Studies of electronic effects of modified pyridine-imine ligands utilized in cobalt-catalyzed *meta*-selective *Diels–Alder* reactions

Gerhard Hilt [a, *], Judith Janikowski [a, 1], Martin Schwarzer [a, 1], Olaf Burghaus [a, 1], Dimitri Sakow [b, 2], Martin Bröring [b, **], Marcel Drüschler [a, 1], Benedikt Huber [a, 1], Bernhard Roling [a, 1], Klaus Harms [a, 1], Gernot Frenking [a, *]

[a] *Fachbereich Chemie, Philipps-Universität Marburg, Hans-Meerwein-Str., 35043 Marburg, Germany*
[b] *Fachbereich Chemie, Institut für Anorganische und Analytische Chemie, TU Braunschweig, Hagenring 30, 38106 Braunschweig, Germany*

A B S T R A C T

The regioselectivity of cobalt-catalyzed *Diels–Alder* reactions can be controlled by the choice of ligands on the cobalt center. Ligands of the pyridine-imine type favor the formation of the 1,3-disubstitution pattern on the dihydroaromatic product. The investigation was aimed to elucidate the factors for controlling the regioselectivities and reactivity induced by electronic effects of the pyridine-imine ligands in the cobalt-catalyzed *Diels–Alder* reaction. For that, electron-withdrawing as well as electron donating substituents were introduced in the 4-position on the pyridine moiety and on the 4′-position of the aniline derivative used in the imine subunit of the ligands. In close synergy DFT calculations and the comparison with experimental results proved that electronic variation of the substituents at both positions have a negligible influence on the regioselectivity. However, the kinetic data for the cobalt-catalyzed *Diels–Alder* reactions revealed that there are great differences in the lengths of the induction periods when different cobalt pyridine-imine complexes are applied. These results could be elucidated by conductivity experiments showing that ionic homoleptic complexes $Co(L)_2^{2+}/CoBr_4^{2-}$ are in equilibrium with their corresponding neutral heteroleptic complexes of type $Co(L)Br_2$ in solution. The equilibrium position depends on the electronic characteristics of the pyridine-imine ligands (L), thereby influencing the length of the induction period.

1. Introduction

The regiodivergent synthesis of carbocyclic six-membered ring systems via atom economic cobalt-catalyzed *Diels–Alder* reactions is an excellent example of a transformation where the regioselectivity is efficiently controlled by the choice of the ligand system [1] (Scheme 1).

Thereby, the highly selective synthesis of disubstituted dihydroaromatic compounds, such as **1**, can be accomplished when a bidentate phosphine ligand, such as dppe, is applied, leading eventually to arenes of type **3** [2]. On the other hand, the application of pyridine-imine-type ligands in the cobalt-catalyzed *Diels–Alder* reaction leads to the highly selective formation of regioisomer

2 in excellent yields which can be easily oxidized by DDQ (=2,3-dichloro-5,6-dicyano-benzoquinone) to the corresponding arene **4** [3]. In recent applications also silyl- and boron-functionalized alkynes could be applied in the regiodiverse *Diels–Alder* reactions with similarly high regioselectivities leading to very interesting functionalized building blocks for follow-up transformations [4].

In a detailed quantum mechanical investigation the mechanism of the cobalt-catalyzed *Diels–Alder* reaction was evaluated and the regiodivergent behavior of the Co(dppe)$^+$-complex [5] leading to the *para*-substituted product **1**, and of the Co(pyridine-imine)$^+$-complex [6] predominantly generating the *meta*-substituted product **2** could be explained [7]. A total of eight different reaction pathways were found for the stepwise rather than concerted mechanism yielding the *para*- or the *meta*-product, respectively. The calculated ratios of the primary cycloaddition products **1** and **2** were in excellent agreement with the experimentally observed regioselectivities.

As quintessence from the analysis of the lowest lying transition states for both reaction pathways we came to the conclusion that different steric hindrances of the ligands caused the change in
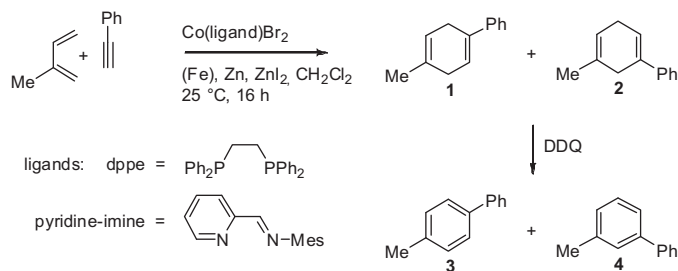
* Corresponding authors. Fax: +49 6421 2825677.
** Corresponding author. Fax: +49 531 391 5387.
 E-mail addresses: Hilt@chemie.uni-marburg.de (G. Hilt), m.broering@tu-bs.de (M. Bröring), frenking@chemie.uni-marburg.de (G. Frenking).
 [1] Fax: +49 6421 2825677.
 [2] Fax: +49 531 391 5387.

Scheme 1. Regiodivergent synthesis of dihydroaromatic compounds **1** and **2** by cobalt-catalyzed Diels–Alder reaction and follow-up oxidation to the arenes **3** and **4**.

regioselectivity. Accordingly, electronic modifications in a remote position of the pyridine-imine ligand should not influence the regioselectivity of the Co(pyridine-imine)-catalyzed cycloaddition process. To test this hypothesis we set out to start this investigation utilizing theoretical methods to evaluate those ligands which cannot be synthesized in a few steps. Thereby, *in silico* evaluations for those hypothetical ligands should be obtained.

