ChemPubSoc Europe

DOI: 10.1002/cctc.201300825

Expanding the Chemical Diversity in Artificial Imine Reductases Based on the Biotin–Streptavidin Technology

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We report on the optimization of an artificial imine reductase based on the biotin-streptavidin technology. With the aim of rapidly generating chemical diversity, a novel strategy for the formation and evaluation of biotinylated complexes is disclosed. Tethering the biotin-anchor to the Cp* moiety leaves three free coordination sites on a d^6 metal for the introduction of chemical diversity by coordination of a variety of ligands. To test the concept, 34 bidentate ligands were screened and a selection of the 6 best was tested in the presence of 21 streptavidin (Sav) isoforms for the asymmetric imine reduction by the resulting three legged piano stool complexes. Enantiopure α-amino amides were identified as promising bidentate ligands: up to 63 % *ee* and 190 turnovers were obtained in the formation of 1-phenyl-1,2,3,4-tetrahydroisoquinoline with [IrCp*^{biotin}-(L-ThrNH$_2$)Cl]⊂SavWT as a catalyst.

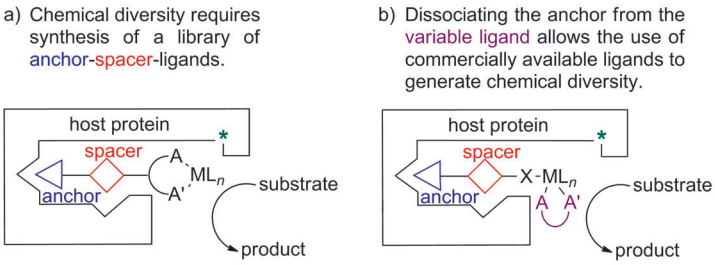
Introduction

Artificial metalloenzymes result from the incorporation of an organometallic catalyst or a catalyst precursor within a macromolecular scaffold (protein or oligonucleotide).[1–19] The resulting hybrid catalyst can be optimized by using either genetic or chemical methods.[1–8,18–21] In the context of artificial metalloenzymes based on the biotin-streptavidin technology, we and others have relied on synthesizing various biotinylated ligands to provide chemical diversity.[1,4,15,20,21] To generate larger artificial cofactor libraries quickly, we reasoned that separating the necessary biotin anchor moiety and variable ligand elements would enable us to screen commercially available ligands in the presence of streptavidin (Sav; Scheme 1). To test the validity of this strategy, we selected the asymmetric transfer hydrogenation of prochiral imines catalyzed with biotinylated moieties (M = Rh, Ir).

Considering the robustness of the MCp* moiety,[22,23] we reasoned that for d^6 transition metals tethering the biotin anchor to the Cp* unit would leave three free coordination sites around the metal for further functionalization. It is widely accepted that three-legged piano stool complex-catalyzed asymmetric transfer hydrogenation proceeds via an outer sphere hydride transfer mechanism, which requires only one free coordination site around the metal for the reaction to proceed.[24–27] This reaction is thus ideally suited to test the concept outlined in Scheme 1 b.

Results and Discussion

The synthesis of the biotinylated catalyst precursors [MCp*^{biotin}Cl$_2$]$_2$ (M = Ir, Rh) is described elsewhere.[12,19,28,29] The dimeric precursor was reacted in situ with a selection of commercially available bidentate ligands (Scheme 2). To identify



Scheme 1. Artificial metalloenzymes consist of an organometallic catalyst or a catalyst precursor incorporated within a protein scaffold. The optimization of their catalytic performance is achieved either by mutating the protein (*) or by varying the bidentate ligand (A–A'). a) The recognition element (◁) and the variable bidentate ligand are covalently linked. b) The recognition element and the bidentate ligand (A–A') are distinct, thus allowing for screening of commercially available ligands.

suitable coordination conditions, the chiral ligand L-ProNH$_2$ was complexed in situ with the dinuclear catalyst precursors [MCp*^{biotin}Cl$_2$]$_2$ (M = Ir, Rh) at different pH values within the buffer range of 3-(*N*-morpholino)propanesulfonic acid (MOPS) or 2-(*N*-morpholino)ethanesulfonic acid. As the best conversion for the asymmetric transfer hydrogenation of prochiral imine **1 a** was observed at pH 7.8, this value was selected for all subsequent studies.

