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Josiphos Ligands with an Imidazolium Tag and their Application for the Enantioselective Hydrogenation in Ionic Liquids

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Abstract: Josiphos ligands bearing an imidazolium moiety show high efficiency and reusability for the rhodium-catalyzed enantioselective hydrogenation of methyl acetamidoacrylate (MAA) and dimethyl itaconate (DMI) in biphasic co-solvent/ionic liquid combinations.

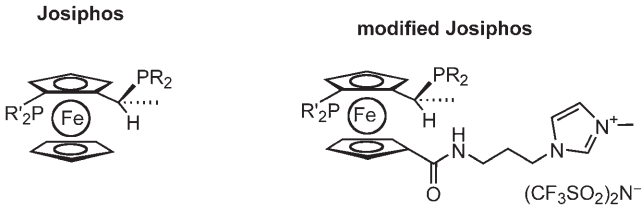
Keywords: asymmetric hydrogenation; homogeneous catalysis; imidazolium tag; ionic liquids; ligand design; rhodium catalysis

Introduction

For several reasons, ionic liquids (ILs) are interesting new media for homogeneous catalysis.[1] Their chemical properties can be varied widely and can be adapted to a specific catalytic reaction. The often low solubility for many apolar solvents, substrates and products allows reactions in a two-phase mode and finally, their high affinity to ionic catalytic species facilitates efficient catalyst separation and product isolation. On the other hand, replacing classical solvents by ILs frequently results in unpredictable (often negative) effects on the catalyst performance and catalyst separation is not always complete due to leaching of the metal and/or complex into the organic co-solvent phase.[2] The attachment of so-called ionic tags was recently demonstrated to be an efficient way to minimize catalyst leaching from the IL, at the same time improving catalyst stability and reusability in various catalytic reactions.[3] To continue our efforts on the separation and re-use of homogeneous catalysts in biphasic co-solvent/IL systems, we decided to utilize this ionic tag concept and modify Josiphos ligands for the Rh-catalyzed enantioselective hydrogenation of model olefins. In this communication we describe a modular synthesis concept to prepare modified Josiphos ligands and demonstrate that the resulting catalysts closely parallel the performance of the unmodified system but can be separated and recycled more efficiently.

Results and Discussion

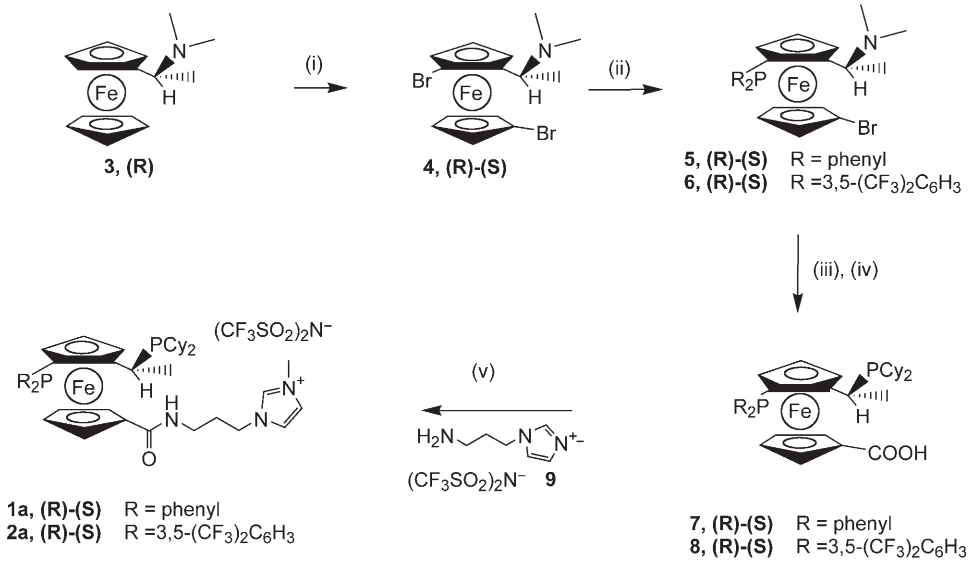
Two Josiphos ligands (see Figure 1) were chosen for the following reasons. First, they are highly modular ligands where the steric and electronic properties can be varied broadly rendering the ligands effective for a variety of enantioselective transformations.[4] Secondly, their technical feasibility has been demonstrated in a number of large-scale applications and various members of this ligand family have been prepared on a multi-kg scale.[5] Finally, effective methods for their immobilization on polymers, dendrimers, inorganic materials as well as in water without significantly affecting their catalytic performance have been developed.[6] This last point is especially important in the context of process development because the results of the primary catalyst screening (which is carried out with the native ligands) are likely to be valid for the modified catalysts as well. Since Rh-Josiphos catalysts gave good enantioselectivities for the hydrogenation of enamides in imidazole-based ILs,[2] we decided to modify selected ligands with an imidazolium tag[3].



