ORGANOMETALLICS

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pubs.acs.org/Organometallics

How Accurate is DFT for Iridium-Mediated Chemistry?

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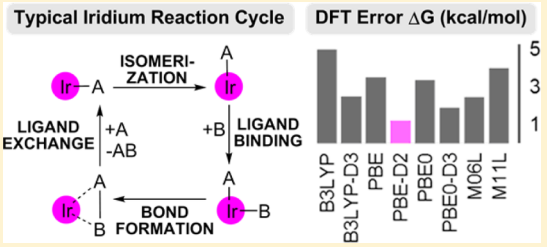
Supporting Information

ABSTRACT: Iridium chemistry is versatile and widespread, with superior performance for reaction types such as enantioselective hydrogenation and C−H activation. In order to gain insight into the mechanistic details of such systems, density functional theory (DFT) studies are often employed. But how accurate is DFT for modeling iridium-mediated transformations in solution? We have evaluated how well DFT reproduces the energies and reactivities of 11 iridium-mediated transformations, which were carefully chosen to correspond to elementary steps typically encountered in iridium-catalyzed chemistry (bond formation, isomerization, ligand substitution, and ligand association). Five DFT functionals, B3LYP, PBE, PBE0, M06L, and M11L, were evaluated as-is or in combination with an empirical dispersion correction (D2, D3, or D3BJ), leading to 13 combinations. Different solvent models (IEFPCM and SMD) were evaluated, alongside various correction terms such as big basis set effects, counterpoise corrections, frequency scaling, and different entropy modifications. PBE-D type functionals are clearly superior, with PBE-D2,IEFPCM providing average absolute errors for uncorrected Gibbs free energies of 0.9 kcal/mol for the nine reactions with a constant number of moles (1.2 kcal/mol for all 11 reactions). This provides a straightforward and accurate computational protocol for computing free energies of iridium-mediated transformations in solution. However, because the good results may originate from favorable error cancellations of larger and oppositely signed enthalpy and entropy errors, this protocol is recommended for free energies only.



INTRODUCTION

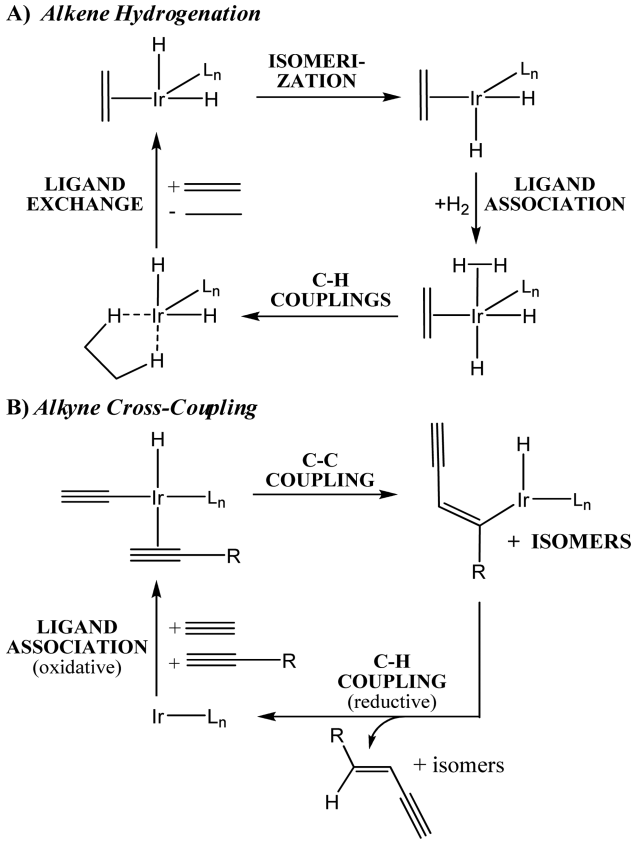
Iridium is widely employed in homogeneous catalysis, for example, for hydrogenation and dehydrogenation reactions, C−H functionalizations, and allylic substitutions.[1] The superior selectivity of iridium in asymmetric hydrogenation of unfunctionalized substrates has also proven useful for industrial applications.[2] The mechanistic steps and the associated energetics of iridium-catalyzed reactions are of great interest because such detailed insights can be employed to rationally improvement systems.[3] Mechanistic studies of transition metal-mediated transformations often involve computational modeling, mainly employing density functional theory (DFT).[4−7] With the computational power available today, DFT allows for modeling of full catalysts and substrates, without the need for molecular truncations, which might alter the steric and electronic properties of a given system. But how accurate is DFT for modeling organometallic reactions? Several benchmarks on transition metal complexes and organometallic systems have been reported,[8−14] which provide general insights into the performance of DFT. Although promising results have been reported, e.g., for relative bond energies and trends,[15] standard DFT in some cases fails spectacularly. For example, an underestimation of absolute metal−ligand bond strengths of up to ∼40 kcal/mol is seen with one of the favorite functionals in the literature, B3LYP.[11,12] A part of this error can be recovered if empirical dispersion corrections are included,[11] such as those reported by Grimme and coworkers (D2,[16] D3,[17] or D3BJ[18]), leading to the so-called DFT-D methods. A different approach to including dispersion corrections in DFT are the Minnesota functionals, which are parametrized to reproduce dispersion effects.[8] Of these, M06L is reported to provide accurate thermodynamics for a variety of organometallic reactions.[14]