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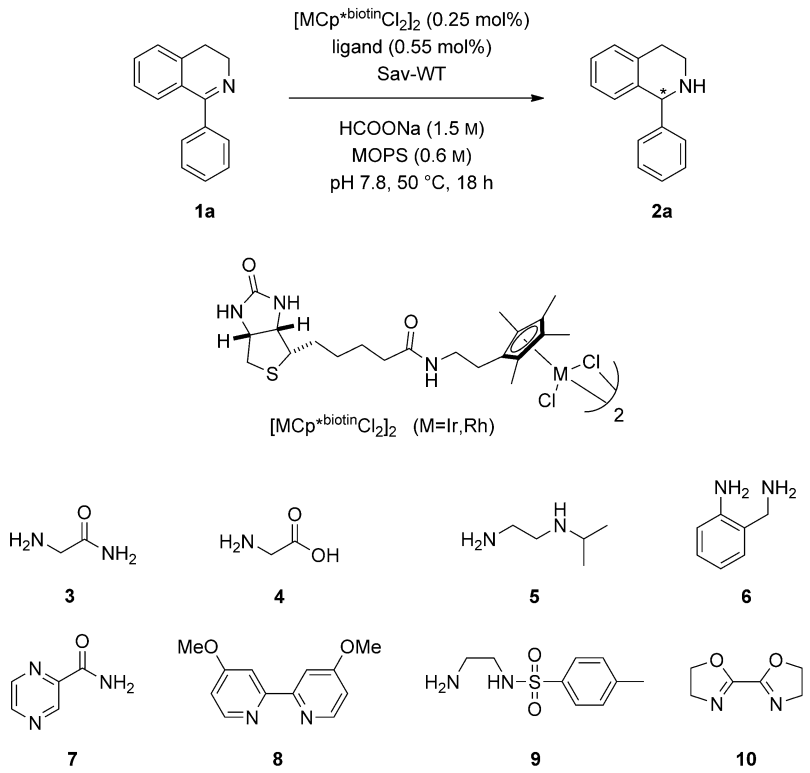
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cctc.201300825.



Scheme 2. Initial selection of bidentate ligands (**3**–**10**) for the creation of artificial imine reductases based on the biotin–streptavidin technology.

A preliminary screening was performed with eight commercially available bidentate ligands using $[MCp^{*biotin}Cl_2]_2$ (M = Ir, Rh) for the reduction of 1-phenyl-3,4-dihydroisoquinoline **1a** with formate as a hydride source. The results are presented in Table 1.

The following trends emerged from these results:

1) The dinuclear catalyst precursor $[IrCp^{*biotin}Cl_2]_2$, devoid of any additional ligands, demonstrates only low detectable artificial transfer hydrogenase (ATHase) activity both in the absence and in the presence of Sav, whereas $[RhCp^{*biotin}Cl_2]_2$ demonstrates significant activity only in the absence of Sav (Table 1, entry 1).

2) Although most ligands tested afford >60 turnovers (>30% yield) if combined with $[RhCp^{*biotin}Cl_2]_2$, only four ligands give rise to >60 turnovers with $[IrCp^{*biotin}Cl_2]_2$. Notably, the widely used amino sulfonamide ligand scaffold (ligand **9**) performs only moderately in comparison to the best ligands under the experimental conditions adopted for this screening. With high-throughput screening in mind, no effort was made to improve the performance of individual metal–ligand combinations.

3) Incorporation within Sav leads to a significant decrease in conversion in all but two metal–ligand combinations. Both glycine amide **3** and bisoxazoline **10** combined with $[IrCp^{*biotin}Cl_2]_2$ afforded more than 180 turnovers for the reduction of cyclic imine **1a**. Owing to the enantiopure environment provided by the Sav host, the corresponding amine **2a** is produced in enantioenriched form: (*S*)-**2a** in 43% *ee* with **3** and (*S*)-**2a** in 14% *ee* with **10** (Table 1, entries 2 and 9 with $[IrCp^{*biotin}Cl_2]_2$). The ATHase derived from glycine **4** performs poorly in the presence of Sav compared with glycine amide **3** (Table 1, entries 2 and 3 with $[IrCp^{*biotin}Cl_2]_2$).