1, (R)-(S) R = phenyl, R' = Cy
2, (R)-(S) R = 3,5-$(CF_3)_2C_6H_3$, R' = Cy
1a, (R)-(S) R = phenyl, R' = Cy
2a, (R)-(S) R = 3,5-$(CF_3)_2C_6H_3$, R' = Cy

Cy = cyclohexyl

Figure 1. Structure of the original and the modified Josiphos ligands

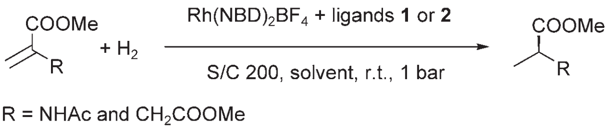


Scheme 1. Synthesis of **1a** and **2a**. (i) (a) 2.2 equivs. *n*-BuLi, TMEDA in diethyl ether, −78 °C, 3 h, then room temperature overnight; (b) 2.1 equivs. dibromotetrafluoroethane, −60 °C, 5 h, then HCl, (**4**, 84 %). (ii) (a) 1.2 equivs. *n*-BuLi in *n*-hexane −40 °C; (b) 1.3 equivs. Ar_2PCl, −78 °C, 2 h, then room temperature overnight, (**5**, 62 %, **6**, 70 %). (iii) 1.2 equivs. Cy_2PH in HOAc, 100 °C, 4 h. (iv) (a) 1.1 equivs. *n*-BuLi in diethyl ether, −40 °C; (b) CO_2, (**7**, 56 % from **5**; **8**, 51 % from **6**). (v) 2 equivs. **9** in THF, DCC, room temperature overnight, (**1a**, 72 %, **2a**, 75 %).

In the modified Josiphos, the imidazolium moiety is attached to the lower cyclopentadiene ring *via* a robust amide bond and a propyl chain in order to avoid interaction between the metal center and the positively charged tag as much as possible. The synthesis route and reaction conditions for two modified ligands **1a** and **2a** are outlined in Scheme 1. The same method is feasible for the preparation of a variety of modified Josiphos ligands with different steric and electronic properties.

Starting from commercial Ugi amine **3**, dibromide **4** was synthesized *via* selective dilithiation and subsequent bromination with dibromotetrafluoroethane in an isolated yield of 84 %. The bromide at the substituted cyclopentadiene ring reacted selectively with *n*-BuLi followed by reaction with Ar_2PCl to give the monophosphines **5** and **6**, respectively. The second P substituent was introduced by reaction with Cy_2PH in AcOH and **7** and **8** were prepared by classical Br/Li exchange and reaction with CO_2. DCC-promoted amidation with **9**, afforded **1a** and **2a** as yellow solids. Overall, non-optimized yields over 5 steps were 21 % and 23 %, respectively.

The two Josiphos ligands **1** and **2** were chosen because their enantioselectivity in the reduction of the model substrates methyl acetamidoacrylate (MAA) and dimethyl itaconate (DMI) (see Scheme 2) differs significantly in classical solvents such as toluene, isopropyl alcohol or *tert*-butyl methyl ether (TMBE). While **1** gives high *ee*s only for DMI (see Table 1, entries 1–3 and 23, 24), **2** is highly selective for both substrates (entries 11–13 and 30). We wanted to know if this difference would also be observed for the modified ligands especially under biphasic conditions.



Scheme 2. Hydrogenation of model substrates.