For iridium systems, a small number of DFT benchmarks have been reported in the literature. These included reproduction of a single ligand exchange energy,[19] the enantiomeric excess with a particular iridium catalyst,[20] or Ir−H bond enthalpies for a set of complexes.[21] All studies evaluating the importance of dispersion corrections concluded that these improve results significantly.[19,20] However, benchmark studies focusing on a single property do not provide insights into the performance of DFT for predicting the energetics of a full reaction cycle. An iridium-catalyzed transformation will typically consist of several steps with very different chemical nature. For example, an Ir-mediated alkene hydrogenation might involve formation of different isomers of an Ir−alkene complex, followed by H_2 association, C−H bond formation steps, and a product−substrate ligand exchange (Scheme 1a).[22−24] Equally, a proposed mechanism for alkyne cross-coupling might consist of substrate association, C−C coupling involving formation of different isomers, and C−H coupling (Scheme 1b).[25] In order to be able to make reliable conclusions, a chosen computational protocol should adequately describe the energetics of all steps in a reaction cycle. This is

Received: May 11, 2016
Published: September 27, 2016

DOI: 10.1021/acs.organomet.6b00377
Organometallics 2016, 35, 3795−3807

Scheme 1. Elementary Steps in Ir-Catalyzed Reactions[a]

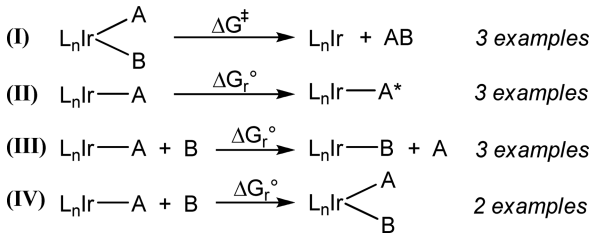


[a]Proposed mechanisms: (A) Ir-catalyzed alkene hydrogenation.[22] (B) Ir-catalyzed alkyne cross-coupling[25] (alkenes and alkynes drawn simplified, L_n = other ligands on iridium).

difficult to benchmark because experimental energies for all species in a given reaction cycle normally are not available. However, an alternative approach is to benchmark different single-step iridium-mediated transformations, whose chemical nature corresponds to the elementary steps in iridium-catalyzed reactions.

Here we evaluate the accuracy of DFT for reproducing the activation or reaction free energies of 11 iridium-mediated transformations in solution (Scheme 2). The studied reactions

Scheme 2. Free Energies Included in This Benchmark[a]



[a](I) Barriers for C−H/C-C coupling,[26−28] (II) energies for isomerization of Ir−A to Ir−A*,[24,29,30] (III) ligand exchange energies,[30−32] and (IV) ligand association energies,[29,33] (L_n = other ligands).

were compiled from the literature and correspond to the elementary steps introduced in Scheme 1: three C−H or C−C couplings,[26−28] three isomerization reactions,[24,29,30] three ligand exchanges,[30−32] and two ligand association reactions.[29,33] Five DFT functionals are evaluated (B3LYP, PBE, PBE0, M06L, and M11L), as is or in combination with a Grimme empirical dispersion correction, leading to 13 combinations: B3LYP, B3LYP-D2, B3LYP-D3, B3LYP-D3BJ, PBE, PBE-D2, PBE-D3, PBE-D3BJ, PBE0, PBE0-D3, M06L, M06L-D3, and M11L. Several of these have been reported to provide good results for organometallic systems, including M06L[9,13,14] PBE0 and PBE0-D3,[34,35] and B3LYP-D2 and B3LYP-D3.[12,22] Two different solvent models are considered, IEFPCM and SMD. We further give a comprehensive overview of additional correction terms that can be included in computational studies and evaluate the effect of several of these, including standard state conversions, counterpoise corrections, big basis set effects, scaling of frequencies, and different entropy modifications. The purpose of this study is to evaluate the accuracy of currently employed DFT functionals and to establish a reliable but straightforward computational protocol for studying iridium-mediated transformations in solution.

