Nickel catalysed asymmetric cycloisomerisation of diethyl diallylmalonate†

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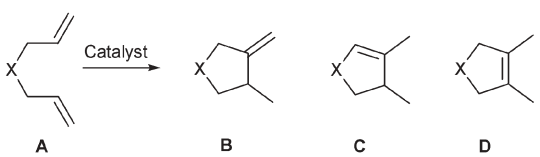
Cationic nickel catalysts with monodentate phosphoramidites and Wilke's azaphospholene as ligands are highly regio- and enantioselective catalysts for the cycloisomerisation of diethyl diallylmalonate.

Chiral carbo- and heterocycles represent an important structural motif in biologically active substances. Therefore, the development of efficient stereoselective synthetic methods to generate this class of compounds is highly desirable. The transition metal catalysed cycloisomerisation of 1,6-dienes (**A**) offers an atom economic[1] route to 5- or 6-membered carbo- or heterocycles.[2] A number of achiral transition metal catalyst systems, for example based on Pd-,[3] Ni-,[4] Rh-,[5] Ru-[6] and Ti,[7] are known to allow high levels of chemo- and regioselectivity towards the individual 5-membered ring products **B**–**D** (Scheme 1). In contrast, only very few examples of enantioselective catalysts have been published so far.

A particular challenge is the design of catalytic systems that show high chemo-, regio-, and enantioselectivity for the formation of the thermodynamically least favoured product **B** providing an exocyclic methylene group for further transformation. A catalyst based on $[(CH_3CN)_2PdCl_2]$, 2 $AgBF_4$ and (*R*,*R*)-4,4′-dibenzyl-bisoxazoline or (−)-sparteine as chiral ligands gave promising enantiomeric excesses (ee's) up to 60% for the cyclisation of diethyl diallylmalonate (X = $C(CO_2Et)_2$), but conversions and regioselectivities remained disappointingly low.[8] Much earlier, a menthyl phosphine modified cationic nickel complex was found to catalyse the asymmetric cyclisation of 1,6-heptadiene (X = CH_2) and of diallylether (X = O) with optical yields up to 37%.[9] In spite of this pioneering work, we are not aware of attempts to develop nickel-catalysed asymmetric cycloisomerisation as a synthetic strategy to date.

Herein we report a nickel based catalyst system for the cycloisomerisation of diethyl diallylmalonate (**1**) showing high activities, very high regioselectivities towards diethyl 3-methylene-4-methylcyclopentane-1,1-dicarboxylate (2) and ee values up to 80% (Scheme 2). Representative key results are summarised in Table 1.‡



Scheme 1 Cycloisomerisation of 1,6-dienes (X = CH_2, $C(CO_2R)_2$, O, N–R *etc.*).

† Dedicated to Professor Günther Wilke on the occasion of his 80th birthday.

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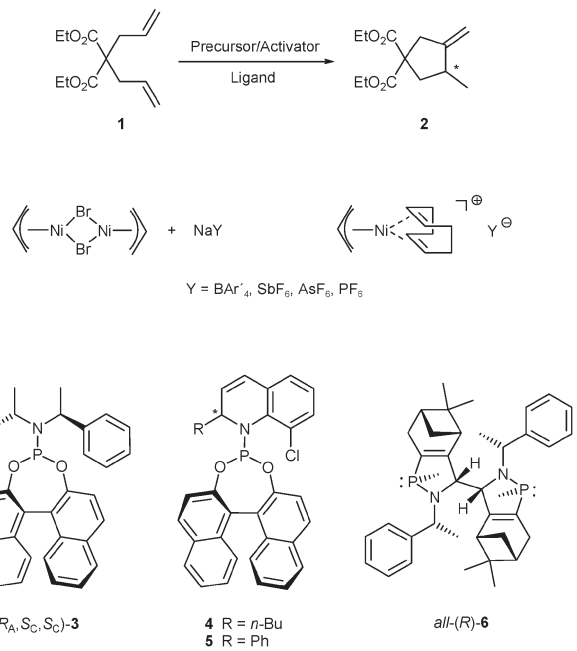
Based on the formal analogy between the intermolecular hydrovinylation and the intramolecular cycloisomerisation process, we have chosen catalysts with proven potential for the first reaction type[10,11] as the starting point of our study.