The results obtained with the modified ligands presented in Table 1 were very satisfying. The performance of the modified ligands closely parallels that of native ligands both in classical organic solvents as well as under biphasic conditions. Solubility permitting (**1a** is not soluble in classical solvents), the enantioselectivities of the ligands with the ionic tag are the same as those without, demonstrating that the imidazolinium moiety does not interfere with the Rh center. The catalyst activities in the biphasic systems vary but in general are comparable to those in classical solvents (note the different reaction times for MAA). Nevertheless, compared to both mono- and biphasic systems, conversions were often lower for ligands **1** and **1a** and for the combination *i*-PrOH/[bmim]BF_4.

An important motivation to use IL/co-solvent concept is improved separation and re-use of the catalyst. A first qualitative assessment of the degree of catalyst leaching is the coloring of the co-solvent phase.[2] As expected, the introduction of an imidazolium group in the Josiphos ligand improved the affinity of the Rh

Table 1. Enantioselective hydrogenation of MAA and DMI in various/organic co-solvent/IL combinations and in conventional apolar organic solvents.[a]

Entry	Substrate	Ligand	Solvent	Conversion [%]	*ee* [%]
1	MAA	**1**	TBME[b]	100	55
2	MAA	**1**	Tol[b]	100	53
3	MAA	**1**	*i*-PrOH[b]	100	57
4	MAA	**1a**	*i*-PrOH[b]	100	58
5	MAA	**1**	TBME/[bmim]BF_4	38	25
6	MAA	**1**	Tol/[bmim]BF_4	17	26
7	MAA	**1**	*i*-PrOH/[bmim]BF_4	83	42
8	MAA	**1a**	TBME/[bmim]BF_4	42	32
9	MAA	**1a**	Tol/[bmim]BF_4	14	30
10	MAA	**1a**	*i*PrOH/[bmim]BF_4	76	45
11	MAA	**2**	TBME[b]	100	99
12	MAA	**2**	Tol[b]	100	98
13	MAA	**2**	*i*-PrOH[b]	100	97
14	MAA	**2a**	TBME[b]	100	99
15	MAA	**2a**	Tol[b]	100	99
16	MAA	**2a**	*i*-PrOH[b]	100	97
17	MAA	**2**	TBME/[bmim]BF_4	100	99
18	MAA	**2**	Tol/[bmim]BF_4	100	97
19	MAA	**2**	*i*-PrOH/[bmim]BF_4	60	94
20	MAA	**2a**	TBME/[bmim]BF_4	100	99
21	MAA	**2a**	Tol/[bmim]BF_4	100	99
22	MAA	**2a**	*i*-PrOH/[bmim]BF_4	47	92
23	DMI	**1**	TBME	100	99
24	DMI	**1**	*i*-PrOH	100	99
25	DMI	**1a**	*i*-PrOH	100	99
26	DMI	**1**	TBME/[bmim]BF_4	100	99
27	DMI	**1**	*i*-PrOH/[bmim]BF_4	100	97
28	DMI	**1a**	TBME/[bmim]BF_4	100	99
29	DMI	**1a**	*i*-PrOH/[bmim]BF_4	100	98
30	DMI	**2**	*i*-PrOH	100	99
31	DMI	**2a**	*i*-PrOH	100	99
32	DMI	**2**	*i*-PrOH/[bmim]BF_4	92	97
33	DMI	**2a**	*i*-PrOH/[bmim]BF_4	83	99

[a] *Reaction conditions:* 0.004 mmol $[Rh(NBD)_2]BF_4$, Rh/L = 1/1.1, 0.8 mmol substrate (s/c 200), 5 mL solvent, solvent/IL *ca.* 1/1, room temperature, 1 bar, reaction time 10 min.

[b] Reaction time 20 min.

complex for the IL significantly: Colorless co-solvent phases for the cases of the modified Josiphos ligands indicated very low catalyst leaching in the combination of TBME/[bmim]BF_4 and toluene/[bmim]BF_4, while in most cases strongly to very strongly colored co-solvent phases were obtained for the unmodified Josiphos. This was especially so for ligand **2**, where ICP-AES analysis of the TBME phase after hydrogenation of MAA (entry 17) indicated that 19% of Rh was actually in the organic phase. Obviously, the 4-trifluoromethyl groups in ligand **2** considerably decrease the polarity of the Rh complex and its affinity to the polar [bmim]BF_4 phase. However even this very lipophilic ligand can be immobilized efficiently in IL by the introduction of an imidazolium group. After reaction, a nearly colorless TBME phase was obtained (entry 20) and ICP-AES analysis showed 3 ppm Rh, corresponding to 0.85% leaching. For the *i*-PrOH/[bmim]BF_4 combination, only the **1a** gave a colorless organic phase and there was significant IL leaching, as detected by ^{1}H NMR measurements. This means that, in contrast to TMBE and toluene, isopropyl alcohol is clearly not suitable a suitable component for a biphasic system.

