Influence of the temperature on the enantioselectivity of the cobalt catalysed homo Diels–Alder reactions

Olivier Pardigon [a], Alphonse Tenaglia [b], Gérard Buono [b],*

[a] *Centre de Recherches d'Ingénièrie et Technologie, Aventis, 24 Av. Jean Jaurès, F 69053 Decines Charpieu Cédex, France*
[b] *Ecole Nationale Supérieure de Synthèse, de Procédés et d'Ingénièrie Chimiques d'Aix-Marseille, Université Aix-Marseille, UMR CNRS 6516, Av. Escadrille Normandie-Niemen, F 13397 Marseille Cedex 20, France*

Abstract

Depending on the variation of the temperature and on the nature of the substituent of alk-1-ynes **2**, the enantioselectivity of the deltacyclene formation in the cobalt catalysed $[2 + 2 + 2]$ cycloaddition of norbornadiene **1** and acetylenes **2**, can be achieved with up to 98%. The best enantioselectivities observed around 14 °C are in agreement with the *Isoinversion principle* (IIP).
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1. Introduction

The cobalt-catalysed homo Diels–Alder (HDA) cycloaddition of norbornadiene **1** (NBD) and acetylenes **2** first reported by Lyons et al. [1a,1b] has allowed a facile access to condensed tetracyclic structures termed deltacyclenes **3** [1c]. The enantioselective version of these cycloadditions has been achieved by Lautens et al. [1c,2], Brunner et al. [3a], Brunner and Prester [3b], Brunner and Reimer [3c], Binger et al. [4] and our group [5] by the use of catalysts associated with chiral phosphines. We reported a convenient method for the preparation of chiral deltacyclenes in high e.e. using a $[CoI_2/Zn/L_n]$ catalyst system with enantio-pure organophosphorus ligands readily

available from cheap amino acids [5].[1] The deltacyclenes **3** feature an interesting framework which can be viewed as an entry to the less strained tricyclic structures *brendanes*, *brexanes* or *quinanes* [6].

During our investigations, we have been intrigued by the variation of the enantiomeric excess (e.e.) of the cycloadducts **3** at different reaction temperatures. We report now a detailed study and a rationalisation of the results making use of the *Isoinversion principle* [7].

2. Experimental

2.1. Catalytic HDA reactions

General procedure: Alkyne **2** (10 mmol) and norbornadiene **1** (921 mg, 10 mmol) were added to a

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* Corresponding author. Tel.: +33-4-91-28-86-81;
fax: +33-4-91-28-27-42.
E-mail address: buono@spi-chim.u-3mrs.fr (G. Buono).

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[1] Metal catalysed deltacyclene formation can also be achieved using Co(II)-complexes activated with Lewis acids such as ZnI_2 or $ZnCl_2$ (see [4]).
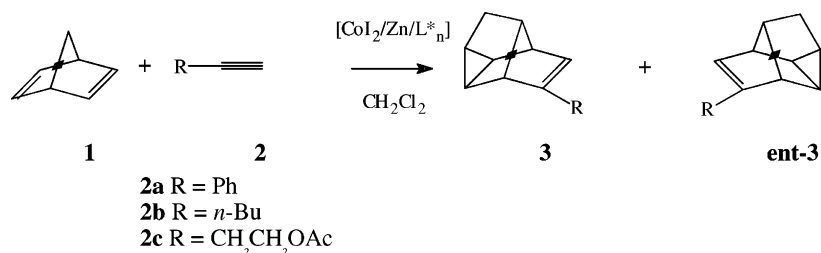
Scheme 1. Enantioselective HDA reaction of norbornadiene **1** and alkynes **2** catalysed by cobalt species.

suspension of CoI_2 (78 mg, 0.25 mmol), organophosphorous ligand (0.5 mmol for **4**, 0.25 mmol for **5** or **6**), and zinc powder (163 mg, 2.5 mmol) in dry CH_2Cl_2 (6 ml). The mixture was stirred in a thermostated bath ($\pm 1\,^\circ$C) until completion, diluted with Et_2O (15 ml), and filtered through a Celite pad. The crude product was purified by medium pressure liquid chromatography on silica gel column. The enantiomeric excesses (e.e.) were determined by GC using He as a carrier gas (0.55 bar) on a 40-m Lipodex E (Heptakis (6-*O*-methyl-2,3-di-*O*-pentyl)-β-cyclodextrin) column at 90 °C (injection temperature 170 °C) [5b].

