measured in 0.1N KOAc/methanol and 1.0N NH_4OAc/methanol solutions at 25 °C and 60000 rpm; both protocols gave similar results. In pure methanol the sample sedimented very slowly as a result of electrostatic repulsion. The partial specific volume of 0.6305 $mL\,g^{-1}$ was used.[16]

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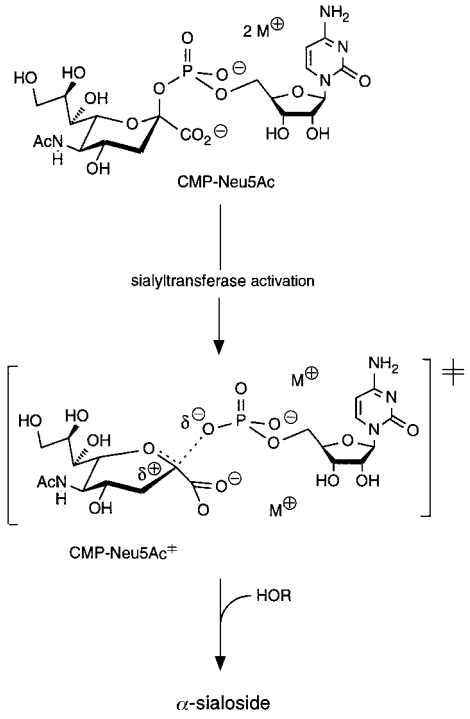
Efficient Sialyltransferase Inhibitors Based on Transition-State Analogues of the Sialyl Donor**

Bernd Müller, Christoph Schaub, and Richard R. Schmidt*

Sialic acid containing epitopes are involved in important biological processes, such as cell adhesion and inflammation.[1] There is also a correlation between the sialyl content of glycoconjugates and the malignancy of tumor cells.[2] Furthermore, differences in sialylation type between tumor cells and normal cells were found;[3, 4] for instance, although *N*-glycolylneuraminic acid has not been observed thus far on the surface of normal human cells, 30–50% of tumor cells of different origin contain this compound in small amounts.[3] Recently, an interesting correlation between α(2-6)-sialylation of *N*-acetyllactosamine and B lymphocyte activation and immune function was reported, which could find medicinal application.[5] Therefore, to study the influence of sialyl residues in biological systems it is highly desirable to develop efficient inhibitors for sialyltransferases.

The various sialyltransferases employ, independent of their source and their acceptor specificity, cytidine monophosphate *N*-acetylneuraminic acid (CMP-Neu5Ac, Scheme 1) as sialyl



Scheme 1. Mechanism of the sialylation.

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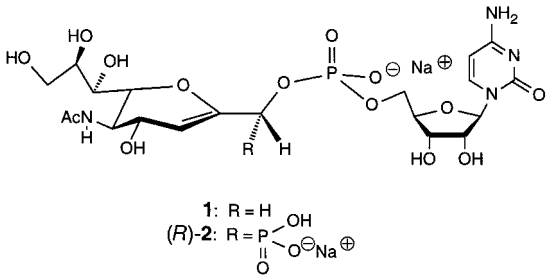
donor.[6] Analogues derived from the transition state of the proposed reaction course (CMP-Neu5Ac$^+$ in Scheme 1)[7, 8] could exhibit high enzyme affinity and thus lead to particularly efficient inhibitors. So far, only a few donor and acceptor analogues (=substrate analogues) which serve as sialyltransferase inhibitors have been reported;[7–13] however, their potency is only in the micromolar range and thus close to that of the substrate CMP-Neu5Ac, which binds to α(2-6)-sialyltransferase from rat liver (EC 2.4.99.1) with $K_M = 46$ μM (Table 1).[7] Therefore, we have initiated a program on the

Table 1. Affinity of CMP-Neu5Ac (K_M) to α(2-6)-sialyltransferase of rat liver and inhibition constants (K_i) of transition-state analogues (*R*)-**2**, **3h**, **3l**, **4h**, **4l**, (*R*)-**6**, (*S*)-**6**, (*R*)-**7**, (*S*)-**7**, (*E*)-**8**, and (*Z*)-**9**.[a]

