Studies on aluminium mediated asymmetric Friedel–Crafts hydroxyalkylation reactions of pyridinecarbaldehydes

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The reaction of pyridinecarbaldehydes with aromatic C–H bonds mediated by chiral and achiral aluminium complexes has been investigated both experimentally and theoretically. It was found that pyridine-2-carbaldehyde activated by (R)-BINOL–AlCl reacts with *e.g.* N,N-dimethylaniline in a Friedel–Crafts hydroxyalkylation reaction to give the resulting alcohol in moderate yield and enantiomeric excess, whereas the pyridine-3- and -4-carbaldehydes give a diarylated product. The mechanism of the reaction has been investigated using theoretical calculations. The calculations show that the uncatalyzed reaction proceeds *via* a concerted, one-step mechanism, having a four-membered transition state with an energy barrier of 81 kcal mol^{-1}. However, for the Lewis acid-mediated reaction using AlCl$_3$ as the Lewis acid, the reaction proceeds through a zwitterionic intermediate in which the transition-state energy is significantly reduced. For the reaction of pyridine-2-carbaldehyde, the aluminium Lewis acid can coordinate in both a mono- and bidentate fashion to the substrate. Furthermore, two Friedel–Crafts intermediates have been found depending on the orientation of the incoming aromatic compound. Several transition states have been calculated for the formation of the Friedel–Crafts intermediates starting from the two different coordination modes of pyridine-2-carbaldehyde to AlCl$_3$. The lowest energy for the reaction has been calculated to be 5.6 kcal mol^{-1} for pyridine-2-carbaldehyde activated by AlCl$_3$ in a monodentate fashion. The mechanistic aspects of these observations will be discussed.

Introduction

The Friedel–Crafts reaction is a well-known and well-established reaction and among the most fundamental C–C bond forming reactions known.[1] Traditionally, the Friedel–Crafts alkylation and acylation reactions involve alkyl halides or acyl halides, respectively, that are activated by a Lewis acid to perform an electrophilic substitution on the aromatic C–H bond.[1] Compared to the numerous reports on Friedel–Crafts alkylation and acylation of alkyl and acyl halides, alkylation reactions using aldehydes or ketones as the substrates have not been as well developed [eqn. (1)].[2]

$$R^1 \overset{O}{\underset{}{\|}}C R^2 + Ar{-}H \xrightarrow[\text{Lewis acid}]{H^{\oplus}} R^1 \overset{Ar\ OH}{\underset{}{C}} R^2 \quad (1)$$
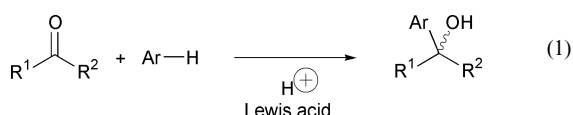
Both Brønsted and Lewis acids can mediate the hydroxyalkylation reaction through an activation of the carbonyl moiety. In both cases, the resulting electron deficiency at the carbonyl carbon makes it susceptible to a nucleophilic attack from the aromatic compound.

In spite of the high importance of the Friedel–Crafts reaction only very limited attention has been paid to the application in catalytic asymmetric synthesis of optically active Friedel–Crafts products. Recently, the first examples of catalytic enantioselective addition reactions of aromatic and heteroaromatic C–H bonds to activated carbonyl compounds,[2] α-dicarbonyl compounds[3] and imines[4] have been presented. This paper presents the first investigation of an enantioselective hydroxyalkylation reaction of pyridine-2-carbaldehyde with N,N-dimethylaniline mediated by chiral aluminium catalysts. The reaction will also be studied for other aromatic compounds reacting with various types of pyridinecarbaldehydes. Furthermore, the reaction has also been investigated from a theoretical point of view in an attempt to obtain detailed insight into the mechanism for the aluminium-mediated Friedel–Crafts reaction of aromatic aldehydes with aromatic compounds.

Results and discussion

The reaction of pyridine-2-carbaldehyde **1a** with N,N-dimethylaniline **2a** mediated by aluminium complexes containing chiral ligands leads to the formation of alcohol **3a** [eqn. (2)]. In this reaction a new stereogenic center is produced and in order to

(2)

(R)-**4a**
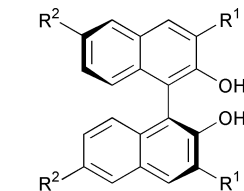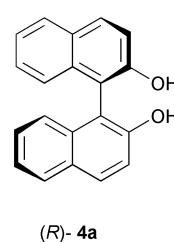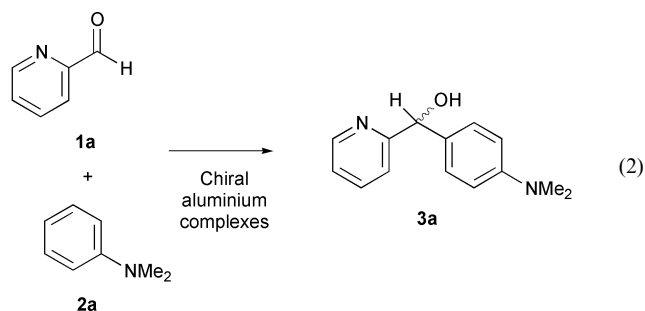
(S)-**4b**, R^1 = Ph, R^2 = H
(S)-**4c**, R^1 = 2,6-OC$_6$H$_{13}$C$_6$H$_3$, R^2 = H
(S)-**4d**, R^1 = H, R^2 = Ph
(S)-**4e**, R^1 = H, R^2 = Br