Finally, we turned our attention to catalyst recycling and reuse of the modified Josiphos ligands. These catalyst recycling experiments were carried out with the TBME/[bmim]BF_4 combination, which showed minimal IL leaching and where efficient product isolation by simple decantation was possible. Experiments were carried out with both model substrates under the conditions described in Table 1 both with the unmodified ligands **1** and **2** and the two modified Josiphos **1a** and **2a**. The turnover frequencies (TOF) for each cycle

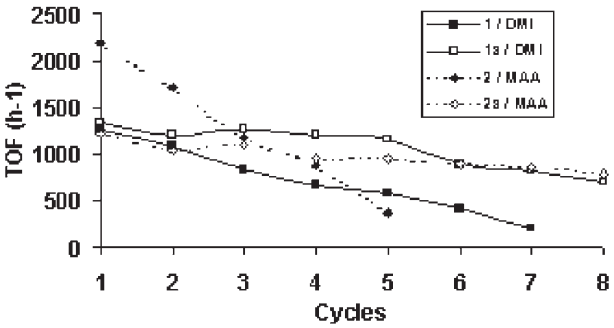


Figure 2. TOF in catalyst re-use study in TBME/[bmim]BF_4. Reaction conditions, see Table 1, TOF = 2 × conversion/reaction time.

are plotted in Figure 2, the *ee*s remained constant throughout the investigated cycles.

In the experiments with MAA and ligand **2**, the first reaction was very fast (full conversion after *ca.* 5 min) but then the TOFs dropped rapidly. In contrast, the reaction with the modified Josiphos **2a** was slower but TOFs decreased only about 15 % for the 8th cycle. A similar trend was observed for the reactions with DMI, except that the initial activities were the same for both the unmodified **1** and the modified ligand **1a**. ICP-AES analysis of the TBME phase after the first cycle indicated 12 ppm Rh, corresponding to 2.3 % catalyst leaching for ligand **1** and 0.4 ppm (0.1 % catalyst leaching) for **1a**. While this confirmed that the attachment of the imidazolium moiety reduces catalyst leaching, the 2.3 % catalyst leaching of the Rh-**1** catalyst cannot be the only reason for its poor catalyst re-usability. A possible explanation could be that at least part of the catalyst deactivation occurred during the recycling of the catalyst due to some contamination with oxygen. Since the oxygen solubility in TBME is much higher than in [bmim]BF_4, Rh-**1a** which has a high affinity to IL might be better protected against reaction with oxygen. Another reason might be that the doubly charged complex is generally more stable in an ionic liquid.

Conclusions

We have demonstrated that the concept of an ionic tag is feasible for the modular Josiphos ligand family. The introduction of an imidazolium moiety at the lower Cp ring of the ferrocene backbone affords catalysts with sufficient affinity to [bmim]BF_4, the IL most frequently used. While the enantioselectivity of modified ligands closely parallels the behavior of the unmodified ligands both in classical organic solvents and under biphasic conditions, the modified ligands show much better reusability in the TBME/[bmim]BF_4 combination. Further work to demonstrate the generality of the imidazolium ionic tag strategy for other types of ligands applied in ILs is currently in progress.

Experimental Section

Chemicals

All solvents and reagents were purchased from Aldrich, Fluka, Merck and Lancaster and used without further purification. The ionic liquids [bmim]BF_4 was purchased from Solvent Innovation and purified as described in literature[8] before use. 3-(3-Aminopropyl)-1-methylimidazolium bis(trifluoromethylsulfonyl)amide (**9**) was obtained from Novartis and directly used without further purification. The ligands **1** and **2** are commercially available from Solvias AG. All manipulations were performed under argon and with degassed solvents.

Chromatography

Analytical thin layer chromatography (TLC) was performed using layers of silica gel (Merck, $60F_{254}$). Column chromatography was carried out using silica gel (Merck Silica gel 60, Fluka 60, 0.040–0.063 mm). All solvents (Synopharm) for chromatography were technical pure grade.