	K_M [μM]	K_i [μM]	Ref.
CMP-Neu5Ac	46 ± 7	–	[7]
(*R*)-**2**	–	0.35 ± 0.05	[8]
3h	–	0.20 ± 0.05	–
3l	–	1.0 ± 0.2	–
4h	–	0.28 ± 0.06	–
4l	–	1.0 ± 0.3	–
(*R*)-**6**	–	10 ± 2	–
(*S*)-**6**	–	7 ± 2	–
(*R*)-**7**	–	15 ± 3	–
(*S*)-**7**	–	23 ± 5	–
(*E*)-**8**	–	6.0 ± 0.5	[8]
(*Z*)-**9**	–	0.04 ± 0.008	–

[a] For details see ref. [7a].

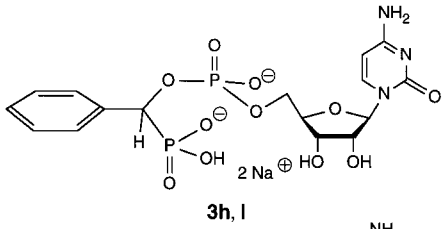
synthesis of transition-state analogues.[7, 14] Compounds **1** and **2** were derived from the transition-state model CMP-Neu5Ac$^+$ (Scheme 1), which is deduced from the recently supported S_N1-type mechanism;[7, 8, 15] they were considered as



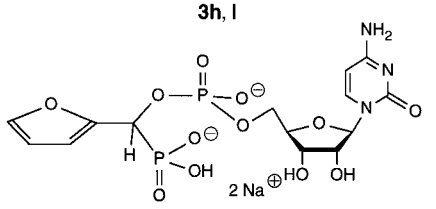
1: R = H
(*R*)-**2**: R = P(O)(OH)(O$^\ominus$Na$^\oplus$)

potential inhibitors because the distance between the anomeric center (C-2 of the Neu5Ac residue) and the leaving group (CMP) is increased, and thus similar to the distance in the transition-state model (CMP-Neu5Ac$^+$). In particular compound **2**[8] was of interest, because it contains two negative charges separated by five bonds, as in CMP-Neu5Ac. In addition, the anomeric center is trigonal planar, thus favoring a conformation assumed for a S_N1-type transition state. This concept turned out to be very fruitful, because (*R*)-**2** is a very potent inhibitor which binds in the nanomolar range to α(2-6)-sialyltransferase (Table 1).[8] This result led to two questions: 1) Is the neuraminyl residue as shown in (*R*)-**2** required at all or can it be replaced by a simple aryl, hetaryl, or related moiety, thus making these type of compounds readily accessible? 2) Will a different geometry of the substituents around the anomeric center increase the binding affinity?

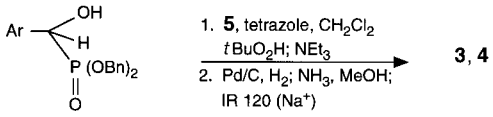
To investigate the first question, compounds **3** and **4** were prepared (Scheme 2). To this end, benzaldehyde and furfural were transformed with dibenzyl phosphonate into the corresponding α-hydroxyphosphonates[16] (racemic mixtures).

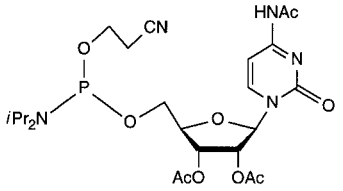


3h, l



4h, l





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Scheme 2. Synthesis of **3** and **4**. Bn = benzyl.

