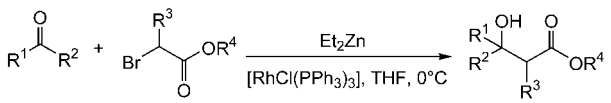
Multicomponent Reactions

Highly Enantioselective One-Pot, Three-Component Imino-Reformatsky Reaction**

Pier Giorgio Cozzi and Eleonora Rivalta*

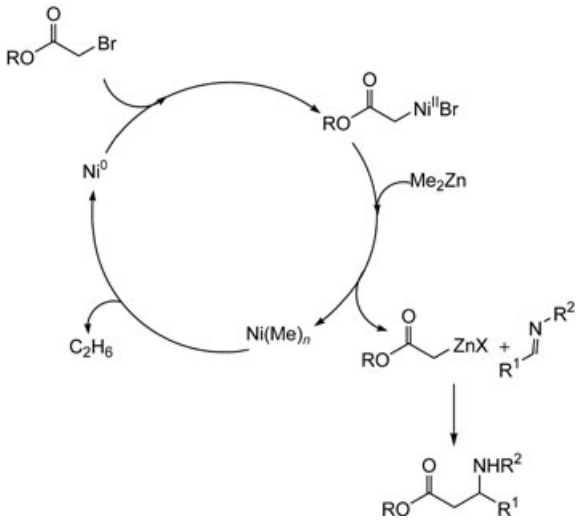
The Reformatsky reaction,[1] discovered more than 115 years ago, is still widely used in synthesis.[2] High functional-group tolerance and the in situ preparation of the reagent have contributed to its success. The reagent is prepared by the activation of zinc metal through a variety of different methods.[3] Recently, renewed interest in the catalytic redox reaction[4] has positively influenced further studies in the field.[5] Honda and co-workers have developed a new, interesting variant of the Reformatsky reaction, which uses Et_2Zn and $[RhCl(PPh_3)_3]$ in catalytic amounts (Scheme 1).[6]

Imines are suitable substrates for the Reformatsky reaction, and the so-called imino-Reformatsky reaction was first described by Gilman 60 years ago.[7] Although the use of this reaction in synthesis has great potential, it can be problematic, as a mixture of β-aminoesters and β-lactams is generally obtained. Recently, this problem was solved by using imines derived from 2-methoxyaniline.[8] In view of the increasing importance of β-amino acids as valuable synthetic tools[9] we were attracted by the interesting work published by Adrian and co-workers,[8b] who presented an efficient, nickel-catalyzed Reformatsky-type three-component condensation that combines aldehyde, 2-methoxyaniline, and a bromocarbonyl reagent (esters, ketones, and amides) in a one-pot reaction. The method was successfully applied on the micro- and macroscale and to combinatorial synthesis. Herein, we present the first practical one-pot three-component enantioselective imino-Reformatsky reaction, which is based on the use of *N*-methylephedrine as a cheap and recoverable chiral ligand.[10]



Scheme 1. Rhodium-catalyzed Reformatsky reaction developed by Honda and co-workers.

The efficient three-component Reformatsky reaction developed by Adrian and co-workers[8b] uses Me_2Zn in the presence of a catalytic amount of inexpensive $[NiCl_2(PPh_3)_2]$.[11] On the basis of detailed electrochemical study by Périchon, Sibille, and co-workers,[12] a reasonable mechanistic picture was presented by Adrian and co-workers. The mechanism involved the reduction of the Ni^{II} complex to a Ni^0 complex, oxidative addition of the bromoester to the Ni^0 complex, and a Ni^{II}/Zn^{II} exchange, which leads to an organozinc Reformatsky reagent. The proposed catalytic cycle (Scheme 2) was our starting point in developing an enantioselective variant. We reasoned that, contrary to other nickel-catalyzed[13] processes, a chiral ligand able to coordinate nickel was not crucial to transmit chiral information. Instead, we decided to surround the zinc enolate formed by transmetalation and the chelating imine with a chiral ligand able to coordinate zinc. Carreira and co-workers have developed a



Scheme 2. Catalytic cycle for the imino-Reformatsky reaction mediated by nickel.

