# Ni(II)-catalyzed enantioselective Nazarov cyclizations†

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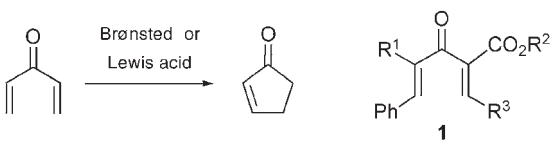
**Nazarov cyclizations are catalyzed by a dicationic Ni(II) complex containing the chiral tridentate phosphine Pigiphos; the catalyst exerts a high degree of torquoselectivity and affords the products in up to 88% ee.**

The Nazarov reaction involves the cyclization of divinyl ketones to cyclopentenones under the influence of strong acids (Scheme 1).[1] Its potential for the synthesis of cyclopentane building blocks is therefore quite vast.[2] Hence, it is hardly surprising that since the work of Denmark and Jones[3] who demonstrated that this reaction can proceed with high chemoselectivity, the number of studies concerning Nazarov cyclizations has grown significantly.[4]

Furthermore, the Nazarov cyclization is one of the few electrocyclic transformations that can be promoted in an enantioselective fashion by chiral catalysts. Problems such as the torquoselectivity of the cyclization step, as well as the regioselectivity of the deprotonation–reprotonation sequence, have attracted considerable interest and led to a number of specific solutions.[5] A remarkable example consists of catalytically controlling the ring-closing step with a chiral binol phosphate, thereby generating highly enantiomerically enriched cyclopentenones.[6] However, this process is limited to highly reactive dihydropyrane substrates. Despite recent progress, the genuine control of torquoselectivity of the cyclization step in truly catalytic Nazarov reactions remains very rare.[7] Several early and late transition-metal salts and complexes bearing a variety of ligands have been shown to be selective.[8] For example, we recently reported that dicationic V(IV) complexes bearing salen-type ligands are highly active catalysts for the cyclization of divinyl ketones bearing an ester group adjacent to the carbonyl unit (**1**, Scheme 1).[8a]

Given the demonstrated Lewis acidic properties of dicationic Ni(II)–Pigiphos‡[9] complexes **3** (Scheme 2) for the activation of




**Scheme 1** General formulation of the Nazarov cyclization and substrate type used in this study.

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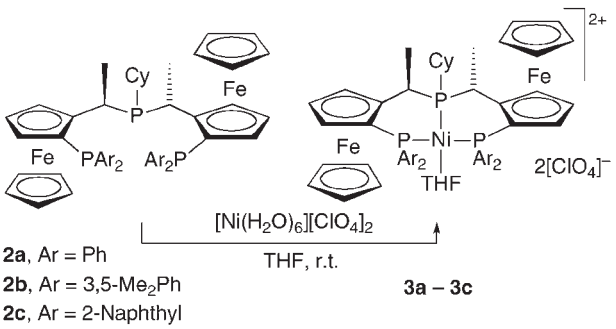
† Electronic supplementary information (ESI) available: Spectroscopic data for selected new compounds. CCDC reference number 682373 for compound **5**. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b806870d



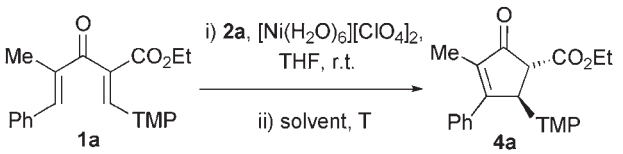

**Scheme 2** Pigiphos ligands **2** and their Ni(II) complexes **3**.

α,β-unsaturated nitriles in hydroamination[10] and hydrophosphination[11] reactions, we decided to embark on a study addressing their activity and selectivity in Nazarov cyclizations of substrates of type **1**. These compounds are tetra substituted divinyl ketones and at the same time unsaturated β-keto esters. They have been prepared by standard synthetic procedures and were partly reported before.[8a] We have chosen these substrates for the present study because the cyclopentenones generated upon the corresponding Nazarov cyclizations contain two new contiguous stereogenic centers, but are formed as single diastereoisomers. Since the stereogenic center at position 4 of the cyclopentenone ring is installed in the course of the electrocyclic step, the enantioselectivity of the reaction corresponds to the degree of torquoselectivity exerted by the catalyst. The dicationic Ni(II)–triphosphine complexes **3** can be easily prepared *in situ* by mixing Pigiphos ligands **2** with $[Ni(H_2O)_6][ClO_4]_2$ in dry THF.

