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Phosphabarrelene-modified Rh-catalysts: a new and selective route towards hydroxy-functionalized bicyclic imidazoles *via* tandem reactions†‡

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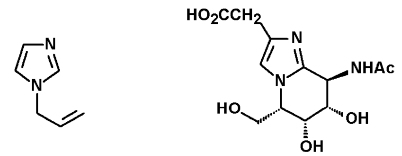
8-Hydroxy-6-methyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine was formed selectively in high yields from *N*-(β-methallyl)imidazole by a tandem hydroformylation–cyclization sequence, representing a novel one-pot catalytic synthesis of bicyclic imidazole derivatives.

The metal-catalyzed hydroformylation of alkenes is an industrially important, atom efficient reaction for the production of aldehydes.[1] A developing area is the integration of hydroformylation reactions in tandem or domino-type sequences, in which the initial CO/H_2 addition to an alkene is combined with a subsequent reaction.[2] Yet not trivial to achieve, these multistep reactions are powerful tools for the construction of more complex products by making economical use of available functional groups within the same molecule. In this respect, vinyl and allyl heteroaromatic substrates are especially interesting and potentially relevant for both pharmaceutical and fine chemical industry, because the generated frameworks are often found in biologically active compounds, such as alkaloids. Vasylyev and Alper recently reported on a rhodium-catalyzed hydroformylation–silica-promoted deformylation sequence, leading to hexahydropyrrolo[2,1]oxazoles.[3] The formation of 5,6-dihydroindolizines and 5,6,7,8-tetrahydroindolizines was observed by Lazzaroni and co-workers after hydroformylation of *N*-(β-methallyl)pyrrole with $Rh_4(CO)_{12}$ as catalyst precursor. Under relatively harsh reaction conditions ($p(CO/H_2) > 100$ bar, $T > 100$ °C) subsequent intramolecular cyclization and dehydration and, eventually, hydrogenation occurred.[4]

Interestingly, analogous reactions starting from *N*-allyl-imidazole (**1**) could lead to bicyclic imidazole derivatives, which often have antiulcer, anticancer, antidepressant or antimicrobial activity, such as nagstatin **2** (Fig. 1).[5] Surprisingly, tandem reactions on such substrates have never been investigated, which is most likely due to the fact that the imidazole moiety is much less prone to electrophilic substitution reactions compared to pyrrole, although the intermolecular thermal condensation of imidazoles with carbonyl compounds has been reported before.[6] The access to 1,2-fused bicyclic imidazoles typically requires multistep synthetic protocols and often the presence of strong Lewis acids, such as $SnCl_4$ or $TiCl_4$.[7]

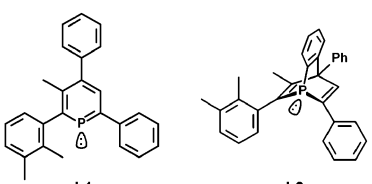


1 2

Fig. 1 *N*-Allyl-imidazole **1** and nagstatin **2**.

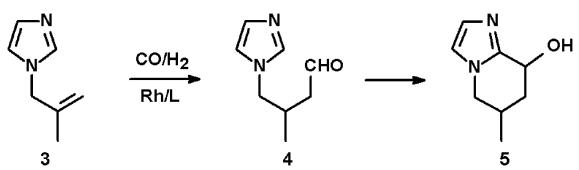
During the course of our investigations on functionalized phosphinine-based heterocycles we anticipated that **L1** and **L2** might be suitable ligands for reaction sequences under hydroformylation conditions (Fig. 2).[8] In fact, these types of phosphorus compounds have been shown to be efficient ligands for the Rh-catalyzed hydroformylation of terminal and less reactive internal alkenes before.[9]

We chose the methyl-substituted *N*-(β-methallyl)imidazole substrate **3** (Scheme 1) rather than **1**, since hydroformylation reactions of 1,1′-disubstituted alkenes are almost always completely regioselective for the formation of linear *versus* quaternary aldehydes according to Keulemans empirical rule.[10] **3**



L1 L2

Fig. 2 Phosphinine **L1** and corresponding phosphabarrelene **L2**.



3 4 5

Scheme 1 Rh-catalyzed hydroformylation of **3** and subsequent cyclization to **5**.

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‡ Electronic supplementary information (ESI) available: A list of all experimental details. CCDC reference number 736069. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b911612e

could easily be synthesized in high yields by reaction of imidazole with 3-chloro-2-methylpropene.[11] The Rh-catalyzed hydroformylations of **3** (S : Rh : L = 1500 : 1 : 20) were performed at T = 80 °C and $p(CO/H_2 = 1:1)$ = 20 bar in toluene.