3. Results and discussion

Seven combinations organophosphorus ligand (monodentate oxazaphospholidine **4**, or bidentate AMPP **5** and **6**[2]/represented as L_n^*)/acetylene **2a–c** characterised by fair to good enantioselectivities were selected (Schemes 1 and 2).

According to the Eyring's formalism [8], the logarithm of the ratio of the relative global rates $\ln(k_R/k_S) = -\Delta\Delta H^\#/RT + \Delta\Delta S^\#/R$[3,4,5] was

found to be linearly dependent on the reciprocal of the temperature near the inversion point T_{inv} for each temperature range $T > T_{inv}$ and $T < T_{inv}$. Strict linearity on both the sides afforded two sets of activation parameters $(\Delta\Delta H_1^\#, \Delta\Delta S_1^\#)$, $(\Delta\Delta H_2^\#, \Delta\Delta S_2^\#)$, deduced by the slope and the intercept of the two lines, respectively (Fig. 1 and Table 1).

The experimental values of the e.e. were determined with five analytical results taking into account the shape of each enantiomer signal. Therefore, statistical values such as means and variances are available, and the uncertainties on the calculated e.e., Δe.e. have been taken in account for the determination of the uncertainties on the slopes and origin ordinate.[4] These values have been used to express the gaps framing the whole set of activation parameters $\Delta\Delta H_i^\#$, $\Delta\Delta S_i^\#$.

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[2] AMPP stands for aminophosphinophosphinite. Depending on the class of the ligand (mono or diphosphine) and more specifically on the nature of the heteroatom (N, O) bounded to phosphorus, the cycloaddition proceeds smoothly with temperature ranging from −25 to +40 °C, affording deltacyclenes 3 in moderate to good yields and good to excellent enantioselectivities (see [5]).

[3] We assumed the following formalism: k_R and k_S are the relative global rates of formation of each enantiomer **3** and **ent-3**. The capitals *R* and *S* refers to the absolute configuration of carbon bearing the oxygen atom of compounds after hydroboration-oxidation and esterification with Mosher's MTPA used for the determination of the absolute configuration of deltacyclenes 3. Due to the CIP sequential rules, the designation [*R*] or [*S*] might be inverted when the alkyl moiety is replaced by a phenyl group, without inversion

of the absolute configuration of the deltacyclene framework (see [5]). We also assumed the ratio of the global rates k_R/k_S as the distribution ratio [*R*]/[*S*] of enantiomers at the completion of the reaction (related to the measured e.e. values), since we shown that the reaction was not reversible, and enantioselectivity remaining unchanged.

[4] The uncertainties on the slopes and on the origin ordinates depend on the number of experimental values which have been taken into account to draw a half straight line. The resolution between two signals and the return to the baseline mainly depends of the sensibility of the analytical method used for the determination of e.e. (GC, 1H NMR or 19F NMR; see ref. [5a]). The second part of the Eyring diagram (temperatures ranging from 0 to (15–20) °C) involves less experimental values than the first part (temperatures ranging from (15–20) to 45 °C). Therefore, the former is characterised by more increased uncertainties on $\Delta\Delta S_2^\#$ and $\Delta\Delta H_2^\#$ values. The poor reactivity of the catalytic system [$CoI_2(L_n^*)$/Zn] at temperatures below 0 °C has restricted the present study (former part), and the low boiling point of dichloromethane has limited the extension at higher temperatures (later part).

[5] The uncertainties evaluated for the determination of $\Delta\Delta H_i^\#$, $\Delta\Delta S_i^\#$, were used to evaluate the uncertainties of $\delta\Delta\Delta H^\#$ and $\delta\Delta\Delta S^\#$ values.
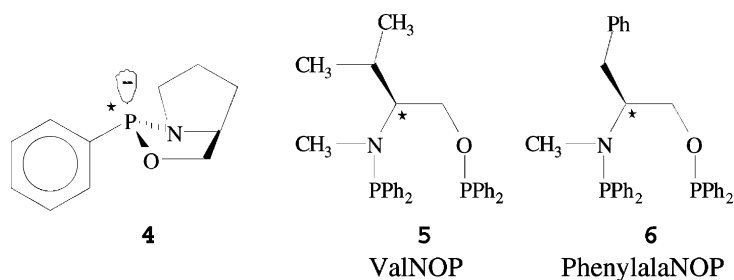
Scheme 2. Selected organophosphorus ligands for the [2 + 2 + 2] cycloaddition.