[*] Prof. Dr. P. G. Cozzi, Dr. E. Rivalta
Dipartimento di Chimica "G. Ciamician"
Università di Bologna
Via Selmi, 2, 40126 Bologna (Italy)
Fax: (+39) 051-2099-456
E-mail: piergiorgio.cozzi@unibo.it

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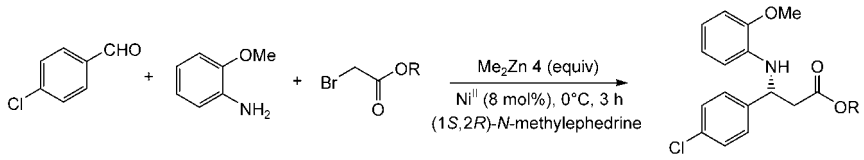
very efficient and simple method based on the use of *N*-methylephedrine for the addition of acetylides to aldehydes,[14] and Tan et al. have used *N*-alkylephedrine derivatives to add zinc acetylides to a ketone precursor of the anti-HIV drug efavirenz.[15] *N*-Methylephedrine can be considered as a privileged ligand[16] for zinc derivatives. For this reason we explored the Me_2Zn-mediated one-pot three-component imino-Reformatsky reaction with *N*-methylephedrine[17] as the chiral ligand. Me_2Zn plays several important roles in the reaction: a) Me_2Zn is the dehydrating agent responsible for the formation of the imine in situ; b) Me_2Zn can reduce the Ni^{II} salt to Ni^0; c) Me_2Zn reacts with the incipient nickel enolate to form the reactive zinc enolate; and, finally, d) Me_2Zn can coordinate *N*-methylephedrine, the amino alcohol used as a chiral ligand. We have chosen the imine obtained in situ from 2-methoxyaniline and *p*-chlorobenzaldehyde as a model substrate, in conjunction with different bromoacetates, Ni^{II} salts in catalytic amounts, and *N*-methylephedrine. We adjusted the protocol developed by Adrian and Snapper[8b] to investigate several experimental conditions of our process in detail (Table 1). In light of its multiple roles in this reaction, 4 equivalents of Me_2Zn was used. To ensure good enantiomeric excess, 1.5–1.6 equivalents of *N*-methylephedrine were employed in our process (Table 1, entries 2–5). *N*-methylephedrine can easily be separated from the adducts by acidic workup and recovered after extraction of the aqueous alkaline layer. The two solvents tested in the model reaction, CH_2Cl_2 and toluene, gave comparable results.[18] The crucial difference that determines the choice of solvent concerns the use of the nickel catalyst. $[NiCl_2(PPh_3)_2]$ is soluble in CH_2Cl_2 but is poorly soluble in toluene. We have also used $[Ni(acac)_2]$ hydrate, which is poorly soluble in both solvents. To compare results and guarantee reproducibility, we decided to add Ni^{II} salts as a solid to the reaction mixture containing Me_2Zn, imine, bromoester, and *N*-methylephedrine (see Supporting Information for details), at the indicated reaction temperature. The Ni^{II} salts are quickly dissolved in the reaction mixture and initiate the catalytic cycle. The $[RhCl(PPh_3)_3]$ complex also promotes the reaction, although the product was isolated with lower *ee* values than those obtained in the presence of nickel complexes (Table 1, entry 6). We also examined the enantiomeric excess attained in the model reaction with different bromoesters. Apart from the hindered *tert*-butyl bromoacetate (Table 1, entry 14), which gave a lower *ee* value than the others, similar enantiomeric excesses were attained with all type of esters examined.[19] Toluene was chosen as the solvent owing to the slightly better results obtained, and the scope of the reaction was investigated.