Surprisingly, the Rh-catalyst based on the π-acceptor phosphinine **L1** leads to only 32% conversion after 72 h and exclusively to the linear aldehyde **4**, which shows a characteristic resonance for the aldehyde-proton at δ = 9.7 ppm (t, J_{H-H} = 1.1 Hz) in the ^{1}H NMR spectrum (Scheme 1). However, applying the more σ-donating phosphabarrelene **L2**, almost complete conversion to **4** (98%) could be achieved, but unfortunately only traces of **5** (~2%) were detected. For comparison reasons we also applied the bulky phosphite $P(OPh\text{-}o\text{-}^tBu)_3$[12] (**L3**) as well as PPh_3 (**L4**) as ligand. Catalyst Rh/**L3** showed hardly any conversion (<5%), whereas Rh/**L4** led to 92% yield of the aldehyde **4** within 72 hours (~1.5% of **5**, see ESI†). Catalysts based on strong π-acceptor ligands (**L1** and **L3**) are obviously not suitable for the hydroformylation of these types of heterocyclic substrates, while catalysts based on the more σ-donating phosphabarrelenes[9d,13] (**L2**) and the strong σ-donating PPh_3 show much better results. A possible explanation might be competition for the metal center between the donor-functionalized substrate present in large excess and the poor σ-donating π-acceptor ligands.

The best performing phosphabarrelene-modified Rh-catalyst (Rh/**L2**) was subsequently applied in the hydroformylation of **3** at T = 120 °C. Under these conditions, **3** is almost quantitatively converted to 8-hydroxy-6-methyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine **5** within 45 h (93%, determined by GC, Scheme 1). Apparently, compound **5** is produced by a tandem hydroformylation–cyclization sequence, in which the fused bicyclic imidazole structure is formed by an intramolecular nucleophilic attack of the imidazole C^2 carbon atom on the carbonyl group of the aldehyde under formation of an alcohol. This new one-pot tandem reaction was investigated by GC-analysis of the product composition during the course of the reaction and the corresponding distribution-of-species plot is shown in Fig. 3.

The substrate **3** is rapidly consumed at the beginning of the reaction with a turnover frequency (TOF) of 700 h^{-1} (determined at 20% conversion). The maximum aldehyde concentration is reached after 6 h and the final cyclization product **5** is selectively generated and accumulated within the reaction time of 45 h. No formation of any byproducts could be detected. The PPh_3-based catalyst Rh/**L4** shows essentially the same selectivity under identical reaction conditions but is less active compared to Rh/**L2** (TOF = 390 h^{-1}). Isolation of pure **4** and subsequent transformation into **5** (toluene, 120 °C) further showed that the cyclization step is not metal-catalyzed, as anticipated.[6]

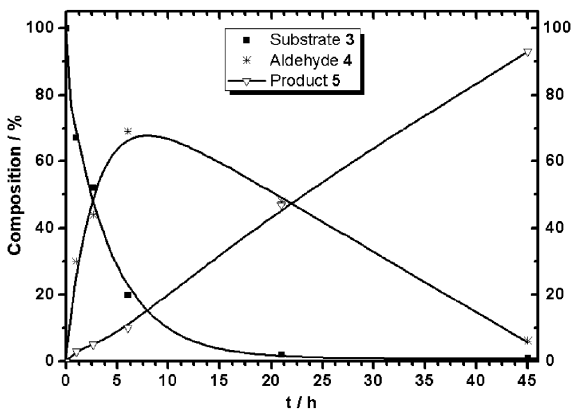

Fig. 3 Distribution-of-species plot for the tandem hydroformylation–cyclization sequence of substrate **3**. S : Rh : **L2** = 1500 : 1 : 20, c_{Rh} = 1 mM, V = 8 mL, T = 120 °C, p = 20 bar (CO/H_2 = 1 : 1).

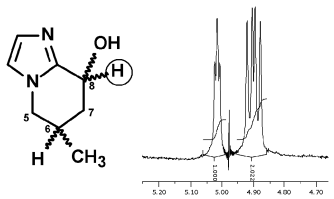

Fig. 4 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of the C^8–H region of **5**.

The bicyclic imidazole **5** was obtained as an off-white solid in 80% isolated yield after removal of all volatiles and subsequent recrystallization from toluene. **5** was fully characterized by ^{1}H and ^{13}C NMR spectroscopy as well as by elemental analysis. The tandem reaction generates the two stereogenic carbon atoms C^6 and C^8 and thus, the presence of 2 pairs of enantiomers is expected. In fact, the ^{1}H NMR spectrum of the product shows two sets of protons of which the set assigned to the C^8–H proton is the most distinctive.[14] Two characteristic resonances and couplings with the two protons of the adjacent methylene spacer are observed at δ = 4.90 ppm (dd, $^3J_{H-H}$ = 6.6, 10.0 Hz) and δ = 5.02 ppm (t, $^3J_{H-H}$ = 3.3 Hz), respectively, in a ratio of 2 : 1 (Fig. 4).