The combinations A, B and C involving ValNOP **5** and phenylacetylene **2a** or hex-1-yne **2b** are well characterised by very similar values for the slopes of each half straight line in the two areas $T < T_{inv}$ and $T > T_{inv}$, the slope of each straight line are reversed before and after the inversion points T_{inv} (Fig. 2). For combinations D and E, which concern acetylene **2c** featuring an oxygen atom at remote position, the slopes have lower values, with no significant change of the sign

before and after the inversion points T_{inv} (moderate to low incidence of the temperature on the enantioselectivity of the cycloaddition) [5b]. This typical change of behaviour of oxygenated alkynes suggests a quite different and less temperature dependent mechanism for the formation of cycloadducts **3c** and **ent-3c**.

With combination F, involving a monodentate ligand **4**, the e.e. was somewhat lower than those observed with a bidentate ligand such as ValNOP **5** or
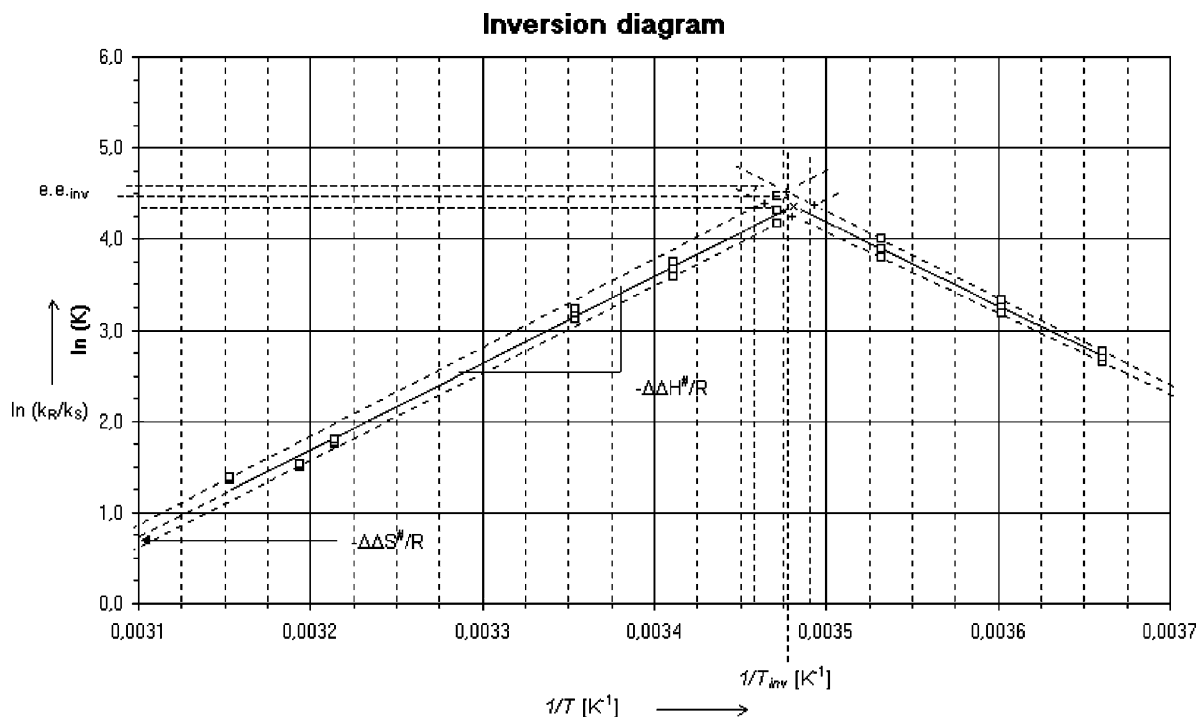

Fig. 1. Eyring plot for the enantiomeric excess of the HDA of norbornadiene **1** and phenylacetylene **2a** using ValNOP **5** (combination (A) CoI$_2$/**5**/Zn/**2a**/**1**: 0.025/0.025/0.25/1.0/1.0).