Their condensation with cytidine-phosphitamide **5**[17] in the presence of tetrazole followed by oxidation with *tert*-butyl hydroperoxide and base-catalyzed cleavage of the cyanoethyl group afforded the target molecules **3h**, **3l** and **4h**, **4l** (Table 2) after hydrogenolytic debenzylation, deacylation, chromatography over RP-18 silica gel ($Et_3NH \cdot HCO_3$ buffer as eluent), and ion exchange with IR-120 (Na^+); the diastereoisomers were separated based on their different R_f values (*h*igh, *l*ow); the configuration of the new stereogenic center was not assigned. Compounds **6** and **7**, in which the phosphonate residue is replaced by a carboxylate group, can be readily obtained from methyl (*R*)- and (*S*)-mandelate and methyl (*R*)- and (*S*)-phenyllactate in a similar fashion (Scheme 3, Table 2).

As can be seen in Table 1, phenyl derivative **3h** exhibits an even higher binding affinity to α(2-6)-sialyltransferase than does neuraminyl derivative (*R*)-**2**, and furyl derivative **4h** is also a very good competitive inhibitor.[18] Apparently, the configuration at the carbon atom bearing the CMP moiety has no dramatic influence on inhibition (K_i values: **3h**:**3l** ≈ 1:5; **4h**:**4l** ≈ 1:4). Replacement of the phosphonate group by a carboxylate group as in (*R*)- and (*S*)-**6** and in (*R*)- and (*S*)-**7** decreases the binding affinity by about one order of magnitude; again the configuration at the carbon atom bearing the

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Table 2. Selected physical data of **3h**, **3l**, **4h**, **4l**, (*R*)-**6**, (*S*)-**6**, (*R*)-**7**, (*S*)-**7**, and (*Z*)-**9**.[a]

3h: HPLC (2% CH_3CN, 10 mL min^{-1}): $t_R = 10.1$ min; $[\alpha]_D^{20} = -37.9$ ($c = 0.8$, H_2O); ^1H NMR: $\delta = 3.38$ (br d, 1H; 4′-H), 3.60 (m, 1H; 5a′-H), 3.81–3.95 (m, 3H; 2′-, 3′-, 5b′-H), 5.04 (dd, $^3J(1'',P) = 13.0$ Hz, $^2J(1'',P) = 11.0$ Hz, 1H; 1″-H); MS: $m/z = 494$ $[M - 3Na + 2H]^-$, 559.30 for $C_{16}H_{18}N_3Na_3O_{11}P_2$

3l: HPLC (2% CH_3CN, 10 mL min^{-1}): $t_R = 12.5$ min; $[\alpha]_D^{20} = +23.3$ ($c = 0.8$, H_2O); ^1H NMR: $\delta = 3.66–3.95$ (m, 5H; 2′-, 3′-, 4′-, 5a,b′-H), 5.02 (dd, $^3J(1'',P) = 14.0$ Hz, $^2J(1'',P) = 10.0$ Hz, 1H; 1″-H); MS: $m/z = 494$ $[M - 3Na + 2H]^-$, 559.30 for $C_{16}H_{18}N_3Na_3O_{11}P_2$

4h: HPLC (1% CH_3CN, 8 mL min^{-1}): $t_R = 15.7$ min; ^1H NMR: $\delta = 3.5–4.0$ (m, 5H; 2′-, 3′-, 4′-, 5a,b′-H), 5.04 (dd, $^3J(1'',P) = 15$ Hz, $^2J(1'',P) = 9.2$ Hz, 1H; 1″-H); ^{31}P NMR: $\delta = 0.73$ (d, $^3J(P,P) = 33.4$ Hz; phosphate), 12.56 (d; phosphonate); MS: $m/z = 486$ $[M - 2Na + H - H_2O]^-$, 504 $[M - 2Na + H]^-$, 525 $[M - Na]^-$, 549.2 for $C_{14}H_{16}N_3Na_3O_{12}P$

4l: HPLC (1% CH_3CN, 8 mL min^{-1}): $t_R = 19.9$ min; ^1H NMR: $\delta = 3.65–3.82$ (m, 2H; 5a,b′-H), 3.9–4.0 (m, 3H; 2′-, 3′-, 4′-H), 5.03 (dd, $^3J(1'',P) = 15.1$ Hz, $^2J(1'',P) = 9.5$ Hz, 1H; 1″-H); ^{31}P NMR: $\delta = 1.07$ (d, $^3J(P,P) = 33.4$ Hz; phosphate), 12.49 (d; phosphonate); MS: $m/z = 486$ $[M - 2Na + H - H_2O]^-$, 504 $[M - 2Na + H]^-$, 525 $[M - Na]^-$, 549.2 for $C_{14}H_{16}N_3Na_3O_{12}P$