We first examined the influence of various solvents as well as temperature on the enantioselectivity of the cyclization of divinyl ketone **1a** catalyzed by complex **3a**. The results shown in Table 1 clearly demonstrate that dichloromethane is the best solvent in view of achieving good selectivities. We were pleased to find that the Nazarov product **4a** could be obtained with 86% enantioselectivity when working at room temperature though with a relatively high catalyst loading of 10 mol% and a 1 : 2 nickel : ligand ratio. However, a temperature increase reduced the selectivity of the cyclization reaction (compare entry 1 with 2 and 3 in Table 1). THF was found to be as similarly suited a solvent as $CH_2Cl_2$ for the cyclization of dialkenyl ketone **1a** (82% ee). However, only 31% of the product could be isolated after a reaction time of ten days. Similar considerations apply to toluene (44% yield after ten days and 76% ee). The strongly coordinating solvent acetonitrile hampered the reaction completely and no conversion could be observed.

Further experiments were carried out with the two modified Pigiphos ligands **2b–c** under the above best conditions. The 3,5-dimethylphenyl (**2b**) and 2-naphthyl substituted (**2c**)

**Table 1** Influence of solvents and reaction temperature on the selectivity




| Entry | Solvent | *T* (°C) | Yield (%) | ee (%) |
|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | r.t. | 84 | 86 |
| 2 | $CH_2Cl_2$ | 40 | 79 | 85 |
| 3 | $Cl(CH_2)_2Cl$ | 60 | 91 | 60 |
| 4 | THF | r.t. | 31 | 82 |
| 5 | toluene | r.t. | 44 | 76 |
| 6 | MeCN | r.t. | no reaction | n.a. |

TMP = 2,4,6-trimethoxyphenyl.

Pigiphos afforded the cyclopentenone **4a** with only 43% and 62% enantioselectivity, respectively.

Next we examined the influence of the three different substituents $R^1$, $R^2$ and $R^3$ on the dialkenyl ketone scaffold **1** on the selectivity of the cyclization (Table 2). No significant effect appears to derive from the nature of $R^1$, both in steric and electronic terms, at least as illustrated by **4a** ($R^1$ = Me) and **4b** ($R^1$ = Ph). Both these products have been obtained at the same level of enantioselectivity (87% ee). The only difference between the two substrates **1a** and **1b** is that the latter requires a longer reaction time. Similar considerations appear to apply to $R^3$ when comparing the formation of the trimethoxyphenyl (TMP) derivative **4b** with that of **4d** (83% ee), bearing a 4-methoxyphenyl (PMP) group instead, which required a significantly extended reaction time.

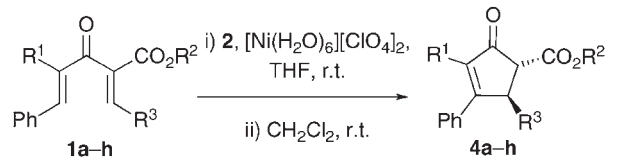
However, a significant drop in both enantioselectivity and yield was found for the combination $R^1$ = Me and $R^3$ = PMP. The Nazarov product **4c** could be isolated in only 32% yield and 71% ee. The ester group, as illustrated by the series **1a–1e–1g–1h** having otherwise the same $R^1$ and $R^3$ substituents, displays a more drastic influence on the outcome of the reaction. A very pronounced drop in both reactivity and selectivity resulted in going from ethyl and propyl to benzyl and 1-naphthyl ester, respectively. In the latter case no reaction could be observed even after exposing **1h** to the catalyst for one month.

Thus, a size match between the ester group and the aromatic substituent $R^3$ is essential in order to maintain reactivity and to obtain a high enantioselectivity. Since both the ester group and $R^3$ are connected to the same alkene unit, this might indicate that they are very influential in determining the ideal substrate conformation needed for the electrocyclic step.

The absolute configuration of the newly formed stereogenic centers in product **4a** was determined by X-ray crystallographic analysis of a sample obtained after transesterification to the corresponding (1*R*)-menthyl ester **5**. Compound **4a** itself is accessible in enantiomerically pure form by preparative chiral HPLC, however, we did not succeed in obtaining crystals suitable for an X-ray study. As shown in Fig. 1 the absolute configuration of both centers C4 and C5 of the cyclopentenone ring is *R*. This means that for the catalyst containing (*R*)-(*S*)-Pigiphos the conrotatory ring closure of **1a** must have taken place in an anti clockwise manner.