Analysis

NMR spectra were recorded on a Bruker B-ACS60 (300 MHz) instrument using TMS as internal standard. The chemical shifts are given in ppm and coupling constants in Hz in the indicated solvent. Some abbreviation for NMR: singlet (s), broad singlet (bs), doublet (d), triplet (t), quartet (q), quintet (quint), multiplet (m), imidazol (Im).

LC/MS data were recorded on a Agilent 1100 series for LC and Water MicromassZQ for MS.

Conversion and enantiomeric excess were determined by GC (CE instruments MFC 800, equipped with Chirasil-Val and lipodex E capillary column).

General Procedure for the Hydrogenations and for Catalyst Recycling

The hydrogenations at 1 bar were performed in a 25-mL vial equipped with a septum, a connection to an argon line, a vacuum line and an H_2 reservoir *via* a pressure valve and a magnetic stirring bar. Hydrogen consumption was calculated by the pressure drop in the reservoir and used for the calculation of TOF in the Figure 2. To a solution of the ligand (0.0034 mmol) in 2 mL IL, a solution of $[Rh(NBD)_2]BF_4$ (0.003 mmol) in dichloromethane was added. The dichloromethane was removed under reduced pressure and a solution of the substrate in TBME (total approx. 3 mL) co-solvent(s) added. Typically 2 mL IL and 2–3 mL co-solvent were used. Then the reaction mixture was set under H_2 (1 bar) and the hydrogenation started at room temperature by switching on the magnetic stirrer. Substrate concentration was 0.25 M. Care was taken that the mixing in all cases was turbulent. For catalyst recycling, the upper phase of TBME containing product was removed by a syringe and a degassed solution of substrates in TBME was added again to the ionic liquids remaining in the reaction vials.

Experimental Details for the Preparation and Characterization of Compounds 6 and 8, 1a and 2a

Synthesis of 6: The synthesis followed the published procedure[2] and the crude product was chromatographed over silica gel (hexane/EE, 10/1, 1% NEt_3) and **6** was obtained as an orange oil; yield: 69.5% (from **4**). ^{1}H NMR(300 MHz, $CDCl_3$): $\delta=1.03$ (d, 3H, CH*Me*N, $^3J_{H,H}=6.7$ Hz), 1.64 (s, 6H, N*Me*$_2$), 3.43 (m, 1H, Cp-H), 3.45 (m, 1H, Cp-H), 3.60 (m, 1H, Cp-H), 3.95 (m, 1H, Cp-H), 3.95-4.05 (overlapped m, 4H, 3Cp-H, 1C*H*MeN), 7.65 (s, 1H, Ph-H), 7.70–7.75 (bs. 2H, Ph-H), 7.78 (s, 1H, Ph-H), 7.95 (s, 1H, Ph-H), 8.05 (s, 1H, Ph-H); ^{31}P{^{1}H}-NMR (300 MHz, $CDCl_3$): $\delta=-21.6$; LC/MS (ESI): *m/z* = 795 (M + H$^+$), 751 (M–NMe_2 + H$^+$), 495.

Synthesis of 8: The synthesis followed the procedure described in the literature[2] with slight modification. Chromatography over silica gel eluting with EE/*n*-hexane (5:1) afforded **8** as orange crystals; overall yield: 51% (from **6**). ^{1}H NMR(300 MHz, $CDCl_3$): $\delta=1.02$–1.85 (overlapped m, 25H, Cy-H, PCy_2CH*Me*), 3.30–3.40 (dq, 1H, PCy_2C*H*Me, $^3J_{H,H}=2.5$ Hz), 3.45 (m, 1H, Cp-H), 3.60 (m, 1H, Cp-H), 3.80 (m, 2H, Cp-H), 4.20 (m, 1H, Cp-H), 4.40 (m, 1H, Cp-H), 4.45 (m, 1H, Cp-H), 7.65 (s, 1H, Ph-H), 7.70 (s. 1H, Ph-H), 7.80 (s, 1H, Ph-H), 7.82 (s, 1H, Ph-H), 8.10 (s, 1H, Ph-H), 8.15 (s, 1H, Ph-H); ^{31}P{^{1}H}-NMR (300 MHz, $CDCl_3$): $\delta=-24.5$ (d, PAr_2, $^4J_{P,P}=35.5$ Hz), 19.0 (d, PCy_2, $^4J_{P,P}=35.5$ Hz); LC/MS (ESI): *m/z* = 911 (M + H$^+$).