(*R*)-**6**: HPLC (3% CH_3CN, 8 mL min^{-1}): $t_R = 13.67$ min; $[\alpha]_D^{20} = -41$ ($c = 1.09$, H_2O); ^1H NMR: $\delta = 3.55–3.64$ (m, 2H; 5a,b′-H), 3.80–3.92 (m, 3H; 2′-, 3″-, 4′-H), 5.19 (d, $^3J(1'',P) = 8.9$ Hz, 1H; 1″-H); ^{31}P NMR: $\delta = -0.13$ (s; phosphate); MS: $m/z = 455$ $[M - 2Na + H]^-$, 501.3 for $C_{17}H_{18}N_3Na_2O_{10}P$

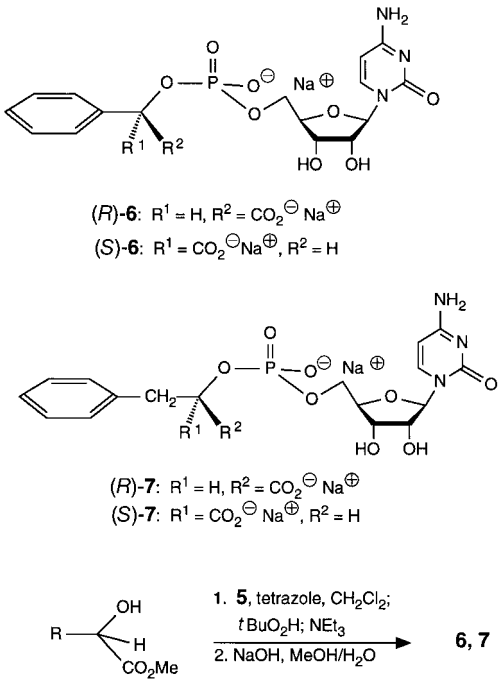
(*S*)-**6**: HPLC (3% CH_3CN, 8 mL min^{-1}): $t_R = 21.32$ min; $[\alpha]_D^{20} = +37.6$ ($c = 0.5$, H_2O); ^1H NMR: $\delta = 3.70–3.91$ (m, 5H; 2′-, 3′-, 4′- 5a,b′-H), 5.16 (d, $^3J(1'',P) = 9.1$ Hz, 1H; 1″-H); ^{31}P NMR: $\delta = 0.20$ (s; phosphate); MS: $m/z = 455$ $[M - 2Na + H]^-$, 501.3 for $C_{17}H_{18}N_3Na_2O_{10}P$

(*R*)-**7**: TLC: $R_f = 0.81$; $[\alpha]_D^{20} = +5.5$ ($c = 1$, H_2O); ^1H NMR: $\delta = 2.80–2.97$ (m, 2H; 2a,b″-H), 3.50–3.58 (m, 1H; 5a′-H), 3.80–3.94 (m, 4H; 2′-, 3′-, 4′-, 5b′-H), 4.38–4.48 (m, 1H; 1″-H); ^{31}P NMR: $\delta = 0.07$ (s; phosphate); MS: $m/z = 470$ $[M - 2Na + H]^-$, 515.07 for $C_{18}H_{20}N_3Na_2O_{10}P$