Table 1 Friedel–Crafts reaction of pyridine-2-carbaldehyde **1a** with *N*,*N*-dimethylaniline **2a** catalyzed by the chiral BINOL ligands (*R*)-**4a** and (*S*)-**4b**–**e** in combination with AlClMe$_2$ as the Lewis acid under different reaction conditions

| Entry	Ligand	Solvent	Reaction temp./°C	Reaction time/h	Yield[a] (%)	Ee[b] (%)
1	(*R*)-**4a**	CH$_2$Cl$_2$	20	19	63	43
2	(*R*)-**4a**	CH$_2$Cl$_2$	0	27	36[c]	35
3	(*R*)-**4a**	Et$_2$O	20	18	44	9
4	(*R*)-**4a**	CH$_3$NO$_2$	20	19	93	5[d]
5	(*R*)-**4a**	CH$_3$CN	20	18	53	14
6	(*R*)-**4a**	C$_6$H$_6$	20	18	25	50
7	(*R*)-**4a**	THF	20	19	93	15[d]
8	(*S*)-**4b**	CH$_2$Cl$_2$	20	18	14	13
9	(*S*)-**4c**	CH$_2$Cl$_2$	20	18	50	29
10	(*S*)-**4d**	CH$_2$Cl$_2$	20	18	26	36
11	(*S*)-**4e**	CH$_2$Cl$_2$	20	18	52	16[d]
12[e]	—	CH$_2$Cl$_2$	20	2 days	0	—

[a] Isolated yield. [b] Ee measured by HPLC using a Daicel Chiralcel OD column. [c] Conversion measured by ^{1}H NMR spectroscopy. [d] Opposite enantiomer. [e] No catalyst present.

investigate the possibility of controlling the enantioselectivity of this reaction a series of optically active aluminium complexes formed by reaction of Me$_2$AlCl with the optically active BINOL (BINOL = 1,1′-binaphthyl-2,2′-diol) ligands (*R*)-**4a** and (*S*)-**4b**–**e** were investigated. The chiral Lewis acids are prepared by dissolving the BINOL ligand in the appropriate solvent used for the reaction followed by the addition of a commercially available heptane solution of AlMe$_2$Cl which gives the chiral Lewis acid as a white solid. After stirring for 1 h at room temperature the chiral Lewis acid is ready for use. Addition of the reagents gives upon stirring for a period of time a homogeneous and slightly orange-coloured reaction mixture.

The reaction of pyridine-2-carbaldehyde **1a** with *N*,*N*-dimethylaniline **2a** proceeds smoothly giving the resulting alcohol ((4-dimethylaminophenyl)pyridin-2-ylmethanol) **3a** in 63% yield. The reaction proceeds with the formation of an optically active product and the study of the Friedel–Crafts reaction in various solvents mediated by different chiral BINOL–aluminium complexes gives the results presented in Table 1. The most successful conditions found are to perform the reaction at room temperature in CH$_2$Cl$_2$ as the solvent, which gives **3a** in 63% yield and with 43% ee. This is, according to our knowledge, the first example of a simple aromatic aldehyde reacting with an aromatic C–H bond to give an optically active Friedel–Crafts product in the presence of a chiral Lewis acid. The highest ee of **3a** is obtained in benzene as the solvent, however, the yield was low (entry 6). The highest yield of **3a** is produced in CH$_3$NO$_2$ and THF where 93% isolated yield of **3a** is obtained, but in these solvents low ee's are found (entry 4 and 7). As the product alcohol **3a** binds to and deactivates the chiral Lewis acid due to the strong Al–O bond, a stoichiometric amount of the Lewis acid is required in order to obtain reasonable conversion in the reaction. Fortunately, it was found that the chiral BINOL ligand is easily recovered after the reaction by column chromatography and can be recovered in 80–90% yield. The Friedel–Crafts reaction of **1a** with **2a** has also been studied for (*S*)-**4b**–**e** in combination with AlClMe$_2$ as the Lewis acid. The chiral BINOL ligands studied have proven to greatly increase the enantioselectivity of other BINOL–aluminium-mediated reactions,[5] however, the results in entries 8–11 show that only moderate yield and enantioselectivity of **3a** were obtained.

Pyridine-2-carbaldehyde **1a** also reacts with other aromatic compounds than *N*,*N*-dimethylaniline; reaction of 4-methoxy-phenol **2b** and 1,3-dimethoxybenzene **2c** in CH$_2$Cl$_2$ proceeds also in the presence of (*R*)-**4a**-AlCl to give the corresponding Friedel–Crafts products in 54% and 49% isolated yield; however, less than 15% ee of the products was obtained. Furthermore, it was found that the 3- and the 4-isomer of the pyridinecarbaldehyde, **1b** and **1c**, respectively, react with **2a** in

the presence of the various chiral aluminium complexes, although in both cases the final product was the diarylated species, **3b** and **3c**, respectively, in moderate yield [eqns. (3) and (4)]. As is observed in an early example of this type
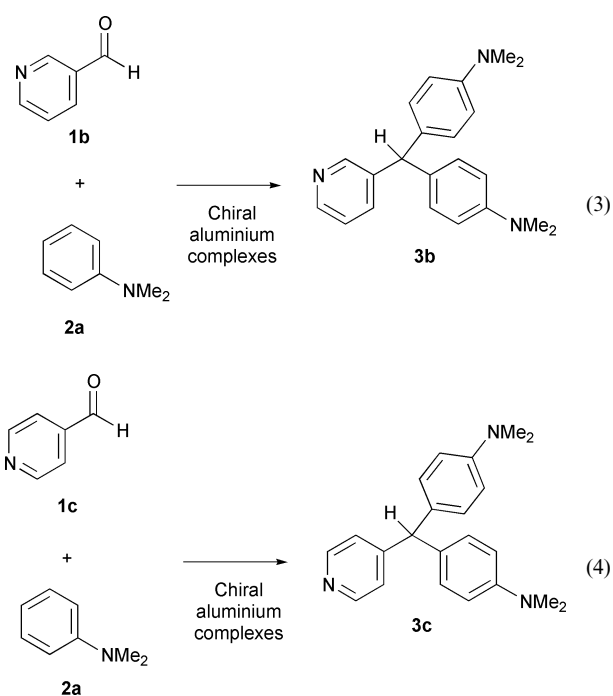
of reaction—the Bayer reaction—the alcohol-intermediate formed is even more reactive than the starting material and thus reacts with yet another molecule of aromatic compound resulting in the diarylated product with loss of water.[6]

A compound such as benzaldehyde, in which the carbonyl is less activated compared to *e.g.* pyridine-2-carbaldehyde **1a**, does not react under the present reaction conditions with *e.g.* **2a** in the presence of a chiral aluminium complex. This implies that the electron-withdrawing effect from the pyridine ring lowers the energy barrier of the reaction.