COMPUTATIONAL DETAILS

Molecular Models. Full experimental complexes were used, without truncations. The conformational analysis included minimum 10 conformers per system and was repeated for different levels of theory, as preferred conformations were not identical for different functionals. No symmetry constraints were employed, unless explicitly stated.

Computations. All calculations were performed with Gaussian 09, Revision D01.[36] Geometry optimizations and energy evaluations were performed with B3LYP,[37] PBE,[38] PBE0,[38,39] M06L,[40] and M11L,[41] as-is or in combination with D2,[16] D3,[17] or D3BJ,[18] leading to 13 combinations: B3LYP, B3LYP-D2, B3LYP-D3, B3LYP-D3BJ, PBE, PBE-D2, PBE-D3, PBE-D3BJ, PBE0, PBE0-D3, M06L, M06L-D3, and M11L. Two basis sets were used: BS1 corresponds to 6-311G(d,p) on all nonmetallic atoms and LANL2DZ with included ECP[44] augmented with one *f*-polarization function (0.938)[45] on Ir. BS2 corresponds to 6-311+G(2d,2p) on all nonmetallic atoms and LANL2TZ(f) with included ECP on Ir (obtained from bse.pnl.gov/bse/portal).[44−46] Sample inputs are given in the Supporting Information.

Solvent effects were included in geometry optimizations and energy evaluations, using either IEFPCM[47] (abbreviated PCM) or SMD.[48] IEFPCM computes only electrostatic contributions by default. Although nonelectrostatic terms (dispersion, repulsion, and cost of cavity creation) can be large, they are often assumed to cancel out.[49] SMD corresponds to IEFPCM with SMD radii and nonelectrostatic terms included. For each reaction, the experimental solvent was used, except for **A**, **B**, and **K**, where $CHCl_2F$ had to be approximated as $CHCl_3$. Default g09 solvent parameters were employed, with dielectric constants (ε) corresponding to 298 K, except for **A**, **B**, **F**, and **K**. For these, ε was adjusted to better match the experimental temperature. For **F** (233 K), ε = 12.1 was employed, obtained from the temperature dependence equation for CH_2Cl_2.[50] For **A**, **B**, and **K**, the ε of $CHCl_2F$ at low temperature is unknown. For **K** (213 K), ε = 8 was employed, which was approximated from the ε at 213 K for related solvents, i.e., ε = 6.8 for $CHCl_3$[51] and ε = 14.9 for CHF_3 (assuming $CHCl_2F$ lies between these).[50] For **A** and **B** (168 and 173 K), the lower temperature can be assumed to lead to a larger dielectric constant, and ε = 10 was employed. Tests at the PBE-D2/BS1,PCM level show that the barrier of **A** increases ~0.1 kcal/mol for each increase of ε by 1. The exact choice of ε is therefore less critical in this case. For PBE, B3LYP, M06L, and M06L-D3, TS optimizations at ε = 10 failed for **A**, which was attributed to an instability of the cavity at high ε due to flexibility of the methyl groups. For these, TS optimizations were performed at ε = 6, followed by electronic single points at ε = 10, with free energies computed as $G(\varepsilon = 10) = G(\varepsilon = 6) - E(\varepsilon = 6) + E(\varepsilon = 10)$.

Energies. The experimental energies were obtained as follows: For **A**−**C**,[26−28] the $\Delta G^{\ddagger}$ values reported on the basis of rate constants determined from NMR studies were employed as is. For **D**−**F**[24,29,30] and **G**−**I**,[30−32] standard state Gibbs free energies were calculated from

DOI: 10.1021/acs.organomet.6b00377
Organometallics 2016, 35, 3795−3807

equilibrium ratios or constants using $\Delta G^\circ = -RT\ln K_{eq}$. For **J** and **K**,[29,33] reported H° and S° values were converted to standard state free energies employing $\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$. For **A**−**C**, **G**, **H**, and **J**, the experimental uncertainty was reported and is given in the relevant schemes and tables.[52]

Computed free energies, entropies, and enthalpies were obtained through standard (harmonic-approximation) frequency calculations at the same level of theory as geometry optimizations. Adjustments to experimental temperatures were performed via the *freqchk* utility.