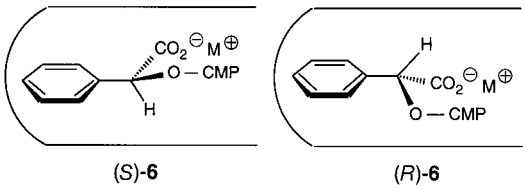
(*S*)-**7**: TLC: $R_f = 0.81$; $[\alpha]_D^{20} = -9.4$ ($c = 1$, H_2O); ^1H NMR: $\delta = 2.81$ (dd; $J(2a'',2b'') = 14.2$ Hz, $J(2a'',1'') = 7.0$ Hz, 1H; 2a″-H), 2.89 (dd, $J(2b'',1'') = 5.3$ Hz, 1H; 2b″-H), 3.60–3.74 (m, 2H; 5a,b′-H), 3.88–3.96 (m, 2H; 2′-,3′-H), 4.00 (dd, $J(4',3') = J(4',5a') = 4.5$ Hz, 1H; 4′-H), 4.38 (ddd, $J(1'',P) = 8.4$ Hz, 1H; 1″-H); ^{31}P NMR: $\delta = -0.04$ (s; phosphate); MS: $m/z = 470$ $[M - 2Na + H]^-$, 515.07 for $C_{18}H_{20}N_3Na_2O_{10}P$

(*Z*)-**9**: HPLC (2% CH_3CN, 10 mL min^{-1}): $t_R = 14.4$ min; ^1H NMR (600 MHz, D_2O): $\delta = 1.89$ (s, 3H; NHAc), 3.42 (dd, $J(7'',8'') = 9.1$ Hz, $J(7'',6'') = 1.9$ Hz, 1H; 7″-H), 3.51 (dd, $^2J(9a'',9b'') = 11.9$ Hz, $J(9a'',8'') = 7.0$ Hz, 1H; 9a″-H), 3.75 (dd, $J(9b'',8'') = 2.8$ Hz, 1H; 9″b-H), 3.84 (dd, $J(6'',5'') = 9.8$ Hz, 1H; 6″-H), 3.91 (m, 1H; 8″-H), 4.13 (m, 2H; 3′,4′-H), 4.15–4.20 (m, 3H; 2′-, 5a,b′-H), 4.73 (ddd, $J(5'',4'') = J(5'',3'') = 1.9$ Hz, 1H; 5″-H), 5.76 (ddd, $J(4'',3'') = 10.4$ Hz, $J(4'',P) = 2$ Hz, 1H; 4″-H), 5.85 (d, $J(1',2') = 4.2$ Hz, 1H; 1′-H), 6.50 (ddd, $J(3'',P) = 2.8$ Hz, 1H; 3″-H); ^{31}P NMR (242.5 MHz, D_2O): $\delta = -3.6$ (br s; phosphate), 3.6 (br s; phosphonate); MS: $m/z = 644$ $[M - 3Na + 2H]^-$, 710.42 for $C_{20}H_{27}N_4Na_3O_{16}P_2$

[a] ^1H NMR: 250 MHz, D_2O, unless indicated otherwise. ^{31}P NMR: 161.7 MHz, D_2O, unless indicated otherwise. MS: MALDI, negative mode, matrix ATT. HPLC: RP-18, 1–3% CH_3CN, 0.05 M $Et_3NH \cdot HCO_3$. TLC: ethyl acetate/methanol/1 M $CH_3CO_2NH_4$ 1/1/1.



Scheme 3. Synthesis of **6** and **7**.