Table 1
Activation parameters $\Delta\Delta H_1^{\#}$, $\Delta\Delta S_1^{\#}$ for $T > T_{\mathrm{inv}}$, and $\Delta\Delta H_2^{\#}$, $\Delta\Delta S_2^{\#}$ for $T < T_{\mathrm{inv}}$ for the A–H combinations

Entry	System	T_{inv} (°C)	e.e._inv (%)	$\Delta\Delta H_1^{\#}$(kcal/mol)	$\Delta\Delta H_2^{\#}$ (kcal/mol)	$\delta\Delta\Delta H^{\#}$ (kcal/mol)	$\Delta\Delta S_1^{\#}$ (cal/mol/K)	$\Delta\Delta S_2^{\#}$ (cal/mol/K)	$\delta\Delta\Delta S^{\#}$ (cal/mol/K)
1	A	14.2 ± 1.4	97.5 ± 0.4	−18.0 ± 0.4	18.2 ± 0.7	37.1 ± 1.0	−57.2 ± 0.8	71.8 ± 2.6	129.0 ± 3.4
2	B	8.3 ± 1.6	97.5 ± 0.3	−14.7 ± 0.3	15.6 ± 1.3	30.4 ± 1.5	−43.7 ± 1.0	64.1 ± 4.8	107.8 ± 5.6
3	C	17.1 ± 2.1	97.5 ± 0.4	−16.6 ± 0.6	1.6 ± 0.2	18.2 ± 0.8	−48.6 ± 2.2	14.2 ± 0.9	62.8 ± 3.1
4	D	18.3 ± 5.3	95.2 ± 0.4	−4.0 ± 0.1	−1.3 ± 0.1	2.7 ± 0.2	−6.5 ± 0.4	2.7 ± 0.1	9.2 ± 0.5
5	E	20.2 ± 6.2	95.0 ± 0.5	−4.0 ± 0.1	−1.8 ± 0.1	2.2 ± 0.3	−6.5 ± 0.4	1.0 ± 0.4	7.5 ± 0.8
6	F	15.0 ± 0.3	76.6 ± 1.0	−6.4 ± 0.3	13.9 ± 0.4	20.3 ± 0.7	−18.1 ± 1.1	52.3 ± 1.4	70.4 ± 2.5
7	G	23.3 ± 1.5	74.4 ± 0.6	−0.6 ± 0.2	−19.4 ± 3.5	−18.7 ± 3.8	1.6 ± 0.8	−61.5 ± 12.2	−63.1 ± 13.0
8	H	18.6 ± 2.4	93.5 ± 0.7	−0.4 ± 0.2	−12.5 ± 1.1	−12.2 ± 1.3	5.5 ± 0.4	−36.3 ± 3.7	−41.8 ± 4.1

A, 1 eq. ValNOP **5**/NBD/phenylacetylene **2a**; B, 1 eq. ValNOP **5**/NBD/hex-1-yne **2b**; C, 2 eq. ValNOP **5**/NBD/hex-1-yne **2b**; D, 1 eq. ValNOP **5**/NBD/4-acetoxybut-1-yne **2c**; E, 2 eq. ValNOP **5**/NBD/4-acetoxybut-1-yne **2c**; F, 4 eq. 2-phenyl-1,3,2-oxazaphospholidine **4**/phenylacetylene **2a**; G, 1 eq. phenylalaNOP **6**/NBD/phenylacetylene **2a**; H, 2 eq. phenylalaNOP **6**/NBD/hex-1-yne **2b**.
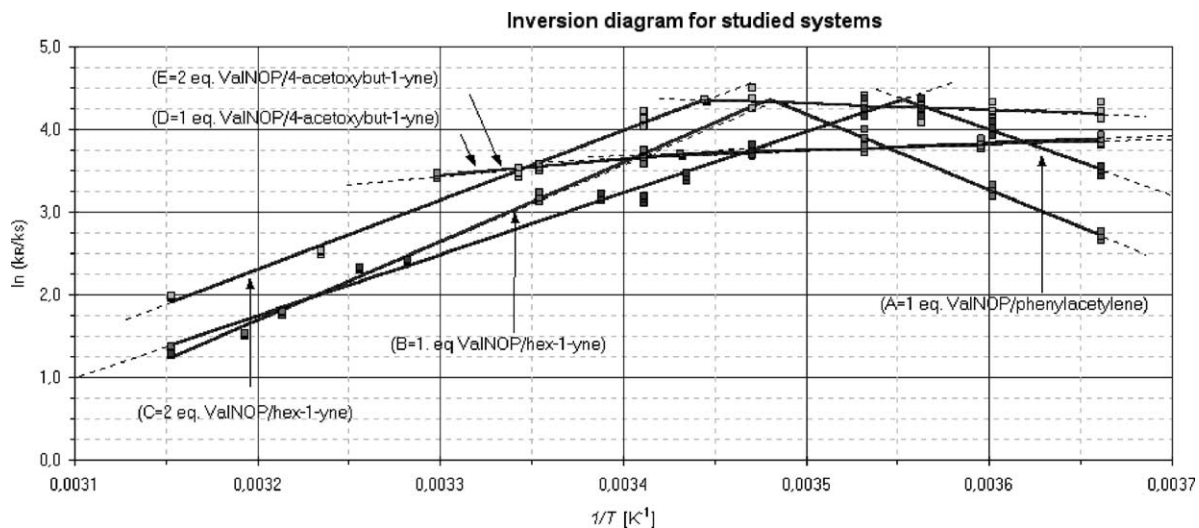
Fig. 2. Eyring plot for the enantiomeric excess of the HDA of norbornadiene **1** and alkynes **2** using ValNOP **5**. A, Col$_2$/**5**/Zn/**2a**/**1** (0.025/0.025/0.25/1.0/1.0); B, Col$_2$/**5**/Zn/**2b**/**1** (0.025/0.025/0.25/1.0/1.0); C, Col$_2$/**5**/Zn/**2b**/**1** (0.025/0.05/0.25/1.0/1.0); D, Col$_2$/**5**/Zn/**2c**/**1** (0.025/0.025/0.25/1.0/1.0); E, Col$_2$/**5**/Zn/**2c**/**1** (0.025/0.05/0.25/1.0/1.0).