The main drawback of the Ni(Pigiphos) catalyst is its low activity. Even at the 10 mol% level the Nazarov cyclization takes several days to go to completion. The fact that strongly coordinating solvents such as acetonitrile completely shut down the reaction indicates that the thermodynamic stability as well as the kinetic lability of $[Ni(Pigiphos)L]^{2+}$ complexes are key to obtain active catalysts. Given that both compounds **1** and **4** are likely to coordinate to the Ni(Pigiphos) fragment *via* the oxygen atom of the ketone unit, one can reasonably expect a possible product inhibition of the catalytic reaction. Indeed, the major Ni(Pigiphos) species that can be observed by $^{31}$P-NMR spectroscopy during the whole course of the catalytic reaction involving substrate **1a** corresponds to the adduct obtained when mixing equivalent amounts of complex **3a** and

**Table 2** Ni-catalyzed Nazarov cyclizations of various dialkenyl ketones[a]§




| Compound | $R^1$ | $R^2$ | $R^3$ | Yield (%) | ee (%) |
|---|---|---|---|---|---|
| **4a** | Me | Et | TMP[b] | 84 | 86 |
| **4b** | Ph | Et | TMP[b] | 85 | 87 |
| **4c** | Me | Et | PMP[c] | 32 | 71 |
| **4d** | Ph | Et | PMP[c] | 96 | 83 |
| **4e** | Me | Pr | TMP[b] | 80 | 82 |
| **4f** | Ph | Pr | TMP[b] | 82 | 88 |
| **4g** | Me | Bn | TMP[b] | 58 | 45 |
| **4h** | Me | Np[d] | TMP[b] | no reaction | n.a. |

[a] Reaction times for full conversion are 6–8 d for substrates having $R^3$ = TMP and 9–15 d for $R^3$ = PMP. [b] TMP = 2,4,6-trimethoxyphenyl. [c] PMP = 4-methoxyphenyl. [d] Np = 1-naphthyl.

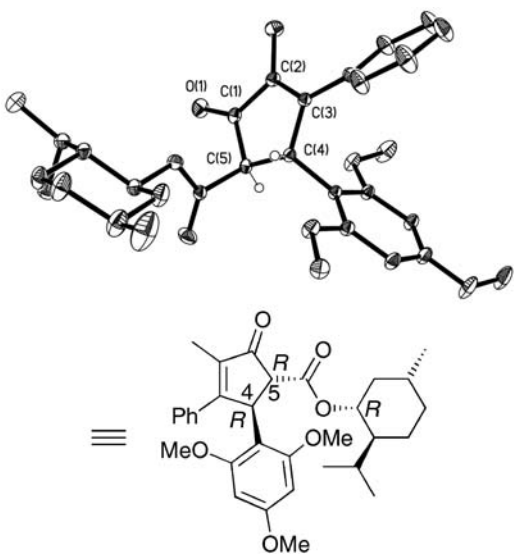
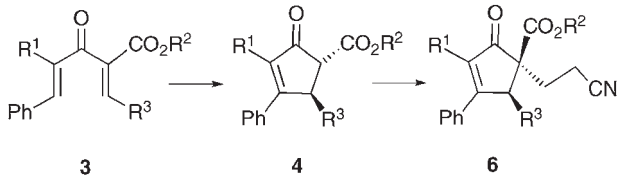



**Fig. 1** Molecular structure and absolute configuration of menthyl ester **5**.



**Scheme 3** Ni-catalyzed tandem Nazarov cyclization–Michael addition.

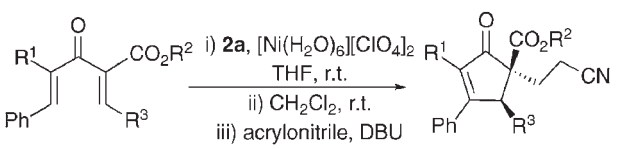
product **4a**. Thus, it appears that the Nazarov product forms a relatively stable complex with the catalyst and that the concentration of the truly catalytically active species must be low.

Despite this observation and because of the ability of the dicationic Ni(Pigiphos) unit to activate α,β-unsaturated nitriles towards nucleophilic attack,[10,11] we envisaged a further functionalization of products **4** as nucleophiles in a Michael-type addition to a cyanoolefin. The concept of this tandem process is shown in Scheme 3.