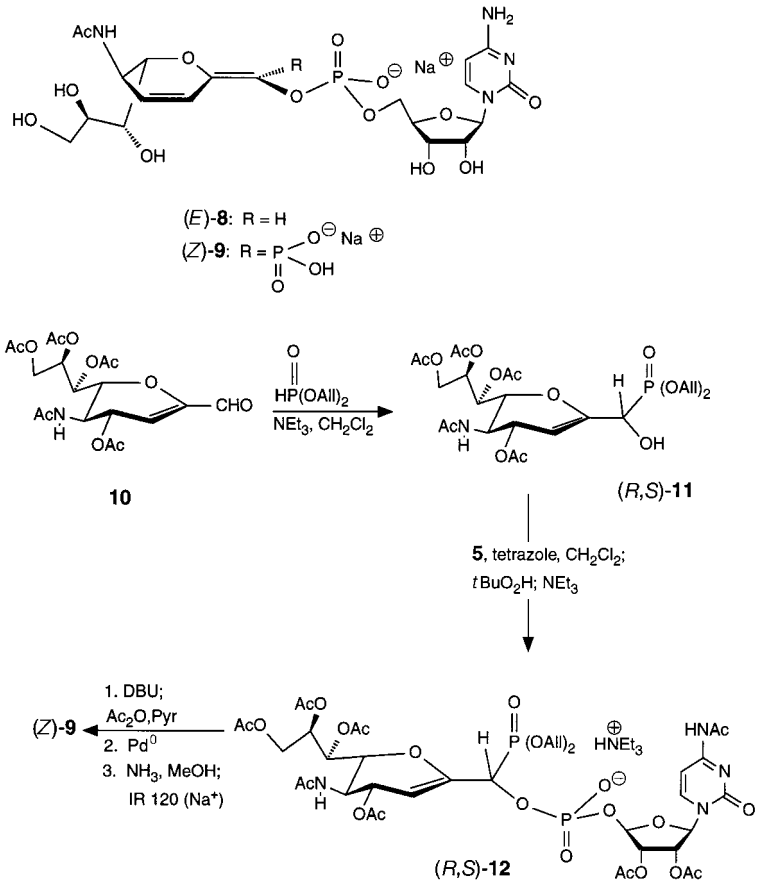


Scheme 4. Formation of **6** with accomodation of the configurational difference.

CMP moiety has no major influence on the K_i values. Thus, binding as depicted for the examples for (*R*)- and (*S*)-**6** in Scheme 4 is supported, which could accomodate the configurational difference.

The high affinity of **3h** (which contains a flat benzene ring), the minor influence of the carbon atom bearing the CMP group, and the unexpected high affinity of elimination product (*E*)-**8** (Scheme 5; obtained during the synthesis of (*R*)-**2** by deacetoxyphosphonylation)[8] led us to combine the positive effects of (*R*)-**2**, **3h** and (*E*)-**8** and to introduce a phosphonate residue at the methylene group of **8**. Thus, in the derived target compound (*Z*)-**9** the orientation of the two decisive moieties—the phosphonate and the CMP moiety—have the desired different geometry, and the pyran ring generated from the neuraminyl residue will be flatter than in (*R*)-**2** and thus more similar to the benzene ring in **3h**. The synthesis of (*Z*)-**9** could be readily accomplished (Scheme 5): Reaction of aldehyde **10**[8] with diallyl phosphonate[19] gave α-hydroxyphosphonate **11** (as a mixture of diastereomers (*R,S*)-**11**), which reacted by condensation with **5** as described above to diastereomers (*R,S*)-**12**. Base-supported (DBU) elimination of acetic acid followed by deallylation with $[Pd(PPh_3)_4]$ in the presence of dimedone and base-catalyzed deacylation afforded target molecule (*Z*)-**9** only (Table 2). This compound exhibited very potent competitive inhibition of α(2-6)-sialyltransferase ($K_i = 40$ nm, Table 1), and its affinity to α(2-6)-sialyltransferase[20] is three orders of magnitude higher than that of the natural substrate CMP-Neu5Ac; this supports the conceptual approach discussed here.

Potent sialyltransferase inhibition can be based on flat pyranosyl ring mimics which possess a methyl or a methylene carbon atom bearing a phosphonate and a CMP residue, as clearly exhibited for **1**, (*R*)-**2**, **3h**, (*E*)-**8**, and (*Z*)-**9**. Thus, further details of the transition-state geometry in the enzymatic sialyl transfer can be deduced, which provides leads for the extension of this research.



Scheme 5. Synthesis of (*Z*)-**9**. All = allyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

Experimental Section

A) Protocol for the synthesis of α-hydroxyphosphonates: The aldehyde (1 equiv) was dissolved in a small amount of CH_2Cl_2, and then the phosphonic acid diester (2 equiv) and a few drops of NEt_3 were added. The solution was stirred for 18 h, concentrated, and purified by chromatography on silica gel.