Theoretical investigations

In the following we will investigate the Friedel–Crafts reaction of especially pyridine-2-carbaldehyde **1a** with *N*,*N*-dimethyl-aniline **2a** in the absence and in the presence of a Lewis acid, from a theoretical point of view using *ab initio* calculations[7] in an attempt to obtain insight into the reaction mechanism and the role of the Lewis acid for the reaction. According to the best of our knowledge, there has only been a very limited number of
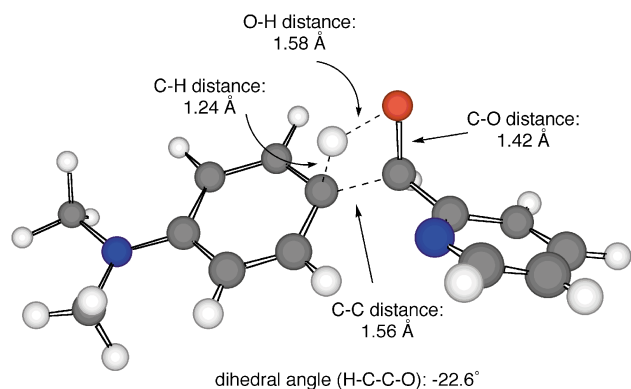
Fig. 1 Calculated transition-state structure for the uncatalyzed Friedel–Crafts reaction of pyridine-2-carbaldehyde **1a** with *N,N*-dimethylaniline **2a**.

theoretical investigations of the role of Lewis acids for the reaction of aromatic C–H bonds with carbonyl compounds.[8]

We will start with an investigation of the uncatalyzed Friedel–Crafts reaction of **1a** with **2a** in order to understand this reaction before moving to the AlCl₃-mediated reaction. The transition state for the reaction of **1a** with **2a** has been localised and characterised and is presented in Fig. 1. All attempts to locate a zwitterionic intermediate for the uncatalyzed reaction failed. However, a four-membered transition state for the reaction in which the formation of the C–C bond and the hydrogen atom (proton) transfer take place simultaneously has been calculated as the transition state for the uncatalyzed Friedel–Crafts reaction. The transition-state energy has been calculated to be 81.0 kcal mol⁻¹ which is a very high energy barrier and is consistent with the fact that we see no reaction of **1a** and **2a** in the absence of a catalyst (Table 1, entry 12). It appears from the transition-state structure for the uncatalyzed Friedel–Crafts reaction in Fig. 1 that the C–C bond being formed is calculated to be 1.56 Å indicating a very late transition state for the reaction, and that the aromatic C–H bond has increased from 1.07 Å in *N,N*-dimethylaniline to 1.24 Å in the transition state. The O–H bond going to be formed is calculated to be 1.58 Å. The transition state also shows that the hydrogen atom (proton) is lined up for transfer to the oxygen atom of the carbonyl bond, which now has increased from 1.22 Å in **2a** to 1.42 Å in the transition state as the H–C–C–O dihedral angle is calculated as −22.6°. The carbonyl bond becomes more polarised in the transition state as the charges on the carbon and oxygen atoms change from 0.34 (C) and −0.52 (O) (see Table 2) in **1a** to 0.18 (C) and −0.81 (O), respectively, in the transition state.

For the Friedel–Crafts reaction between **1a** and **2a** we have used AlCl₃ as the Lewis acid in the calculations to resemble the experimental results as much as possible.[9] There are four possible coordination modes of AlCl₃ to **1a**, depending on the orientation of the carbonyl functionality relative to the nitrogen atom in the pyridine moiety. In Fig. 2, the two lowest energy structures are shown. Complex **I** has a total energy of −1979.814 E_h and is a monodentate coordination of **1a** to AlCl₃, while in complex **II**, pyridinecarbaldehyde **1a** coordinates in a bidentate fashion to AlCl₃ using the nitrogen lone-pair electrons of the pyridine ring for the coordination. The energy of complex **II** is calculated to be 6.4 kcal mol⁻¹ higher in energy than complex **I**. The difference in coordination of AlCl₃ to **1a** is also reflected in the O–Al bond distances in the complexes; in complex **I** (monodentate coordination), a bond length of 1.85 Å has been calculated, while in complex **II** (bidentate coordination) the O–Al bond is 0.14 Å longer.