PhenylalaNOP **6**. The same variation was roughly observed, but the inversion point was less high on the ordinate axis than with previous mentioned combinations when plotting the variation of the enantioselectivity against the reciprocal of temperature (Fig. 3).

Conversely, when PhenylalaNOP **6** was used as ligand, whatever the acetylene involved (**2a** or **2b**) in the [2 + 2 + 2] additions, opposite variations were observed for ln (k_R/k_S). Two half-straight lines were observed for the high-temperature part of the inversion diagram, with slopes close to nought, whereas in the low-temperature diagram part, the half-straight lines with positive slopes were observed. At this stage, we have no explanation for these variations, but we
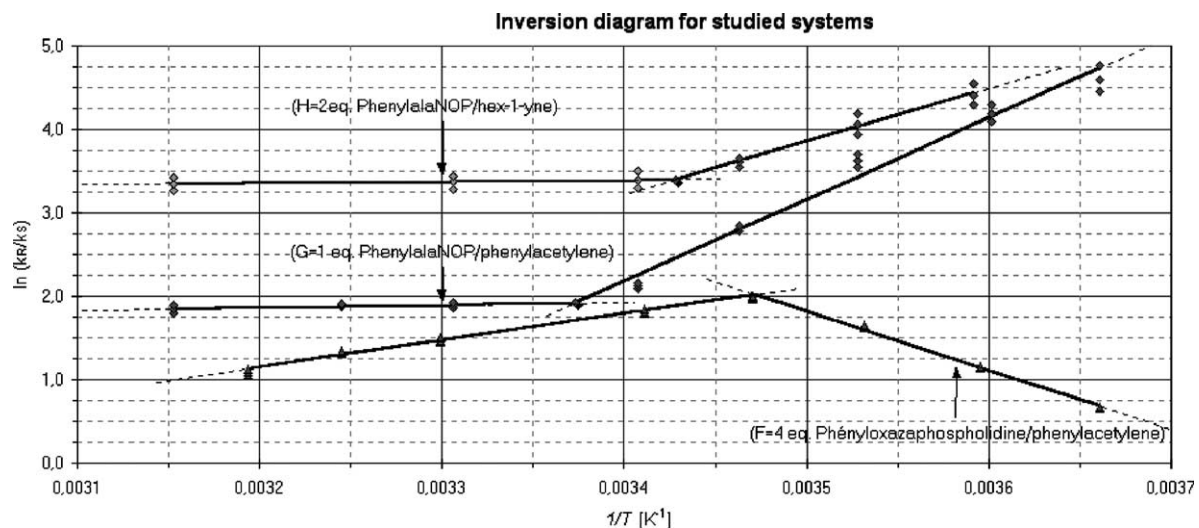