We were further able to detect the four stereoisomers of **5** in a ratio of 1 : 2 : 2 : 1 by analytical HPLC analysis on a chiral stationary phase, using *n*-hexane–isopropanol (95 : 5) as eluent (Chiralcel® OD–H, t_1 = 12.9 min, t_2 = 19.4 min, t_3 = 25.5 min, t_4 = 34.1 min, T = 25 °C, flow-rate 1 mL min^{-1}, see ESI†). In order to gain more information on the stereochemistry of the products we made use of the rather large differences in retention times and were able to separate and characterize all four stereoisomers independently. As anticipated, fractions 1 + 4 show identical ^{1}H NMR spectra and the distinctive triplet at δ = 5.02 ppm for the C^8-proton, while identical

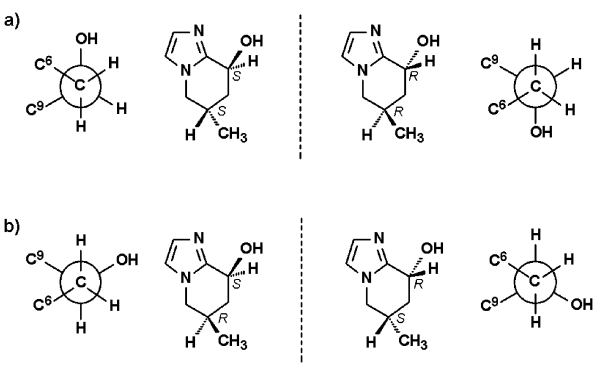

Fig. 5 Stereoisomers of **5** and corresponding Newman-projections; (a) *anti* configuration leading to a triplet for C^8–H in the ^{1}H NMR spectrum (HPLC fractions 1 + 4); (b) *syn* configuration (dd, HPLC fractions 2 + 3).

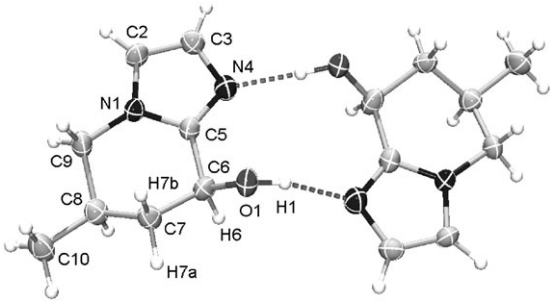

Fig. 6 Hydrogen bonding of **5** in the crystal. Displacement ellipsoids are shown at the 50% probability level. Only the major stereoisomer **5**(*S*,*R*) of the mixture is shown.

^{1}H NMR spectra with the characteristic doublet of doublets at δ = 4.90 ppm was observed for fractions 2 + 3 (see ESI†).

From the Newman-projections of all four stereoisomers it becomes obvious that the *anti* products are expected to show a triplet for the C^8–H proton of the A_2B spin system in the ^{1}H NMR spectrum (Fig. 5a). This pair can consequently be assigned to fractions 1 and 4 in the HPLC chromatogram. In contrast, the pair of enantiomers with *syn* configuration (Fig. 5b) should result in a doublet of doublets for the C^8–H proton of the ABX spin system in the corresponding ^{1}H NMR spectrum, and can therefore be assigned to fractions 2 and 3. Moreover, the Newman-projections indicate the preferred formation of the *syn*-configured enantiomers as both the –OH and –CH_3 groups are located in the preferred equatorial position of the annulated ring.

From the mixture of stereoisomers single crystals suitable for X-ray diffraction were formed by slow crystallization of **5** from toluene. The crystal structure unambiguously confirms the bicyclic nature of the anticipated imidazole derivative. Due to the centrosymmetry of the space group the crystal structure is racemic, but on individual crystallographic sites a mixture of the *syn* products is found in a ratio **5**(*S*,*R*) : **5**(*R*,*S*) = 0.756(4) : 0.244(4) and consequently on an inverted site of 0.244(4) : 0.756(4) (see also ESI†). The molecular structure of the major enantiomer **5**(*S*,*R*) is depicted in Fig. 6 and shows hydrogen bonding between the –OH group and the basic nitrogen atom N4 of an adjacent molecule and *vice versa*.[7a] This stabilizing effect might explain the fact that **5** does not undergo spontaneous elimination of H_2O as observed for related compounds.[4] Furthermore, it can be seen that the hydrogen atoms H6, H7a and H7b adopt the typical positions for the *syn* product (*vide supra*).

In summary we have developed a new route towards functionalized bicyclic imidazole derivatives consisting of a one-pot tandem reaction sequence under hydroformylation conditions. 8-Hydroxy-6-methyl-5,6,7,8-tetrahydroimidazo-[1,2-*a*]pyridine was formed selectively in high yield by hydroformylation of *N*-(β-methallyl)imidazole using a phosphabarrelene-modified Rh-catalyst and subsequent intramolecular cyclization. The stereochemistry of the generated 2 pairs of enantiomers was investigated by ^{1}H NMR spectroscopy in combination with chiral HPLC analysis and the bicyclic nature of the product could unambiguously be confirmed by X-ray crystal structure determination. The full substrate and product scope is currently under investigation in our laboratories.[15]

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