The coordination of AlCl₃ to **1a** leads to an activation of the carbonyl group of **1a** for a nucleophilic attack by *e.g.* the aromatic compound. In Table 2 are shown the electronic and structural changes calculated for the carbonyl group for **1a**–**c** in

Table 2 Structural and electronic changes of the carbonyl functionality of **1a**–**c**, in the absence of a Lewis acid, and when coordinated to AlCl₃ [a]

	1a [b]	**1b**	**1c**
No Lewis acid			
C–O/Å	1.22	1.22	1.21
HOMO/eV	−10.02	−10.14	−10.08
LUMO/eV	1.76	1.67	1.44
$q(C)$ [c]	0.34	0.35	0.34
$q(O)$ [c]	−0.52	−0.52	−0.50
With AlCl₃			
C–O/Å	1.24	1.25	1.24
HOMO/eV	−11.57	−11.70	−11.33
LUMO/eV	−0.76	−0.85	−1.05
$q(C)$ [c]	0.53	0.51	0.51
$q(O)$ [c]	−0.82	−0.83	−0.80

[a] Calculations performed using RHF/6-31G. [b] Values presented for AlCl₃ coordinated to **1a** are calculated from the lowest energy structure, complex **I** in Fig. 2. [c] Charge on the atoms in the carbonyl group obtained from a Mulliken population analysis.
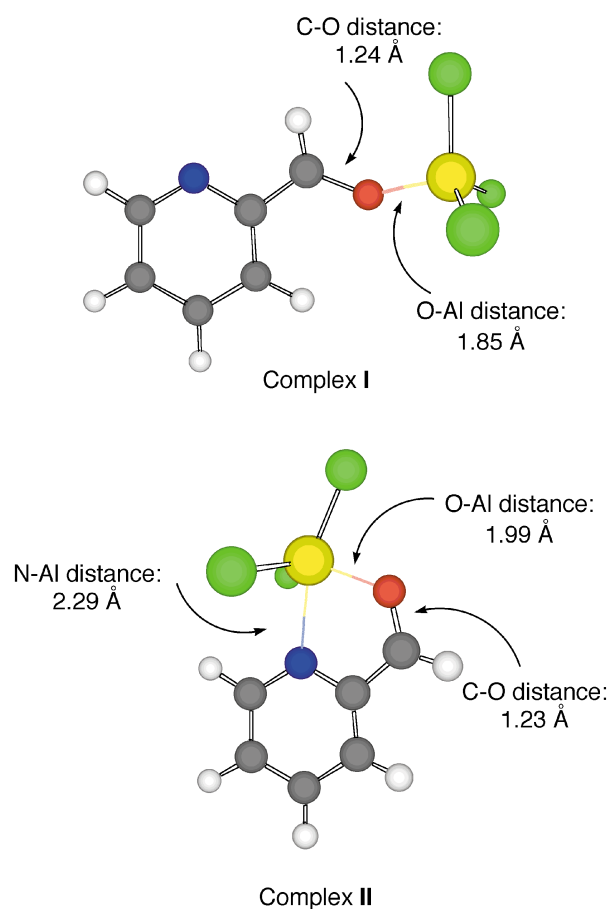

Fig. 2 The two lowest coordination modes of pyridine-2-carbaldehyde **1a** to AlCl₃. Complex **I**: monodentate coordination; complex **II**: bidentate coordination.

the absence of AlCl₃, and coordinated to AlCl₃. It appears from Table 2 that by coordination of AlCl₃ to the carbonyl group of **1a** there are three significant changes of the carbonyl functionality: (i) the C–O bond length increases (ii) the energy of the LUMO ($\pi^*_{\text{C=O}}$) is lowered from 1.76 eV to −0.76 eV and (iii) the charges on the carbon and oxygen atoms in the carbonyl group are changed from 0.34 (C) and −0.52 (O), to 0.53 (C) and −0.82 (O), respectively. For **1a** coordinated to AlCl₃ in a bidentate fashion, complex **II**, the C–O bond length increases similarly to complex **I**, while the polarisation of the carbon atom is

slightly lower compared to complex **I** (longer O–Al bond length in complex **II**, compared to complex **I**). However, the LUMO ($\pi^*_{C=O}$) for complex **II** is significantly lower (−1.05 eV) compared to complex **I**. This low LUMO energy of complex **II** might indicate that complex **II** can be more reactive than complex **I**. The changes found for **1a** coordinated to AlCl$_3$ are also observed for both **1b** and **1c** when activated by AlCl$_3$, however, for **1b** and **1c** coordinated to AlCl$_3$ an increased reactivity, compared to **1a**, might be expected due to the low LUMO energy. This is consistent with the experimental observations that **1b** and **1c** react with *N*,*N*-dimethylaniline **2a** in the presence of the AlCl$_3$ catalyst to give the diarylated product.

The transition-state structures for the reaction of the different complexes for **1a** coordinated to AlCl$_3$ with *N*,*N*-dimethylaniline **2a** have been calculated. In the following the two lowest energy reaction paths, starting from complex **I** and **II** shown in Fig. 2, respectively, will be considered. For the Lewis-acid mediated process, the Friedel–Crafts reaction proceeds as a two-step reaction, with formation of the C–C bond as the first step, followed by the deprotonation as the second step. We will in the following concentrate only on the first step, the Lewis-acid mediated C–C bond formation.

A calculated transition-state structure for the reaction starting from complex **I** is shown in Fig. 3a and is formation of the C–C bond. The transition-state energy for the reaction has been calculated to be 10.6 kcal mol^{-1} which is significantly lower compared to the uncatalyzed reaction (81 kcal mol^{-1}). The C–C bond in the transition state is calculated to be 2.05 Å, which is 0.49 Å longer than in the absence of a Lewis acid. It should be noted that the aromatic C–H bond is virtually unchanged in the transition state, while the O–Al bond length has been reduced to 1.76 Å compared to 1.85 Å in complex **I**. A comparison of the transition-state structures for the uncatalyzed and the AlCl$_3$-mediated reaction reveals that for the Lewis-acid mediated reaction a much more loose transition state (an early transition state) is calculated. Some structural data for the latter transition state are shown in Fig. 3a.