Fig. 3. Eyring plot for the enantiomeric excess of the HDA of norbornadiene **1** and alkynes **2** using ligands **4** or **6**. F, Col$_2$/**4**/Zn/**2a**/**1** (0.025/0.10/0.25/1.0/1.0); G, Col$_2$/**6**/Zn/**2a**/**1** (0.025/0.025/0.25/1.0/1.0); H, Col$_2$/**5**/Zn/**2b**/**1** (0.025/0.05/0.25/1.0/1.0).
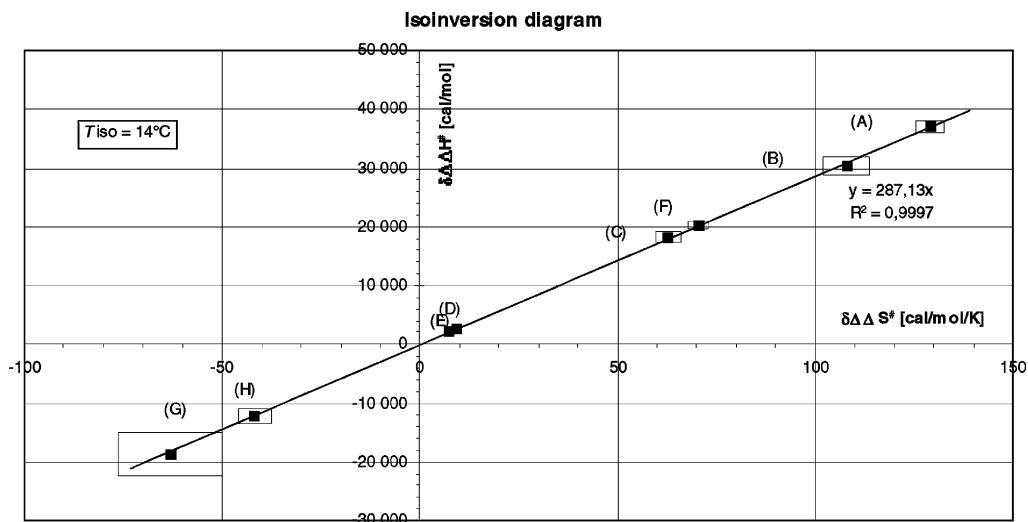
Isoinversion diagram

Fig. 4. Determination of the isoinversion temperature T_{iso} for A–H combinations ligand/NBD/alkyne.

presume that the phenyl group of PhenylalaNOP **6** induce some extra constraints in the transition state.

According to the Scharf's formalism [7a], the differences in the values of $\Delta\Delta H^{\#}$ and $\Delta\Delta S^{\#}$ before and after the point of inversion—in this case, the inversion temperature T_{inv} leads to the isoinversion temperature T_{iso} (Eq. (1)) which describes the selectivity of a reaction as a characteristic quantity.

$$\delta\Delta\Delta H^{\#} = T_{iso} \cdot \delta\Delta\Delta S^{\#} \tag{1}$$

The plot of the variation of $\delta\Delta\Delta H^{\#}$ as a function of $\delta\Delta\Delta S^{\#}$ for all the studied systems, leading to a straight line (Fig. 4) allowed the determination of the *isoinversion relation*. The slope of the regression line furnished the *isoinversion temperature* $T_{iso} = 287 \pm 2$ K or 14 ± 2 °C with a correlation coefficient up to 0.99.

The typical behaviour of combinations G and H could justify the remarks formulated by Hale and Ridd [9] concerning the generalisation of the *isoinversion relationship* for any system [7a]. The explanation suggested by Gypser and Norrby [10] concerning the limits of applicability of the *Isoinversion principle*, seems to prove that in a so narrow temperature range, the determination of the activation parameters using the global relative rates (k_R, and k_S) could lead to values without any experimental fundament [10].

The case of system A, B, F, G and C characterised by experimental insignificant high values for $\Delta\Delta S_1^{\#}$

and $\Delta\Delta S_2^{\#}$ is in agreement with Hale and Ridd [9] and Gypser and Norrby [10] observations. The isoinversion relationship [7] valuable for limited conditions, could give in the transition area values unrelated with the observed selectivity, due to the hypothesis formulated and the size of the transition region towards the full temperature scale selected.