After identifying the α-amino amide scaffold as a promising activating ligand[30–36] in the ATHase assembly for the reduction of imine **1a**, 28 commercially available amino amides were tested in conjunction with $[IrCp^{*biotin}Cl_2]_2$ in the presence of wild-type Sav (Sav-WT; Figure 1 and Table 2).

The following trends emerged from these results:

1) In the absence of Sav, the enantiopure biotinylated piano stool complexes demonstrate up to 29% *ee* for the reduction of imine **1a**. The distant enantiopure biotin anchor does not significantly affect the enantioselectivity either in the presence of achiral ligands (Table 1) or in the presence of mirror-image amino amides. Accordingly (in the absence of Sav), L-phenylalanine amide and D-phenylalanine amide afford the amine (*S*)-**2a** in 17% *ee* and (*R*)-**2a** in 16% *ee*, respectively (Table 2, entries 10 and 11).

2) In most of the cases, the transfer hydrogenation activities in the absence and in the presence of Sav are comparable. However, incorporation within Sav leads to a significant increase in *ee* values for several combinations (Table 2, entries 1, 2, 4, 6, 8, 12, 18, and 20) or to an inversion of the preferred product enantiomer (Table 2, entries 5, 7, 9, 11, and 17). In gen-

Table 1. Identification of the most suitable ligand for activating a biotinylated piano stool catalyst precursor for the reduction of imine **1a**.[a]

Entry	Ligand	Yield (*ee*)[d] [%]			
		No protein[b]	Sav-WT[b]	No protein[c]	Sav-WT[c]
1	–	6 (−1)	3 (38)	81 (0)	5 (−5)
2	3	**93 (0)**	**94 (43)**	60 (0)	5 (7)
3	4	8 (−3)	2 (21)	51 (0)	4 (1)
4	5	0 (0)	0 (0)	34 (0)	3 (−1)
5	6	4 (−2)	0 (0)	16 (−1)	3 (−1)
6	7	31 (0)	13 (16)	35 (−1)	3 (−1)
7	8	44 (0)	0 (0)	6 (−1)	2 (−6)
8	9	16 (−1)	6 (13)	36 (0)	3 (1)
9	10	**99 (0)**	**51 (14)**	37 (0)	4 (0)

[a] The best results are highlighted in boldface. For full experimental details, see the Supporting Information; [b] Metal catalyst precursor = $[IrCp^{*biotin}Cl_2]_2$; [c] Metal catalyst precursor = $[RhCp^{*biotin}Cl_2]_2$; [d] A positive *ee* value refers to the *S* enantiomer; a negative value refers to the *R* enantiomer of amine **2a**.

eral, incorporation in Sav-WT shifts the stereoselectivity in favor of the *S* enantiomer.

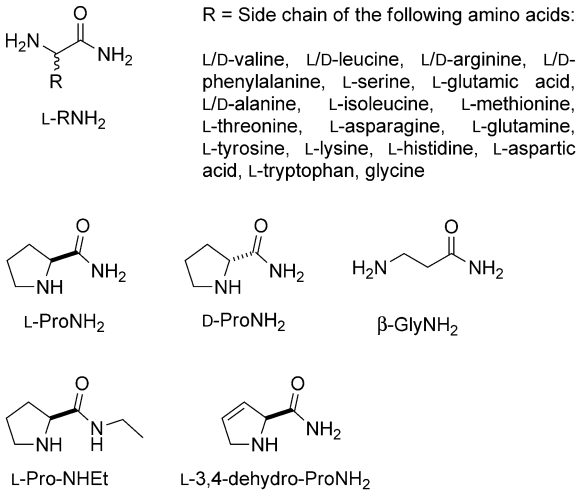


Figure 1. Selection of amino amide ligands screened for the enantioselective reduction of imine **1a**.