In contrast to the uncatalyzed reaction, the AlCl$_3$-mediated reaction proceeds *via* a zwitterionic intermediate of type **A** (Fig. 3a) in which the H–C–C–O dihedral angle is approximately −60°. The total energy for this intermediate is calculated to be 2.0 kcal mol^{-1} lower in energy than the total energy of the reactants (total energy −2343.457 E_h). It is notable that the major changes, when going from the transition state for the Friedel–Crafts reaction presented in Fig. 3a to intermediate **A** (Fig. 3b), are the formation of the C–C bond and the change in hybridisation of the reacting carbon atoms from sp^2 to sp^3, while only minor structural changes are found for the remaining part of the molecules. Due to the early transition state of this reaction the electronic changes in the system are only minor, with the exception of the carbonyl bond. The carbonyl bond in the transition state is more polarised in the AlCl$_3$-mediated reaction, compared with the reaction in the absence of a Lewis acid. The charges on the carbon and oxygen atoms in the transition state, and in the intermediate of type **A** starting from complex **I**, are calculated to be 0.45 (C) and −0.99 (O), and 0.31 (C) and −1.07 (O), respectively.

We have also calculated the transition-state structure for the reaction leading to intermediate of type **A** (H–C–C–O dihedral angle ~ −60°) starting from complex **II** in which AlCl$_3$ is coordinated in a bidentate fashion to **1a**. For this reaction the transition-state energy has been calculated to be 15.3 kcal mol^{-1} (the total energy of the reactants is 6.4 kcal mol^{-1} higher in energy than the reaction starting from complex **I**). The total energy of this Friedel–Crafts intermediate (type **A**) is calculated to be 6.5 kcal mol^{-1} higher in energy than the total energy of complex **I** and *N*,*N*-dimethylaniline. These results show that for the formation of intermediate type **A** (Fig. 3b), a monodentate coordination of AlCl$_3$ to **1a** leads to the most favourable reaction path. Furthermore, the total energy of intermediate type
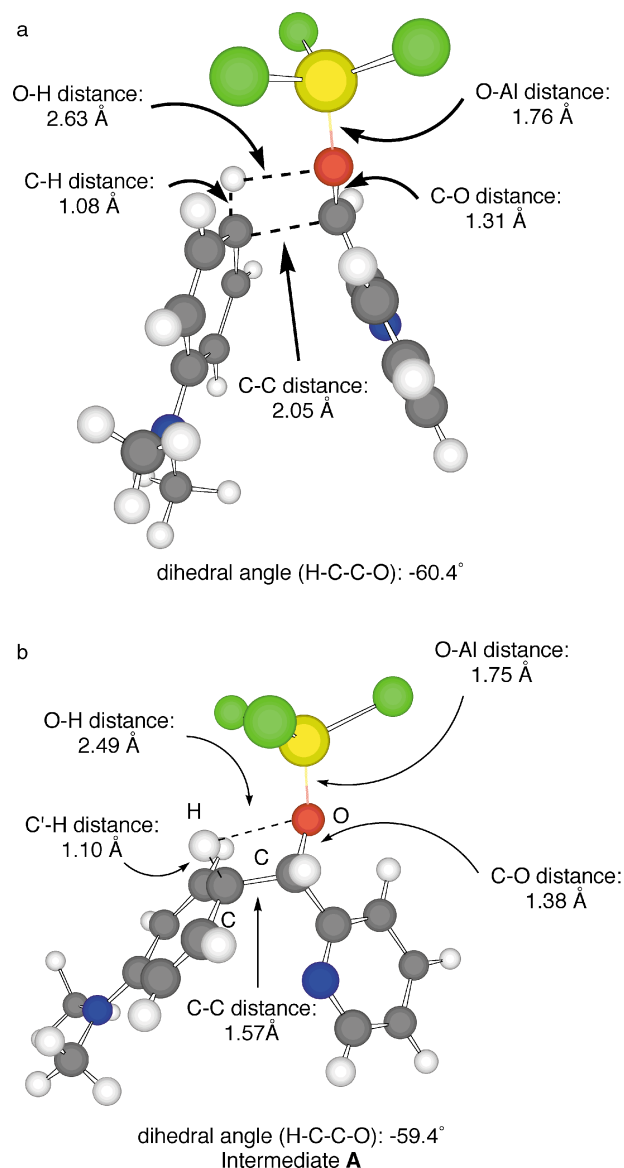

Fig. 3 **a**: The calculated transition-state structure for the formation of a Friedel–Crafts intermediate by reaction of pyridine-2-carbaldehyde **1a** with *N*,*N*-dimethylaniline **2a** starting from complex **I**. **b**: The Friedel–Crafts intermediate of type **A** starting from complex **I**.

A, in which AlCl$_3$ is coordinated in a bidentate fashion to pyridine-2-carbaldehyde **1a**, is 8.5 kcal mol^{-1} higher in energy compared to the same intermediate starting from complex **I**. A schematic representation of the transition-state energies and energies of the intermediates is outlined in Fig. 4.