Despite its excellent performance in the hydrovinylation of styrene,[10] the system $[\{Ni(allyl)Hal\}_2]$/(R_A,S_C,S_C)-**3**/$NaBAr'_4$ (Ar′ = 3,5-$(CF_3)_2$-C_6H_3, Hal = Cl, Br) led to disappointingly low conversions and selectivities in the cycloisomerisation of **1** (Entry 1). Similarly, the system $[\{Ni(allyl)Cl\}_2]$/(R_A,R_C)-**4**/$NaBAr'_4$ is not effective for the cycloisomerisation of **1** (Entry 2) even though it is able to promote the hydrovinylation. The other diastereomer (R_A,S_C)-**4**, however, which forms an active nickel catalyst for styrene oligomerisation but not for styrene hydrovinylation, gave for the first time promising results. In combination with $[\{Ni(allyl)Br\}_2]$ and $NaBAr'_4$ complete conversion within 19 h (5 mol% Ni at room temperature) has been achieved with a regioselectivity of 87% and an *ee* of 48% (Entry 3).

In order to avoid the dehalogenation step during the formation of the *in situ* catalyst we decided to use the cationic precursor $[Ni(allyl)(cod)][BAr'_4]$[12,13] (cod = 1,5-cyclooctadiene) instead of the $[\{Ni(allyl)X\}_2]$/$NaBAr'_4$ system. This led to a dramatic



Scheme 2 Chemo-, regio-, and enantioselective cyclisation of diethyl diallylmalonate (**1**) and precatalysts and ligands used in the present study.

Table 1 Cycloisomerisation of diethyl diallylmalonate (**1**)[a]

No.	Precursor/Activator	Ligand	*t*/h	Cv.(%)	Sel.(%)[b]	*ee* (%)[c]
1	[{Ni(allyl)Br}$_2$]/NaBAr′$_4$	(R_A,S_C,S_C)-**3**	24	75	65	39 (−)
2	[{Ni(allyl)Cl}$_2$]/NaBAr′$_4$	(R_A,R_C)-**4**	17	3	50	—
3	[{Ni(allyl)Br}$_2$]/NaBAr′$_4$	(R_A,S_C)-**4**	19	100	87	48 (−)
4	[Ni(allyl)(cod)][BAr′$_4$]/-	(R_A,S_C)-**4**	0.5	94	97	46 (−)
5	[Ni(allyl)(cod)][BAr′$_4$]/-	(R_A,R_C)-**5**	0.5	90	93	40 (−)
6	[{Ni(allyl)Br}$_2$]/NaBAr′$_4$	*all*-(*R*)-**6**	17	81	91	79 (+)
7	[Ni(allyl)(cod)][BAr′$_4$]/-	*all*-(*R*)-**6**	0.5	96	91	71 (+)
8[d]	[Ni(allyl)(cod)][BAr′$_4$]/-	*all*-(*R*)-**6**	0.5	37	89	71 (+)
9[e]	[Ni(allyl)(cod)][BAr′$_4$]/-	*all*-(*R*)-**6**	0.5	61	84	59 (+)
10[f]	[Ni(allyl)(cod)][BAr′$_4$]/-	*all*-(*R*)-**6**	24	33	97	80 (+)
11	[Ni(allyl)(cod)][SbF_6]/-	*all*-(*R*)-**6**	0.5	92	91	72 (+)
12	[Ni(allyl)(cod)][AsF_6]/-	*all*-(*R*)-**6**	0.5	88	94	74 (+)
13	[Ni(allyl)(cod)][PF_6]/-	*all*-(*R*)-**6**	0.5	57	84	74 (+)

[a] T = 20 °C, dichloromethane, Substrate/Ni = 20, P(Ligand)/Ni = 1, Ar′ = 3,5-$(CF_3)_2$-C_6H_3, cod = 1,5-cyclooctadiene. [b] Regioselectivity towards **2**. [c] The *ee* values were determinated by chiral HPLC (Chiracel OJ-H, *n*-heptane/*i*-propanol: 99.975/0.025, 0.5 ml min^{-1}, 203 nm, retention times: 19 min (−), 21 min (+)). [d] Substrate/Ni = 200. [e] T = 50 °C, dichloroethane, Substrate/Ni = 100. [f] T = 0 °C.