B) Protocol for the condensation with **5**: Compound **5** (1.5 equiv) and α-hydroxyphosphonate (1 equiv) were dissolved in CH_2Cl_2 and evaporated to dryness. The remaining foam was dissolved under nitrogen in dry CH_2Cl_2, and 1*H*-tetrazole (2 equiv) was added. After the reaction mixture had been stirred for 3 h, an anhydrous solution of *tert*-butyl hydroperoxide (1.5 equiv) was added, and after an additional hour NEt_3 (50 equiv) was added. After 18 h of stirring, the reaction mixture was concentrated at 20 °C and purified by chromatography on silica gel (ethyl acetate/methanol 5/1, 1 % NEt_3).

O-Debenzylation and/or O/N-deacetylation was performed as previously described[8] to afford **3h**, **3l**, **4h**, **4l**, (*R*)-**6**, (*S*)-**6**, (*R*)-**7**, and (*S*)-**7**.

C) Synthesis of (*Z*)-**9**: The synthesis of (*R,S*)-**11** and (*R,S*)-**12** followed protocols A and B, respectively. Compound (*R,S*)-**12** (180 mg, 0.16 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 70 µL, 0.48 mmol) were dissolved in dry THF (2 mL) and heated to 60 °C; after 2 h additional DBU (50 µL, 0.33 mmol) was added, and stirring continued for 3 h. Then acetic anhydride (2 mL) and pyridine (4 mL) were added at room temperature, and after 15 h the reaction mixture was concentrated and purified by chromatography on silica gel (ethyl acetate/methanol 5/1, 1 % NEt_3) to give protected (*Z*)-**9** (120 mg, 70 %); $R_f = 0.10$ (ethyl acetate/methanol 4/1, 1 % NEt_3). For the removal of the protecting groups (*Z*)-**9** (40 mg) was dissolved in THF (2 mL) and treated with $[Pd(PPh_3)_4]$ (4.2 mg, 4 µmol) and dimedone (21 mg, 0.15 mmol), and the mixture stirred for 30 min in the dark. The reaction mixture was purified by chromatography on RP-18 silica gel (water/ethanol 3/1) and concentrated in vacuo. Then an aqueous ammonia solution (30 %, 3 mL) was added in order to remove the acetyl groups. The solution was concentrated under reduced pressure and then dissolved in water (1 mL) and stirred with IR-120 (Na^+). Filtration and subsequent addition of ethanol (8 mL) afforded (*Z*)-**9** (yield 24 mg, 80 %).

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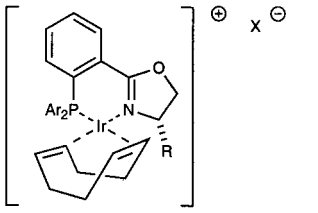
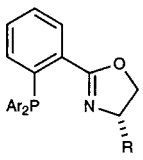
Enantioselective Hydrogenation of Olefins with Iridium – Phosphanodihydrooxazole Catalysts

Andrew Lightfoot, Patrick Schnider, and Andreas Pfaltz*

Enantioselective hydrogenation is one of the most powerful methods in asymmetric catalysis, with the most versatile catalysts being rhodium– and ruthenium – diphosphane complexes.[1] However, with a few exceptions, the range of substrates is still limited to certain classes of olefins bearing polar groups that can coordinate to the catalyst. Moreover, even in standard substrate categories derivatives can be found that give unsatisfactory enantioselectivities. There are only a few examples of highly enantioselective hydrogenations of unfunctionalized olefins.[2, 3] The most impressive results in this field have been obtained by Buchwald, who used Brintzinger's chiral titanocene complexes.[3] Although high *ee* values were obtained, the low catalyst activity required that a relatively high catalyst loading ($\geq$5 mol %) was used. Therefore, the search for new catalysts to fill these methodological gaps continues.