Table 2. Selected results obtained for the screening of amino amide ligands for the reduction of imine **1a** with $[IrCp^{*biotin}Cl_2]_2$ (with or without Sav-WT) as a complex precursor.[a]

Entry	Ligand	Yield (*ee*)[b] [%]	
		No protein	Sav-WT
1	$GlyNH_2$	93 (0)	94 (43)
2	L-$ProNH_2$	99 (17)	**47 (67)**
3	D-$ProNH_2$	**99 (−29)**	**28 (−8)**
4	L-$ValNH_2$	**99 (20)**	**70 (63)**
5	D-$ValNH_2$	99 (−12)	66 (45)
6	L-$LeuNH_2$	97 (9)	**96 (63)**
7	D-$LeuNH_2$	99 (−13)	96 (51)
8	L-$ArgNH_2$	98 (7)	71 (52)
9	D-$ArgNH_2$	71 (−12)	**85 (61)**
10	L-$PheNH_2$	97 (17)	98 (33)
11	D-$PheNH_2$	**99 (−16)**	96 (13)
12	L-$SerNH_2$	99 (1)	98 (52)
13	L-$GluNH_2$	99 (11)	94 (30)
14	L-Pro-NHethyl	83 (13)	5 (44)
15	L-3,4-Dehydro-$ProNH_2$	**94 (24)**	17 (58)
16	L-$AlaNH_2$	57 (6)	87 (34)
17	D-$AlaNH_2$	56 (−6)	88 (36)
18	L-$IleNH_2$	98 (5)	**89 (65)**
19	L-$MetNH_2$	0 (0)	0 (0)
20	L-$ThrNH_2$	86 (6)	**96 (63)**
21	L-$AsnNH_2$	85 (12)	91 (56)
22	L-$GlnNH_2$	45 (12)	86 (39)
23	L-$TyrNH_2$	70 (16)	90 (36)
24	L-$LysNH_2$	99 (1)	89 (26)
25	L-$HisNH_2$	0 (0)	0 (0)
26	L-$AspNH_2$	66 (13)	94 (43)
27	L-$TrpNH_2$	65 (20)	95 (37)
28	β-$GlyNH_2$	7 (2)	3 (28)

[a] The best results are highlighted in boldface. Reaction conditions: 35 mM substrate, 0.25 mol% $[IrCp^{*biotin}Cl_2]_2$, 0.55 mol% amino amide, 7.4 mg mL^{-1} Sav-WT, 0.56 M MOPS, 1.4 M formate, pH 7.8, incubation for 18 h at 50 °C. All listed results are the average of two runs; for full details, see the Supporting Information; [b] A positive *ee* value refers to the *S* enantiomer; a negative value refers to the *R* enantiomer of amine **2a**.

3) Upon incorporation within Sav, >60% *ee* of (*S*)-**2a** and ≥170 turnovers are obtained with L-$LeuNH_2$, D-$ArgNH_2$, L-$IleNH_2$, or L-$ThrNH_2$ (Table 2, entries 6, 9, 18, and 20). The α-amino amides bearing a softer donor side chain (e.g., L-methionine amide and L-histidine amide; Table 2, entries 19 and 25) completely inhibit the catalysis. We hypothesize that the binding mode of these potentially tridentate ligands may differ from that of the other amino amide ligands tested.[34]

4) The absolute configuration of the amino amide has a modest effect on the enantioselectivity of the corresponding artificial metalloenzyme. In the isolated cases tested, Δ*ee* values for the matched versus mismatched combinations differ by ≤20% in the protein (Table 2, entries 4 and 5, entries 6 and 7, entries 8 and 9, entries 10 and 11, entries 16 and 17), except in proline (Δ*ee* = 75%; entries 2 and 3).

After identifying promising amino amide ligands, we proceeded to the genetic optimization of the ATHase activity. For this purpose, six amino amide ligands (L-$ProNH_2$, L-$ValNH_2$, L-$LeuNH_2$, L-$IleNH_2$, L-$ThrNH_2$, and $GlyNH_2$) were selected and screened in the presence of 21 Sav isoforms for the reduction of cyclic imine **1a**. The corresponding results are presented as a fingerprint in Figure 2.

