura, *J. Chem. Soc., C* **1969**, 2774−2776. [41c] C. Wiener, C. H. Schroeder, B. D. West, K. P. Link, *J. Org. Chem.* **1962**, *27*, 3086−3088. [41d] L. R. Zehnder, J. W. Dahl, R. P. Hsung, *Tetrahedron Lett.* **2000**, *41*, 1901−1905. [41e] G. Speranza, A. D. Meo, S. Zanzola, G. Fontana, P. Manitto, *Synthesis* **1997**, 931−936. [41f] G. Speranza, C. F. Morelli, P. Manitto, *Synthesis* **2000**, 123−126.

[42] Solid catalyst-mediated enol lactone synthesis: [42a] A. D. L. Hoz, A. Moreno, E. Vázquez, *Synlett* **1999**, *5*, 608−610. [42b] Y. J. Lee, T. H. Tseng, Y. J. Lee, *Synthesis* **2001**, 2247−2254.

[43] Enol lactone synthesis under microwave irradiation: S. Tu, J. Zhou, P. Cai, H. Wang, J. Feng, *Synth. Commun.* **2001**, *31*, 3729−3733.

[44] Biologically active coumarins, flavonoids, neoflavonoids, and enol lactones: [44a] *The Handbook of Natural Flavonoids* (Eds.: J. B. Harborne, H.s Baxter), Wiley, Chichester, UK, **1999**, vol. 1, pp. 879 and vol 2., pp. 889. [44b] R. D. H. Murray, J. Medez, S. A. Brown, *The Natural Coumarins: Occurrence. Chemistry and Biochemistry*; John Wiley & Sons, New York, **1982**.

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