Both complex **I** and complex **II** can by reaction with *N*,*N*-dimethylaniline **2a** also give another intermediate in which the H–C–C–O dihedral angle is ~−180°, shown as an intermediate of type **B** in Fig. 5b, here represented with a bidentate coordination of AlCl$_3$. The transition-state structure for the formation of this intermediate has also been calculated from both complex **I** and complex **II** and in Fig. 5a is shown the structure of the transition state for the formation intermediate of type **B** formed from complex **II**. The most distinct difference between the transition-state structure shown in Fig. 3a leading to the intermediate of type **A** and the transition-state structure giving the intermediate of type **B** outlined in Fig. 5a is the orientation of the incoming C–H bond relative to the Lewis acid-activated carbonyl bond of pyridine-2-carbaldehyde **1a**. For the transition-state outlined in Fig. 3a the H–C–C–O dihedral angle has been calculated to be −60.4° while for the transition state in Fig. 5a the same dihedral angle is −179.5°. In the former transition-state structure the hydrogen
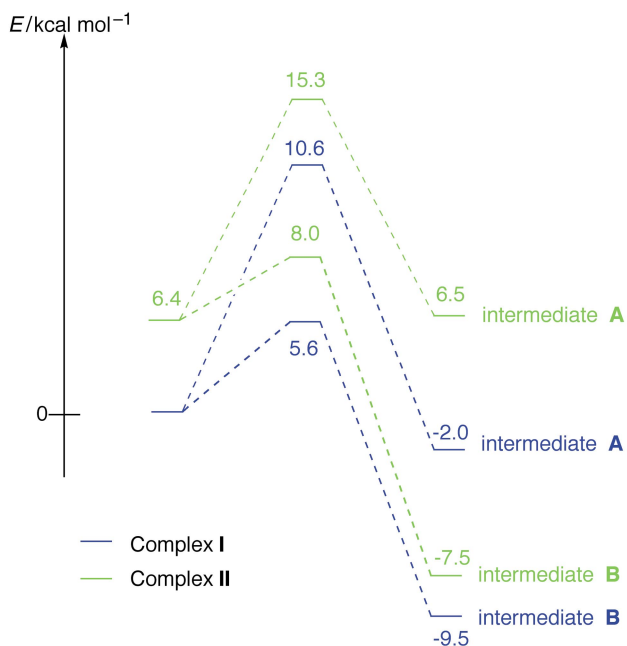
Fig. 4 A schematic presentation of the reaction paths for the formation of intermediates of type **A** and type **B** from complex **I** (blue curves) and complex **II** (green curves). Zero-point energy is −2343.457 E_h. All values are given relative to the zero-point energy.

atom (proton) is in the same direction as the oxygen of the carbonyl functionality, while in the latter case an opposite direction of the hydrogen atom (proton) is found. The transition-state energy for the formation of the intermediate of type **B**, in which the nitrogen atom of **1a** also coordinates to the aluminium atom of the Lewis acid, has been calculated to be only 1.6 kcal mol^{-1}, relative to complex **II** and *N*,*N*-dimethylaniline. Although this energy is lower than the transition-state energy calculated for the formation of intermediate **A**, it has to be taken into account that complex **II** is 6.4 kcal mol^{-1} higher in energy than complex **I**. A comparison of the structure of the two calculated transition states in Fig. 3a and Fig. 5a shows that they are very similar for the most important bond lengths and angles, with the exception of the H–C–C–O dihedral angle. The total energy of intermediate type **B** formed by reaction of complex **II** with *N*,*N*-dimethylaniline is calculated to be 13.9 kcal mol^{-1} lower in energy compared to the starting situation, which is −7.5 kcal mol^{-1} relative to the zero-point energy for the reaction profile in Fig. 4.

The lowest energy transition-state structure for the formation of intermediate of type **B** is obtained from complex **I** reacting with *N*,*N*-dimethylaniline **2a**. This transition-state energy has been calculated to be 5.6 kcal mol^{-1} and some structural data are shown in Fig. 6. It appears from the data that this stucture is also similar to the structure leading to an intermediate of type **B** from complex **II**. The total energy of the intermediate formed by this reaction path is calculated to be the lowest energy intermediate for the AlCl$_3$-catalyzed Friedel–Crafts reaction of **1a** with **2a** and is found at −9.5 kcal mol^{-1} relative to the zero-point energy for the reaction profile in Fig. 4.

The calculations for the formation of the Friedel–Crafts intermediate for the AlCl$_3$-catalyzed reaction of pyridine-2-carbaldehyde **1a** with *N*,*N*-dimethylaniline **2a** show that the most energetically favourable reaction is the one in which **1a** coordinates in a monodentate fashion to AlCl$_3$ to give an intermediate of type **B**. We have considered the formation of the new C–C bond as being the important step in the comparison of the mechanistic possibilities. The second step is the deprotonation or transfer of a proton, which can be mediated by any base present in the reactions mixture, thus having a low barrier despite the high energy barrier (calculated to be 35.5
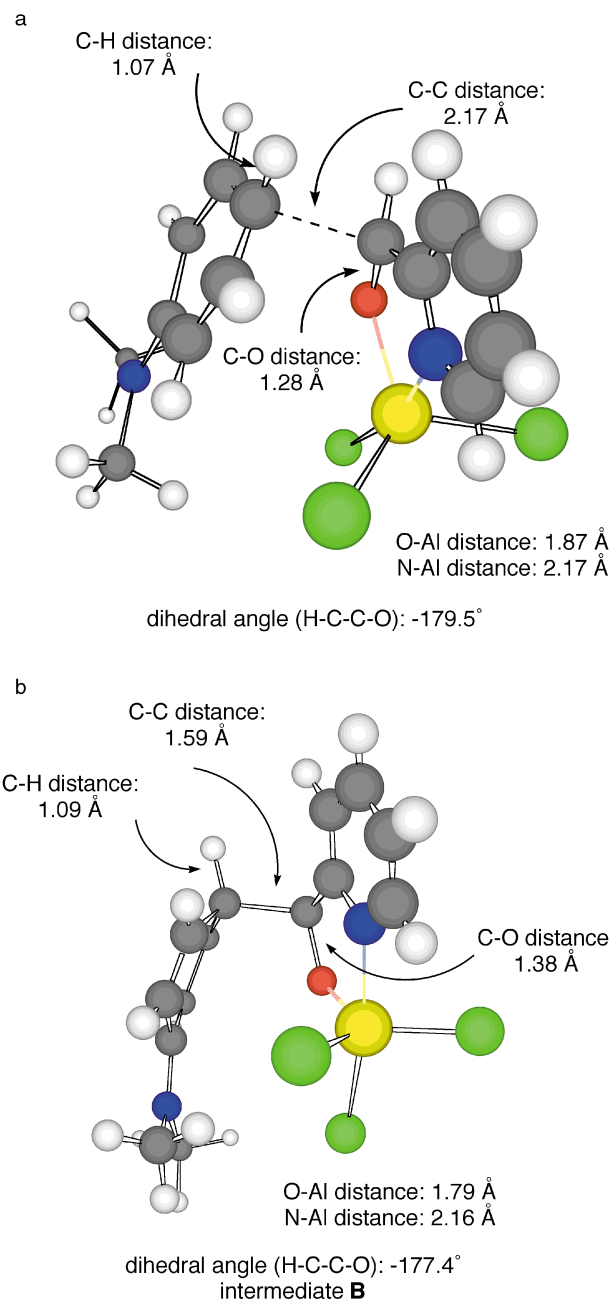