The completion of the Nazarov reaction of substrates **3** may be conveniently monitored by TLC. This was followed by the evaporation of the solvent, addition of an excess of acrylonitrile, both as a solvent and reagent, as well as a co-catalytic amount of the base DBU (10 mol%).[12] We were pleased to find that under these conditions a smooth and complete conversion of the Nazarov cyclization product **4** to the new, highly substituted cyclopentenones **6** took place at room temperature within *ca.* 3 h. Specifically, this procedure has been applied to the three selected dialkenyl ketones **3a**, **3c** and **3f** and in all cases the addition product was isolated in good to almost quantitative yield (see Table 3). The new compounds **6a**, **6c** and **6f** display the same level of enantioenrichment as their corresponding precursors **4**. Although we did not determine the absolute configuration of the new products **6**, it is reasonable to assume that the generation of the new quaternary stereogenic center occurs with inversion of configuration at position 5 of the cyclopentenone ring.

The results obtained with our nickel catalyst are very encouraging because they concern Nazarov substrates that have been so far investigated only with stoichiometric amounts of a chiral Lewis acid.[5a] Furthermore, the Ni(Pigiphos) system is also able to catalyze the addition of the Nazarov products to acrylonitrile, thus representing a bonus with respect to other catalysts. We are

**Table 3** Ni-catalyzed tandem Nazarov cyclization–Michael addition




| Compound | $R^1$ | $R^2$ | $R^3$ | Yield (%) | ee (%) |
|---|---|---|---|---|---|
| **6a** | Me | Et | TMP[a] | 78 | 87 (86)[c] |
| **6c** | Me | Et | PMP[b] | 63 | 72 (71)[c] |
| **6f** | Ph | Pr | TMP[a] | 97 | 88 (88)[c] |

[a] TMP = 2,4,6-trimethoxyphenyl. [b] PMP = 4-methoxyphenyl. [c] Value in brackets is for the Nazarov cyclization.

therefore currently pursuing more active modifications of this nickel catalyst in order to extend the scope of its applications.

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## Notes and references

‡ Pigiphos: bis{(*R*)-1-[(*S*)-2-(diphenylphosphanyl)ferrocenyl]ethyl}-cyclohexylphosphane.

§ General procedure for the nickel(II)-catalyzed Nazarov cyclization (and Michael addition): $[Ni(H_2O)_6][ClO_4]_2$ (5 μmol, 0.1 equiv.) and Pigiphos **2** (0.01 mmol, 0.2 equiv.) were dissolved in dry THF (1 mL) under argon. After stirring for 16 h at room temperature, the solvent was evaporated to dryness and the residue was dried under vacuum for 3 h. Afterwards the Nazarov substrate **1** (0.05 mmol, 1 equiv.) and $CH_2Cl_2$ (1 mL) were added. After the cyclization completed, the solvent was evaporated and the residue was purified by column chromatography. For the Michael addition, the solvent was evaporated after the Nazarov cyclization completed, as monitored by TLC. Acrylonitrile (1 mL) and DBU (5 μmol, 0.1 equiv.) were then added and the mixture was stirred for 3 h, after which time the reaction was complete. After evaporation of the solvent the residue was purified by column chromatography. The enantioselectivities were determined by chiral HPLC (Dr Maisch, ReproSil Chiral DP). All compounds of type **4** bearing a TMP substituent show hindered rotation about the C(4)–$C_{ipso}$ bond at r.t., as shown by NMR spectroscopy (see ESI†).

¶ Crystal data for compound **5**: $C_{32}H_{40}O_6$, $M$ = 520.64, orthorhombic, space group $P2_12_12_1$ (no. 19), $a$ = 10.0389(5), $b$ = 15.9508(7), $c$ = 18.4174(8) Å, $V$ = 2949.2(2) Å$^3$, $D_c$ = 1.173 g cm$^{-3}$, $T$ = 200(2) K, $Z$ = 4, 120 948 reflections measured, 14 329 unique ($R_{int}$ = 0.0493), $R_1$ = 0.0440 [$I > 2\sigma(I)$], w$R_2$ = 0.1089. Some disorder present in the molecule has not been modelled. CCDC reference number 682373. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b806870d


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12 This type of procedure has been used before in our laboratory for similar Ni(Pigiphos)-catalyzed additions of simple, achiral 1,3-diketones to unsaturated nitriles: Y. Liu and A. Togni, to be published. See also: Y. Liu, PhD Thesis Nr. 17006, ETH Zürich, 2007.