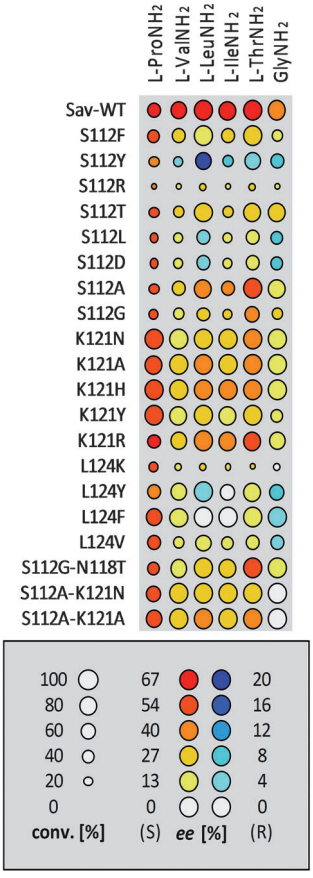


Figure 2. Results of the chemogenetic optimization of ATHases for the asymmetric reduction of imine **1a**, which are presented in the bubble-chart format. The size of the bubbles is proportional to the conversion (between 4 and 99%), and the color codes the enantiomeric excess. See Table 2 for experimental details. The numerical values (conversion and *ee*) are listed in Table S1.

From the results presented in Figure 2, the following conclusions could be drawn:

1) The best results in terms of enantioselectivity for any ligand are obtained with Sav-WT.

2) Mutating single residues at position S112 or K121, or mutating both residues simultaneously, leads to a decrease in enantioselectivity for all ligands tested. The S112Y mutant led, in combination with L-LeuNH$_2$, to an inversion of enantioselectivity compared to Sav-WT (63% *ee* of (*S*)-**2a** in Sav-WT and 20% *ee* of (*R*)-**2a** in the presence of S112Y).

3) All mutants at position K121 typically lead to high conversions with all amino amide ligands tested. In the presence of either L-ProNH$_2$ or L-ValNH$_2$, significantly improved conversions compared to Sav-WT were observed with K121N, K121A, K121H, and K121Y mutants.

4) In the presence of the L124K, L124Y, or L124F mutant, a marked decrease in enantioselectivity compared with that in the presence of Sav-WT is observed for all ligands except L-ProNH$_2$. Conversions were generally good to excellent with the L124Y or L124F mutant.

5) Good to excellent conversions were observed for all double mutant–ligand combinations, which were accompanied by a decrease in enantioselectivity (except L-ProNH$_2$).

Finally, the substrate scope of the artificial imine reductases was evaluated (Figure 3). For this purpose, six prochiral cyclic

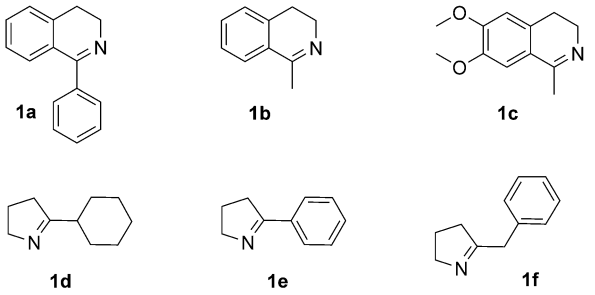


Figure 3. Selection of substrates for the asymmetric transfer hydrogenation of cyclic imines.

imines were tested in the presence of artificial metalloenzymes [IrCp*^{biotin}(amino amide)Cl]⊂Sav-WT (amino amide = L-ProNH$_2$, L-ValNH$_2$, L-LeuNH$_2$, L-IleNH$_2$, L-ThrNH$_2$, GlyNH$_2$). The results of this screening are summarized in Table 3.

Table 3. Screening of different substrates for the [IrCp*^{biotin}(amino amide)Cl]⊂Sav-WT-mediated transfer hydrogenation.

Entry	Ligand	Yield (*ee*)[a] [%]					
		1a	**1b**	**1c**	**1d**	**1e**	**1f**
1	L-ProNH$_2$	**47 (67)**	99 (5)	100 (6)	**69 (−32)**	60 (−11)	100 (18)
2	L-ValNH$_2$	**70 (63)**	100 (17)	100 (17)	84 (−44)	80 (−22)	86 (16)
3	L-LeuNH$_2$	**96 (63)**	100 (3)	100 (18)	**95 (−45)**	96 (−31)	100 (20)
4	L-IleNH$_2$	**89 (65)**	100 (20)	100 (43)	**83 (−32)**	79 (−22)	10 (18)
5	L-ThrNH$_2$	**96 (63)**	100 (25)	100 (41)	**98 (−57)**	**95 (−35)**	91 (20)
6	GlyNH$_2$	**94 (43)**	100 (4)	100 (18)	**96 (−46)**	94 (−9)	79 (2)

[a] Positive and negative *ee* values correspond to *S* and *R* enantiomers, respectively. The absolute configuration of the amines **2d–f** was not determined. The best results are highlighted in boldface.