Also, the cobalt-catalyzed reaction starts from a cobalt(II) precursor and a heterogeneous electron transfer from zinc powder generates the proposed catalytically active cobalt(I) species resulting in an induction period. The redox process should be dependent on the electronic characteristics of the Co(pyridine-imine)Br$_2$ complexes resulting in different length of the induction periods dependent from the electron donating/abstracting ability of the ligand on cobalt. Accordingly, electronic modifications of the ligands in remote positions should result in nearly identical thermodynamic and kinetic profiles, almost identical yields and regioselectivities, but in different length of induction periods.

2. Experimental

All reagents were used as purchased from commercial suppliers without further purification. All reactions were carried out using standard Schlenk techniques under dry argon. Solvents were purified and dried according to conventional methods prior to use. ^{1}H and ^{13}C NMR spectra were recorded with an AVANCE 300 (300 MHz for ^{1}H and 75 MHz for ^{13}C) or an AVANCE 500 (500 MHz for ^{1}H and 125 MHz for ^{13}C). The kinetic measurements were analysed utilizing GC analyses which were recorded with a Shimadzu GC-2010 Plus Gas Chromatograph. For chromatography the separations were carried out on Macherey–Nagel Silica 60 (0.040–0.063 mm, 230–400 mesh ASTM). For TLC Merck TLC plates (Silica 60, F254) were used.

2.1. Computational details

Geometry optimizations of the molecules without symmetry constraints (C$_1$) were carried out using the Gaussian03 [8] optimizer (Berny-Algorithm) [9] together with TurboMole 5.0 [10] energies and gradients at the gradient corrected DFT level of theory using Becke's exchange functional [11] in conjunction with Perdew's correlation functional [12] (BP86) and Ahlrich's def2-SV(P) basis-sets [13]. The resolution-of-the-identity (RI) approximation [14] was applied using auxiliary basis functions [15]. This level of theory is denoted as RI-BP86/def2-SV(P). Stationary points were characterized as minima (number of imaginary frequencies $i = 0$) or transition states ($i = 1$) by calculating the Hessian matrix analytically (AOFORCE) [16]. The solvent-effect on the calculated energies was estimated with COSMO [17] as single point calculations on the optimized structures. This level of theory is denoted as COSMO//RI-BP86/def2-SV(P). The latter calculations were carried out with a dielectric constant $\varepsilon = 8.93$ for the solvent dichloromethane [18].

2.2. Synthesis of the ligands and cobalt complexes

The ligands **6a–6d** were generated by condensation of 2-formylpyridine with aniline derivatives. The cobalt-complexes were synthesized by addition of 1.0 equiv. of the ligand to a solution of cobalt(II) bromide in THF. The mixture was stirred overnight and the solvent was removed. The complexes were stored at ambient temperatures without special preventive measures and used as precatalysts without further purification.

2.3. Representative procedure for the cobalt-catalyzed Diels–Alder reaction

Anhydrous zinc iodide (64 mg, 0.2 mmol, 20 mol%), zinc dust (13 mg, 0.2 mmol, 20 mol%), iron powder (11 mg, 0.2 mmol, 20 mol%) and Co(**5c**)Br$_2$ (45 mg, 0.1 mmol, 10 mol%) were suspended under argon in 1.0 mL dichloromethane. Then isoprene (1.0 mmol) and phenylacetylene (1.0 mmol) were added and the mixture was stirred at room temperature. The conversion of the starting materials was monitored by GC and GC–MS analysis. The reaction mixture was filtered over a short pad of silica gel (pentane) and the solvent was removed under reduced pressure. The residue was dissolved in toluene (10 mL) and stirred with DDQ (1.1 equiv.) for 1 h. The resulting suspension was washed with 10% NaOH/10% Na$_2$S$_2$O$_3$ solution, extracted with diethyl ether, dried over MgSO$_4$ and the solvent was removed under reduced pressure. The product was purified by flash column chromatography on silica gel (eluent: pentane). The analytical data are in accordance with the literature [2,3].
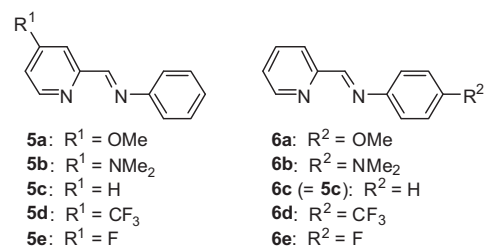
2.4. Kinetic investigations

The Diels–Alder reaction was performed as before and samples were taken by syringe under argon in certain time intervals. The progress of the reaction was determined by GC analysis via integration of the peaks.

3. Results and discussion

In order to investigate the electronic influence of a substituent without causing steric hindrance the substituents (R^1 and R^2) were placed on the 4- and 4′-position in *para*-relation to the nitrogen atoms of the pyridine-imine ligand (Fig. 1). Thereby, very little steric hindrance will occur and the electronic modifications will have a strong influence on the electron density at the reactive sites within the cobalt complex via the *trans*-influence. For this purpose the two ligand systems **5a–e** and **6a–e** were selected with electron-donating as well as electron-withdrawing substituents on position 4 and 4′.

For quantum mechanical investigations the following modifications of the pyridine moiety were selected: substituent R^1 was modified with the electron donating methoxy − (**5a**), the dimethylamino − (**5b**) and the electron withdrawing trifluoromethyl −

5a: R^1 = OMe   **6a**: R^2 = OMe
5b: R^1 = NMe$_2$ **6b**: R^2 = NMe$_2$
5c: R^1 = H   **6c** (= **5c**): R^2 = H
5d: R^1 = CF$_3$ **6d**: R^2 = CF$_3$
5e: R^1 = F   **6e**: R^2 = F

Fig. 1. Modification of electronic parameters of the pyridine-imine ligands **5** and **6** (pyridine-imine) for the *meta*-selective cobalt-catalyzed Diels–Alder reaction.