improvement of catalytic activity and almost complete conversion was reached within 30 min corresponding to lower limit for the turnover frequency of 39 h^{-1}. Gratifyingly, the use of the cationic precursor also gave higher regioselectiviy with only marginal if any reduction of enantioselectivity (Entry 3/4).[14]

With this promising system in hand, we extended the structural variation of the ligand framework. Changing the *n*-Bu group in ligand **4** to a phenyl substituent in **5**[15] resulted again in an active system if the stereochemistry at the chiral carbon center in the 2-position of the quinoline backbone was maintained.[16] Slightly lower regio- and enantioselectivities were observed, however, with the aromatic side group (Entry 4/5).

Finally, we were very pleased to find that Wilke's azaphospholene ligand *all*-(*R*)-**6** affords a very active and stereoselective catalyst system for the cycloisomerisation of **1**. With [{Ni(allyl)Br}$_2$] and NaBAr′$_4$ a conversion of 81%, a regioselectivity of 91% and an *ee* value of 79% were achieved after 17 h (Entry 6). With [Ni(allyl)(cod)][BAr′$_4$] as precursor the activity was again strongly increased accompanied by only a small decrease in enantioselectivity (Entry 7).

Lowering of catalyst loading from 5 mol% to 0.5 mol% (Entry 8) resulted in no depletion of enantiomeric excess and regioselectivity. An average turnover frequency of 148 h^{-1} was achieved under these conditions. Increasing the reaction temperature from 20 °C to 50 °C led to lower regioselectivity and *ee* with no significant improvement of turnover rates, indicating partly decomposition of the catalyst (Entry 9). On the other hand, lowering the reaction temperature led to further increase in regio- and enantioselectivity albeit at the expense of catalyst activity (Entry 10). 80% *ee* were achieved under these conditions at almost perfect chemo- and regioselectivity, currently providing by far the best results for this transformation.

As counterion effects are often very pronounced in olefin dimerisation,[17] this aspect was assessed briefly also for the new cycloisomerisation system (Entry 7, 11–13). Catalyst activity was found to decrease somewhat in the order [BAr′$_4$]$^-$ > [SbF_6]$^-$ > [AsF_6]$^-$ ≫ [PF_6]$^-$. The highest regio- and enantioselectivities were obtained with the [AsF_6]$^-$ counterion. In general, however, the anion effects observed with [Ni(allyl)(cod)][Y]/*all*-(*R*)-**6** in the cycloisomerisation are considerably less pronounced than with the same ligand under hydrovinylation conditions.[17,18]

In summary we have demonstrated that cationic nickel catalysts comprising phosphoramidite and azaphospholene ligands **3**–**6** are able to affect the cycloisomerisation of diethyl diallylmalonate (**1**) to give the corresponding methyl-substituted *exo*-methylenecyclopentane derivative (**2**) with regioselectivities up to 97% and *ee*'s up to 80%, opening a promising synthetic strategy for the formation of chiral 5-membered carbocycles.

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Notes and references

‡ Procedure for a typical catalytic reaction: A solution of the ligand (0.03 mmol P) in CH_2Cl_2 (2 mL) was added at room temperature to a solution of the nickel precursor (0.03 mmol Ni) in CH_2Cl_2 (3 mL) under inert gas conditions. After 15 min of stirring, diethyl diallylmalonate (0.6 mmol) was added *via* a syringe to the yellow catalyst solution. If required, the activator (*ca.* 0.1 mmol) was added at this stage. The mixture was stirred for the desired reaction time and the reaction was then stopped by adding aqueous ammonia (1 mL). The organic phase was washed with water (3 × 2 mL), dried over Na_2SO_4, and analysed by GC and GC-MS. For analysis by chiral HPLC the chlorinated solvent was replaced by *n*-heptane/*i*-propanol and the solution was filtered through a pad of silica. Further details and modifications of the conditions are given in Table 1.

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