Variation of the substrate led to the following observations and trends:

1) Conversion of bulky substrate **1a** generally led to the highest observed enantioselectivities in favor of the *S* product.
2) Reducing the size of the substituent at position 1 of the dihydroisoquinoline moiety from phenyl to methyl resulted in a considerable decrease in enantioselectivity.
3) Introduction of methoxy substituents at positions 6 and 7 of the dihydroisoquinoline moiety only moderately affected the selectivity.
4) With 2-substituted 1-pyrrolines, conversions were generally good to excellent.
5) The highest *ee* value for 1-pyrrolines was observed for the bulky substrate carrying a cyclohexyl substituent in combination with L-ThrNH$_2$. The *ee* values for the benzyl- and phenyl-substituted substrates **1e** and **1f**, respectively, were generally low.

Conclusions

To readily access large chemical diversity, a new artificial metalloenzyme design based on the biotin–streptavidin technology has been presented. Relying on three-legged piano stool complexes and tethering the biotin anchor on the Cp* moiety allowed us to screen various bidentate ligands for the asymmetric reduction of cyclic imines. An initial screening led to the identification of amino amides as versatile bidentate ligands in conjunction with the {IrCp*^{biotin}} moiety. Genetic diversity was introduced by site-directed mutagenesis. Both chemical diversity and genetic diversity were shown to have a significant effect on the activity and selectivity of the resulting artificial metalloenzyme.

By taking into account the versatility of the {Cp*ML$_n$} moiety in catalysis, we reasoned that the strategy disclosed herein will find wide application for the chemical optimization of artificial metalloenzymes. Current efforts are aimed at the structural and kinetic characterization of such hybrid catalysts.

Experimental Section

General method for the asymmetric transfer hydrogenation

Buffer A (100 μL, 0.6 M in MOPS in Milli-Q H$_2$O, pH 7.8) was placed in a polypropylene (PP) tube, followed by the addition of the biotinylated metal complex [MCp*^{biotin}Cl$_2$]$_2$ stock solution (3.75 μL, 5.0 mM in DMSO) and the ligand stock solution (3.75 μL, 11 mM in Milli-Q H$_2$O or DMSO, depending on the ligand). The mixture was agitated for 30 min at 30 °C and 600 rpm in a thermo mixer for precomplexation. The corresponding lyophilized Sav mutant (1.6 mg) was dissolved in buffer B (100 μL, 0.6 M in MOPS, 3.0 M in HCOONa in Milli-Q H$_2$O, pH 7.8). Then, Sav-mixture (100 μL) was added to the PP tube containing the metal complex and agitation was continued for 15 min at 30 °C and 600 rpm to ensure binding of the biotinylated complex to Sav. Finally, the substrate stock solution was added (7.5 μL, 1 M in DMSO) and the mixture was agitated at 50 °C for 18 h. Subsequently, NaOH$_{(aq)}$ (60 μL, 5 M solution) was added to the reaction mixture, followed by the addition of CH_2Cl_2

(1 mL). The phases were mixed thoroughly with a vortex mixer. The organic phase was separated through pipetting and transferred to another PP tube, which contained anhydrous Na_2SO_4. Solids were separated through centrifugation (2 min at 21 000 *g*), and the supernatant was analyzed by using HPLC or GC.

Acknowledgements

We acknowledge the financial support from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement No. FP7-PEOPLE-ITN-2008-238531. Additional funding was provided by the Swiss National Science Foundation (200020_144354) as well as the University of Basel. TRW thanks Umicore for a generous loan of $[Cp^*IrCl_2]_2$ and $[Cp^*RhCl_2]_2$ and Prof. C. R. Cantor for the Sav gene.

Keywords: asymmetric catalysis · biotin–streptavidin technology · imine reduction · metalloenzymes · transfer hydrogenation

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Received: September 27, 2013
Published online on January 16, 2014