In Table 2 we report the results collected with different aldehydes. The reaction shows broad scope, since aromatic, aliphatic, unsaturated, and heterocyclic aldehydes are reactive and result in good to excellent enantioselectivites (up to 92% *ee*). Yields were generally only moderate, but no by-products were isolated. Better yield was obtained by increasing the reaction temperature, but at the expense of enantiomeric excess. We optimized the reaction temperature with all the different aldehydes so as to reach a compromise between yield and enantiomeric excess. Notably, α,β-unsaturated aldehydes are good reaction partners in this reaction and also lead to good enantiomeric excess.[20] The absolute configuration of the products obtained with (1*S*,2*R*)-*N*-methylephedrine as a chiral ligand was established in the case of aliphatic and aromatic aldehydes (isopropyl and phenyl), as shown in Scheme 3, following the general procedure of deprotection of 2-methoxyamines, developed by Josephsohn, Snapper, and Hoveyda (see Supporting Information for details).[21]

In conclusion, we have developed the first practical and highly efficient, enantioselective[22] one-pot three-component imino-Reformatsky reaction, which gives β-aminoesters in moderate to good

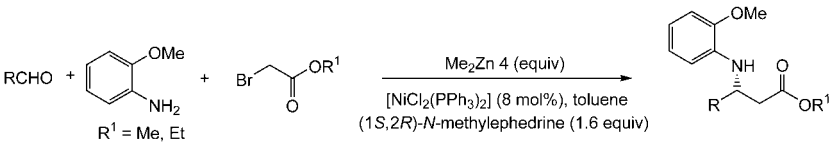
Table 1: Enantioselective one-pot imino-Reformatsky reaction of 4-chlorobenzaldehyde with 2-methoxyaniline and bromoacetates.[a]



Entry	Ni^{II}	R	Solvent	Yield [%][b]	*ee* [%][c]
1[d,e]	$[NiCl_2(PPh_3)_2]$	Et	CH_2Cl_2	82	68
2[e]	$[NiCl_2(PPh_3)_2]$	Et	CH_2Cl_2	92	75
3[f]	$[NiCl_2(PPh_3)_2]$	Et	CH_2Cl_2	85	81
4[f,g]	$[NiCl_2(PPh_3)_2]$	Et	CH_2Cl_2	75	86
5[f,h]	$[NiCl_2(PPh_3)_2]$	Et	CH_2Cl_2	88	86
6[i]	$[RhCl(PPh_3)_3]$	Et	CH_2Cl_2	70	72
7[f]	$[NiCl_2(PPh_3)_2]$	Et	toluene	75	86
8[f]	$[Ni(acac)_2]$	Et	toluene	57	84
9[f]	$[Ni(acac)_2]$	Me	toluene	57	84
10[f]	$[NiCl_2(PPh_3)_2]$	Me	toluene	60	86
11[f]	$[NiCl_2(PPh_3)_2]$	*i*Pr	toluene	66	83
12[f]	$[Ni(acac)_2]$	Bn	toluene	70	82
13[f]	$[NiCl_2(PPh_3)_2]$	Bn	toluene	60	87
14[f]	$[NiCl_2(PPh_3)_2]$	*t*Bu	toluene	50	76
15[j]	$[NiCl_2(PPh_3)_2]$	Et	toluene	73	78

[a] All the reactions were carried out at 0°C for 3 h in the presence of *N*-methylephedrine (1.6 equiv) and the Ni^{II} salt (7.5–8 mol%). [b] Yield of isolated product after chromatographic purification. [c] Determined by HPLC analysis (see Supporting Information for details). [d] *N*-methylephedrine: 1 equiv. [e] $[NiCl_2(PPh_3)_2]$ was added as a solution in CH_2Cl_2 as reported by Adrian and co-workers.[8b] [f] The Ni^{II} salt was added as solid to the reaction mixture. [g] *N*-methylephedrine: 1.8 equiv. [h] *N*-methylephedrine: 2 equiv. [i] Wilkinson catalyst, $[RhCl(PPh_3)_3]$, (5 mol%) was used and added as a solution in CH_2Cl_2.[8b] The reaction was stirred for 13 h at 0°C. [j] Recycling experiment: *N*-methylephedrine, recovered from the reaction, was dried under high vacuum for 3 h. The crude *N*-methylephedrine containing 2-methoxyaniline (10%) (checked by NMR and ES-MS) was used in another model reaction without any purification. The reaction was performed at −10°C for 14 h with $[NiCl_2(PPh_3)_2]$ (8 mol%).