Fig. 5 **a**: The calculated transition-state structure for the formation of a Friedel–Crafts intermediate by reaction of pyridine-2-carbaldehyde **1a** with *N*,*N*-dimethylaniline **2a** starting from complex **II**. **b**: The Friedel–Crafts intermediate of type **B** starting from complex **II**.

kcal mol^{-1} relative to the zwitterionic intermediate) in the intramolecular proton transfer in intermediate **A** (Fig. 3b).

The calculations show that the most favorable Friedel–Crafts reaction of pyridine-2-carbaldehyde **1a** with *N*,*N*-dimethylaniline **2a** catalyzed by AlCl$_3$ proceeds from a monodentate coordination of AlCl$_3$ to **1a** (complex **I**) *via* a transition state in which the H–C–C–O dihedral angle is −179.4°, *i.e.* the incoming aromatic compound approaches the activated carbonyl bond with the C–H bond to be broken in an *anti*-fashion relative to the carbonyl bond. However, it should also be noted that the formation of intermediate of type **B**, in which **1a** has a bidentate coordination to AlCl$_3$ (complex **II**), leads to an intermediate of nearly the same total energy as above. The transition state for this reaction is slightly lower than the one starting from complex **I**, while the energy of the reactants is higher.

It has been reported by Bigi *et al.* that the reaction of pyridine-2-carbaldehyde **1a** with 4-methoxyphenol **2b** catalyzed by AlCl$_3$ proceeded smoothly at room temperature in CH$_2$Cl$_2$.[9]

C-C distance: 2.14 Å

C-H distance: 1.07 Å

C-O distance: 1.29 Å

O-Al distance: 1.75 Å
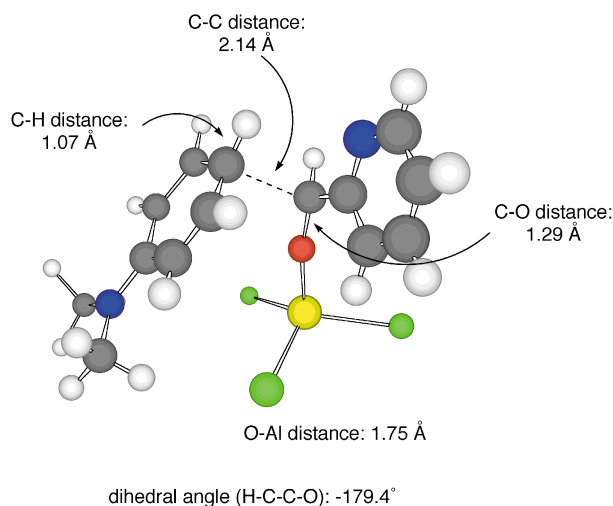
dihedral angle (H-C-C-O): -179.4°

Fig. 6 The lowest transition-state structure for the formation of a Friedel–Crafts intermediate of type **B** by reaction of pyridine-2-carbaldehyde **1a** with *N,N*-dimethylaniline **2a** starting from complex **I**.

They observed higher reactivity for **1a** compared to the corresponding 3- and 4-isomers, **1b** and **1c**, respectively, of pyridine-carbaldehyde, and proposed that this could indicate a possible coordination of the metal by the pyridine nitrogen atom, because they at the same time observed no reactivity of benzaldehyde under similar conditions. Focusing on the hydroxy product (in this product the proton has been transferred from the aromatic C–H bond to the oxygen atom of the activated carbonyl bond) in the reaction of the pyridine-2-carbaldehyde we can observe a stabilisation by chelation of 17.7 kcal mol⁻¹. The fact that bidentate coordination is not possible for the 3- and the 4-isomers and the fact that only the 2-isomer gives the hydroxy product while the 3- and 4-isomers react further to give a diarylated product, **3a** and **3b**, respectively, leads us to believe that (i) chelation could be important for reaction to stop at the alcohol stage, thereby making it possible upon aqueous workup to isolate the hydroxy product **3a**, and/or (ii) that the increased reactivity for **1b** and **1c** is due to the lower LUMO energy of these compounds compared to **1a**.

Summary

We have found that it is possible to mediate an enantio-selective Friedel–Crafts reaction of pyridine-2-carb-aldehyde with *N,N*-dimethylaniline by the application of chiral Lewis acids. The reactions proceed with moderate to good yields depending on the reaction conditions, and moderate enantioselectivity could be obtained by applying an optic-ally active ligand ((*R*)-BINOL) to the catalyst system. The 3- and 4-isomers of the pyridinecarbaldehyde also react with *N,N*-dimethylaniline under similar conditions giving a diarylated product, while benzaldehyde showed no reactivity. The investigation of a mono- *vs.* bidentate coordination of the aluminium catalyst both experimentally and computationally leads us to believe that the bidentate coordination is not necessary for the reaction of **1a** and **2a** to proceed. The computational results point to monodentate coordination making the lowest energy reaction path. Thus, we believe that it is the electron-withdrawing effect of the pyridine ring that enhances the reactivity of the pyridinecarbaldehydes as compared to *e.g.* benzaldehyde. This is consistent with the fact that we also observe reactions of **1b** and **1c** with **2a** in the presence of an aluminium catalyst. However, a bidentate coordination might be important for the reaction to stop at the stage of the hydroxy product. We see a stabilisation of the product by the bidentate coordination; moreover we observe no hydroxy product in the reactions of **1b** or **1c** (in which the coordination of the Lewis acid to the nitrogen atom is not possible for geometrical