We recently reported enantioselective hydrogenation of imines catalyzed by iridium – phosphanodihydrooxazole complexes of the type **1** with PF_6^- as anion.[4] The coordination environment of the iridium center resembles that in Crabtree's catalyst, a cationic iridium complex with a monophosphane and pyridine as ligands.[5] Owing to the remarkable properties of Crabtree's catalyst—that is, the ability to hydrogenate tri- and tetrasubstituted olefins that do not react with rhodium– or ruthenium – phosphane catalysts—we decided to study complexes **1** as catalysts for the hydrogenation of unfunctionalized tri- and tetrasubstituted olefins.

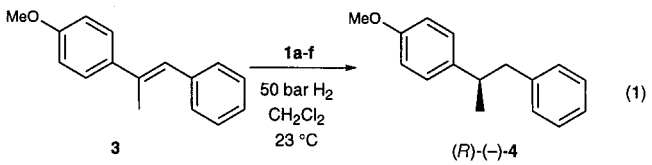




1a	Ar = Ph	R = *i*Pr	X = PF_6
1b	Ar = Ph	R = *t*Bu	X = PF_6
1c	Ar = *o*-Tol	R = *i*Pr	X = PF_6
1d	Ar = *o*-Tol	R = *t*Bu	X = PF_6
1e	Ar = Ph	R = *i*Pr	X = BARF
1f	Ar = *o*-Tol	R = *t*Bu	X = BARF
1g	Ar = Ph	R = CH_2tBu	X = BARF

2a	Ar = Ph	R = *i*Pr
2b	Ar = Ph	R = *t*Bu
2c	Ar = *o*-Tol	R = *i*Pr
2d	Ar = *o*-Tol	R = *t*Bu
2e	Ar = Ph	R = CH_2tBu

Initial experiments with complex **1a** led to encouraging results. Indeed, the hydrogenation of olefin **3** in CH_2Cl_2 with 4 mol % of **1a** [Eq. (1)] gave a good *ee* value of 75 %, albeit with moderate conversion (78 %, Table 1). Lower catalyst loadings led to decreased conversion. Preliminary kinetic data



(1)

with (*E*)-1,2-diphenyl-1-propene as substrate shows a large initial turnover frequency (TOF) of 41 min^{-1} (olefin: 0.31 M, catalyst: 0.003 M), but as the reaction proceeds the TOF decreases to essentially zero within one hour.[6] Deactivation has also been observed with Crabtree's catalyst, which is explained by the formation of inactive hydride-bridged trimers.[5] In our case the origin of deactivation is not known, but traces of water appear to enhance this undesired side reaction. Thus, the addition of molecular sieves to the above system gave an increased conversion. Alternatively, running the reaction under strictly anhydrous conditions, using freshly dried CH_2Cl_2 (distilled over CaH_2) and standard Schlenk techniques, allows full conversion to be obtained with 4 mol % of **1a** with the same *ee* value as before. Analytically pure product **4** was isolated in essentially quantitative yield by removal of the solvent and distillation.

Table 1. Enantioselective hydrogenation of **3** with use of catalysts **1a** – **f** [Eq. (1)].

Entry	Cat. (mol %)	Conversion [%]	*ee* [%]
1	**1a** (4)	78	75
2	**1b** (4)	98	90
3	**1c** (4)	> 99	91
4	**1d** (4)	57	97
5	**1e** (0.3)	> 99	70
6	**1f** (0.3)	> 99	98

A systematic study of ligands **2a** – **d** led to a highly enantioselective catalyst for the hydrogenation of **3** (Table 1). Thus, replacement of the isopropyl group of ligand **2a** with a *tert*-butyl group (**2b**) increased the *ee* value to 90 %. Alternatively, replacement of the diphenylphosphanyl group of **2a** with a bis(*o*-tolyl)phosphanyl group (**2c**) increased the *ee* value to 91 %. The combined use of a *tert*-butyl group and a bis(*o*-tolyl)phosphanyl group (**2d**) led to the highest enantioselectivity (97 % *ee*, 57 % conversion with 4 mol % of **1d**). Attempts to further increase the conversion by varying the reaction conditions and introducing additives, such as iodide, were met with little success.[7] However, replacement of the PF_6^- anion with BARF (tetrakis[3,5-bis(trifluoromethyl)phe-

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