Synthesis of ligand 1: A solution of DCC (128 mg, 0.62 mmol) in THF (2 mL) was added slowly to the solution of **7** (200 mg, 0.31 mmol) and 3-(3-aminopropyl)-1-methylimidazolium bis(trifluoromethylsulfonyl)amide (**9**; 134 mg, 0.37 mmol) in THF (8 mL) at 0 °C under argon atmosphere. The reaction mixture was warmed to room temperature and stirred overnight (no starting material was detected on TLC). After removal of organic solvents under vacuum (bath temperature: 40 °C), the residual solids were re-dissolved in 10 mL chloroform. The white solids were filtered and organic solvent was removed. The rest was chromatographed over silica gel eluting with dichloromethane/methanol (10:1). The desired product was isolated as an orange solid; yield: 200.2 mg (0.19 mmol, 72%). ^{1}H NMR (300 MHz, MeOH + 0.5% Et_3N): $\delta=1.20$–1.80 (overlapped m, 25H, Cy-H, PCy_2CH*Me*), 2.10 (q, 2H, $OCNHCH_2CH_2CH_2$, $^3J_{H,H}=5.7$ Hz), 3.25 (overlapped m, 3H, PCy_2C*H*Me, $OCNHCH_2CH_2CH_2$), 3.70 (m, 1H, Cp-H), 3.90 (s, 3H, Im-*Me*), 4.15 (m, 1H, Cp-H), 4.20–4.25 (overlapped m, 4H, Cp-H, $OCNHCH_2CH_2CH_2$), 4.27 (m, 1H, Cp-H), 4.40 (m, 1H, Cp-H), 4.70 (m, 1H, Cp-H), 7.15–7.75 (5m, 12H, Ph-H, Im-H); ^{31}P{^{1}H}-NMR (300 MHz, MeOD + 0.5% Et_3N): $\delta=-26.4$ (d, PAr_2, $^4J_{P,P}=35.2$ Hz), 16.5 (d, PCy_2, $^4J_{P,P}=35.2$ Hz); LC/MS (ESI): *m/z* = 761 (M$^+$), 381 [(M$^+$ + H$^+$)/2], 282 [(M$^+$–PCy_2 + H$^+$)/2].

Synthesis of ligand 2a: The synthesis was performed as described for ligand **1a**. Chromatography over silica gel eluting with dichloromethane/methanol (15:1) and followed removal of organic solvents afforded ligand **2a** as an orange solid; yield: 75%. ^{1}H NMR (300 MHz, C_6D_6): $\delta=1.20$–1.85 (overlapped m, 25H, Cy-H, PCy_2CH*Me*, OCNHC*H*$_2$), 2.05 (overlapped m, 2H, $OCNHCH_2CH_2CH_2$, 3.05 (s, 3H, Im-*Me*), 3.30 (m, 1H, PCy_2C*H*Me), 3.40 (m, 2H, $OCNHCH_2CH_2CH_2$), 3.60 (m, 3H, Cp-H, $OCNHCH_2CH_2CH_2$), 3.75 (m, 1H, Cp-H), 3.95–4.00 (m, 2H, Cp-H), 4.40 (m, 1H, Cp-H), 4.55 (m, 1H, Cp-H), 4.60 (m, 1H, Cp-H), 4.95 (m, 1H, Cp-H), 7.15–7.75 (5m, 8H, Ph-H, Im-H); ^{31}P{^{1}H}-NMR (300 MHz, C_6D_6): $\delta=-24.2$ (d, PAr_2, $^4J_{P,P}=35.2$ Hz), 18.8 (d, PCy_2, $^4J_{P,P}=35.2$ Hz); LC/MS (ESI): *m/z* = 517 [(M$^+$ + H$^+$)/2], 418 [(M$^+$–PCy_2 + H$^+$)/2]; ^{19}F{^{1}H}-NMR (300 MHz, C_6D_6): $\delta=-63.0$ (s), –63.01(s), –79.1(s).

Acknowledgements

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