Binger et al. [4] has shown that cationic cobalt species could be involved in the HDA reactions. The active catalysts in these new cobalt catalytic systems were generated using a Lewis acid such as ZnI_2 or $ZnCl_2$ with $[L_n*CoI_2]$ to afford cationic species $[L_n*CoI]^{+}[ZnI_3]^{-}$ or $[L_n*Co]^{2+}[ZnI_4]^{2-}$. Based on the coordination ability of cobalt to five or more ligands,[6] a two step process for the formation of **3** can be involved (Scheme 3) [7].

We proposed to consider the reversible formation of two diastereoisomeric five pentacoordinated cobalt intermediates **8** and **ent-8**, which can equilibrate according to the well-known *Berry* pseudorotation[7] [11] and *Turnstile rotation* mechanism[8] [12]. The low

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[6] At different L_n*/Co ratio, tridentate ligands, such as CysteNOP and ThreoNOOP gave neither cycloadduct **3** nor NBD dimers. Moreover, trimerisation of alkyne **2** into aromatic compounds was not observed (unpublished results).

[7] The two trigonal bipyramid (TBP) structures **8** and **ent-8** are related to each other by simple rotation, the entire process is called *Berry pseudorotation*.

[8] This alternative is the so-called *"Turnstile rotation"*.
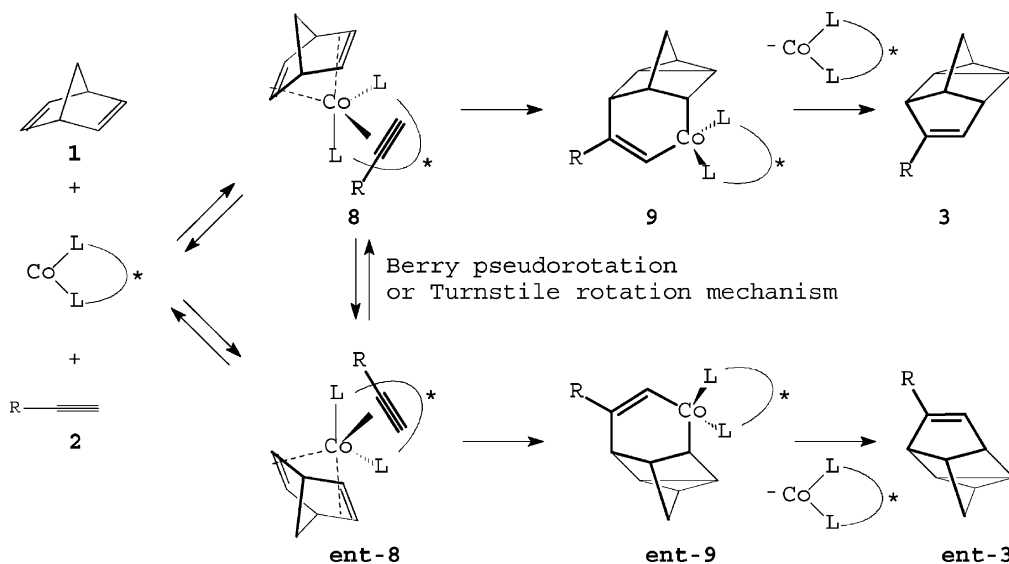
Scheme 3. Proposed mechanism for the cobalt-catalysed [2 + 2 + 2] enantioselective HDA of norbornadiene **1** and alkynes **2**.

energy barriers for interconversion between **8** and **ent-8** associated to a high energy difference of these highly substituted structures as a result of the substitution patterns may be responsible for the high e.e. observed. Cobalt species coordinated with two cyclic ligands in the diastereoisomeric intermediates **8** and **ent-8** [1c] could be an important feature for the high gaps in the difference of the activation parameters. The experimentally determined non-linear temperature dependence of the logarithmic k_R/k_S could be interpreted as a shift in the rate determining step of the HDA reaction with change in temperature [7b,7g].

4. Conclusions

We have validated the *Isoinversion principle* in the HDA reaction catalysed with cobalt complexes coordinated to monodentate chiral oxazaphospholidine ligands and bidentate chiral AMPP ligands. However, we are studying a more detailed investigation of the corresponding influence of enthalpy versus entropy on the basis of the Isoinversion principle in a large temperature range which would give more insight in the selection mechanism of this reaction.

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