reasons). Instead in these cases we only obtain the diarylated product. The calculations show that the most probable aluminim-mediated reaction proceeds by a zwitterionic inter-mediate *via* a transition state in which the H–C–C–O dihedral angle is ~−180°, *i.e.* the incoming aromatic compound approaches the activated carbonyl bond with the C–H bond to be broken in an *anti* fashion.

Experimental and theoretical

General methods

All reactions were carried out using anhydrous solvent and flame-dried glasware using standard Schlenk techniques under N_2. Commercially available compounds were used without further purification. Solvents were dried according to standard procedures. Purification of the products, when necessary, was carried out by flash chromatography (FC) using Merck silica gel 60 (230–400 mesh). TLC was performed using Merck silica gel 60 F_{254} plates and visualized with blue stain. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. ¹H NMR and ¹³C NMR spectra were recorded at 400 and 100 MHz respectivly, using $CDCl_3$ as the solvent, and are reported in ppm downfield from $CDCl_3$ ($\delta = 7.25$) for ¹H NMR and relative to the central $CDCl_3$ resonance ($\delta = 77.0$) for ¹³C NMR. The enantiomeric excess (ee) of the products were determined by HPLC.

General procedure

The appropriate BINOL ligand (0.2 mmol) was placed in the reaction flask and was subjected to vacuum for 1 h. The flask was then refilled with N_2 and solvent (2.5 ml) was then added. A commercially available heptane solution of $AlMe_2Cl$ (0.2 mmol) was added by microsyringe resulting in gas evolution (CH_4) and white precipitate. The reaction mixture was stirred at room temperature for 1 h. If needed the reaction mixture was cooled to the appropriate temperature and the pyridinecarb-aldehyde (1.05 equiv.) and aromatic compound (1.0 equiv.) were added resulting in a brownish color. The reaction was left stir-ring giving a clear orange solution. The mixture was poured on to 10 mL of NH_4Cl (aq. sat.) and additional solvent was added. The phases were separated and the aq. phase was extracted with CH_2Cl_2 (10 ml) and EtOAc (10 ml). The combined organic phases were dried over Na_2SO_4 and the solvent was removed. The product was purified by column chromatography on silica. ($R_{f(product)}$: 0.25 in 5% MeOH–CH_2Cl_2) The BINOL ligand and excess starting material were eluted using ether–petroleum ether (30%) after which the product was collected using 5% MeOH in CH_2Cl_2.

(4-Dimethylaminophenyl)pyridin-2-ylmethanol 3a. ¹H NMR δ 8.54 (d, $J = 5.0$ Hz, 1H), 7.59 (dt, $J = 7.7$ Hz, $J = 1.7$ Hz, 1H), 7.20 (d, $J = 8.7$ Hz, 2H), 7.12–7.22 (m, 2H), 6.68 (d, $J = 8.7$ Hz, 2H), 5.67 (d, $J = 3.6$ Hz, 1H), 5.06 (d, $J = 3.6$ Hz, 1H), 2.91 (s, 6H). ¹³C NMR δ 177.5, 150.3, 147.6, 136.6, 131.1, 128.1, 122.1, 121.3, 112.5, 74.7, 40.6. HPLC (Daicel Chiralcel OD, hexane–*i*-PrOH = 90 : 10, flow rate = 0.5 ml min⁻¹) $t_r = 33.9$ min (major), $t_r = 41.1$ min (minor). HRMS for $C_{14}H_{16}N_2O$ (Na⁺): calcd 251.1160, found 251.1161.

The reactions of 4-methoxyphenol **2b** and 1,3-dimethoxy-benzene **2c** with *N,N*-dimethylaniline in CH_2Cl_2 in the presence of (*R*)-**4a**-AlCl were performed according to the general procedure. The data for for the products are available from the literature.⁹

The reactions of pyridine-3- and -4-carbaldehyde, **1b** and **1c**, respectively, with *N,N*-dimethylaniline were performed according to the general procedure. Compound **3b**: 43% con-version after 24 h. ¹H NMR δ 8.25 (s, 2H), 7.41 (m, 1H), 7.19 (m, 1H), 6.94 (d, $J = 9.2$ Hz), 6.66 (d, $J = 9.2$ Hz), 5.33 (s, 1H), 2.93 (s, 12H). Compound **3c**: 50% conversion after 24h. ¹H

NMR δ 8.46 (d, $J = 6.0$ Hz, 2H), 7.05 (d, $J = 6.0$ Hz, 2H), 6.95 (d, $J = 8.8$ Hz), 6.66 (d, $J = 8.8$ Hz), 5.31 (s, 1H), 2.92 (s, 12H). LRMS: calcd for $C_{22}H_{25}N_3$ 331.2 (M)$^+$, found (M + H)$^+$ 332.4.

Theoretical methods

Calculations were performed using Jaguar version 4.0[7] and using Restricted Hartree–Fock (RHF) using a 6-31G basis set for all calculations. The Hessians were calculated at all stationary points to ensure that minima were characterised by all positive normal modes and the transition states were characterised by one negative normal mode corresponding to the motion of the proper atoms. Energies reported were obtained from single point energy calculations. Atomic charges were obtained from Mulliken population analysis which was performed on structures previously optimized on the RHF/6-31G level.

Acknowledgement

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