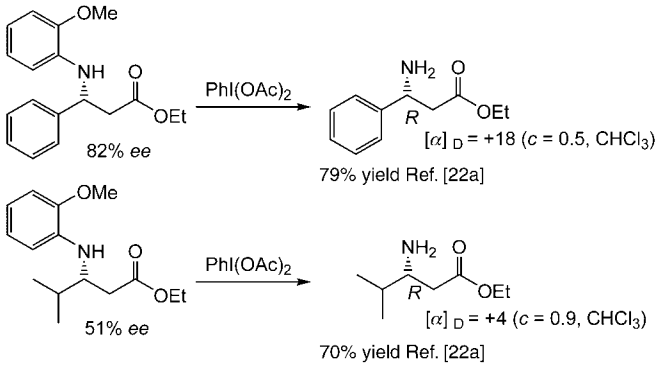
Table 2: Enantioselective imino-Reformatsky reaction with different aldehydes.



R^1 = Me, Et

Entry[a]	R	R^1	T [°C]	t [h]	Yield [%][b]	*ee* [%][c]
1	4-ClPh	Et	−25	3	62	90
2	4-ClPh	Me	−25	3	60	90
3	4-ClPh[d,e]	Et	−20	3	90	83
4	4-CF_3Ph	Et	−28	16	30	90
5	C_6F_5	Et	−28	6	41	90
6	PhCH=CH	Et	−20	48	60	85
7	Ph	Et	−30	48	63	83
8	Ph[d]	Et	−30	3	50	81
9	Ph[d,f]	Et	−20	4	85	57
10	*t*BuPh	Et	−30	24	40	82
11	*t*BuPh	Et	−30	48	76	74
12	2-thiophene	Et	−28	16	49	92
13	2-naphtyl	Et	−5	16	40	84
14	2-naphtyl	Et	25	1	72	74
15	4-MeOPh[d]	Et	−15	48	60	66
16	*i*Pr	Et	−10	48	57	64
17	*i*Pr	Et	−20	48	52	74
18	cyclohexyl[d]	Et	−20	3	67	80

[a] All the reactions were performed at the indicated temperature with *N*-methylephedrine (1.6 equiv) as a chiral ligand (see Supporting Information for experimental details).[b] Yield of isolated product after flash chromatography. [c] Determined by chiral HPLC analysis (Chiralcel OD column). [d] The reaction was slowly allowed to reach 0°C in 3–4 h before quenching. [e] A solution of Et_2Zn in toluene (1 M; 4 equiv) was used. GC–MS analysis performed on the crude reaction mixture after quenching revealed the presence of less than 5% of by-product derived from the attack of the ethyl on the imine. [f] The reaction was performed with the preformed purified imine in the presence of Me_2Zn (3 equiv) and *N*-methylephedrine (1 equiv) as chiral ligand.



Scheme 3. Correlation of aromatic and aliphatic β-aminoesters with known compounds.

yields. The reaction uses an inexpensive nickel salt, bromoesters, and *N*-methylephedrine as a chiral ligand. The chiral auxiliary, *N*-methylephedrine, is completely recovered after workup of the reaction and could be recycled (Table 1, entry 15).[23] The imines are prepared in situ, in the same reaction flask, and Me_2Zn is used as a dehydrating agent. More importantly, the reaction shows broad scope, since aromatic, heterocyclic, aliphatic and unsaturated aldehydes are suitable substrates for the reaction. We believe that the enantioselectivity (64–92% *ee*) can be improved as many other inexpensive homochiral aminoalcohols are available.[24] Further studies of this reaction are in progress in our laboratory and will be reported in due course.

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[17] Other chiral ligands were examined: binol, sparteine, chiral Schiff bases, tartramides gave racemic product; *N*-methylprolinol gave no reaction; cinchonine led to 57% *ee* but low conversion.

[18] The use of THF as reaction solvent gives an incomplete formation of imines compared with toluene and CH_2Cl_2.

[19] Bromoamides are reactive partners in our reaction but we have isolated racemic products by using several amides in the reaction with 4-chlorobenzaldehyde: P. G. Cozzi, E. Rivalta, unpublished results.

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