Corrections. A number of corrections to computed thermodynamical parameters have been proposed, several of which are discussed here. They are only included in the reported energies if explicitly stated.

Larger Basis Set Corrections to the Energies. This correction is applied by computing single-point electronic energies at a larger basis set but keeping all other energy terms as obtained at a smaller basis set, i.e., $G_{BS2} = G_{BS1} - E_{BS1} + E_{BS2}$ (where G are Gibbs free energies, E are electronic energies, and BS1 is a smaller basis set than BS2). We have evaluated the effect of BS2 single points on BS1 geometries, referred to as BS2//BS1 in the text.

Counterpoise (CP) Corrections.[53] If two separately computed molecules are combined, then the formed complex might exhibit an artificial lowering of the energy, arising from the borrowing of basis set functions from neighboring fragments.[54] A CP calculation was here performed for reaction **J** and **K** to estimate the size of this intermolecular Basis Set Superposition Error (BSSE). The full CP was used here (there have been proposals to halve it by 50%).[12] A new scheme, also correcting for the intramolecular BSSE,[55] was not evaluated here.

Standard State (SS) Conversions. Computed free energies correspond to an 1 atm standard state (ΔG°_{atm}). Conversion to a more relevant 1 M solution standard state (ΔG°_{M}) can be done as $\Delta G^\circ_{M} = \Delta G^\circ_{atm} + R_1T\ln(R_2T^{\Delta n})$, where $R_1 = 8.31447$ J K^{-1} mol^{-1}, $R_2 = 0.08206$ L atm K^{-1} mol^{-1}, T = temperature in K, and Δn = change in number of moles.[54] Only reactions where the number of moles change are affected. For an association reaction A + B → C ($\Delta n = -1$), $R_1T\ln(R_2T^{\Delta n})$ equals −1.89 kcal/mol (298 K). Standard state conversions can be applied to entropies only where $S^\circ_{M} = S^\circ_{atm} - R_1\ln(R_2T)$ for each separately computed system.[56] If a solvent molecule is involved in the reaction, then this is adjusted to the solvent standard state (not relevant here).[20]

Scaling of Vibrational Frequencies.[19] This involves computation of thermochemical values with a functional-dependent scaling factor for frequencies, e.g., 0.985 for B3LYP, 0.976 for M06L, or 1.011 for PBE.[19] The scaling can be introduced in the *freqchk* utility or directly in frequency calculations (keyword *scaling*). We have tested this correction on a few cases (see text) and see effects of <0.1 kcal/mol.

Raising of Low-Lying Vibrational Frequencies to 100 cm^{-1}.[19] Such corrections were not included here, partially due to the volume of calculations performed but also because Plata and Singleton have pointed out that this correction increases errors (see Supporting Information of ref 56).

Artificial Pressure Increase to Reduce the Entropy.[14] This was proposed by Martin et al. to reduce the translational entropy of water molecules in water.[57] It can be included by performing frequency calculations with a pressure (in atm), $P = (d/M)RT$,[57] where d (in kg/m^3) is the solvent density at a given temperature T (in K), M is the molecular weight (g/mol) of the solvent, and $R = 0.08206$ L atm K^{-1} mol^{-1}. To our knowledge, a justification for a general applicability of this correction beyond the original system is not reported, but it has been applied in various studies, either arbitrarily with Martin's original water value ($P = 1354$),[11,58−60] or with P derived for the experimental solvent.[14] Only reactions where the number of moles change are significantly affected (here **J** and **K**). For toluene at 298 K, $d = 861$ kg/m^3 and $P = 229$. For $CHCl_2F$ at 213 K, the density is unknown. Therefore, two values were tested: a known density at 282 K ($d = 1409$ kg/m^3 and $P = 334$) and assuming a density increase at lower temperature an arbitrary value of $d = 2000$ kg/m^3 and $P = 475$.

Multiplying the Entropy by 0.5.[56] Plata and Singleton applied this correction,[56] where the free energy of each species is computed with half the raw entropy, $G_{1/2} = H - T(0.5S_{raw})$. This requires postprocessing of all computed energies. It was here evaluated for all 11 reactions with one protocol (PBE-D2/BS1,PCM); see main text.

Correction for Symmetry.[56,61,62] This is motivated by the fact that more symmetric molecules have less entropy and implies adding a correction term, $\Delta S_{sym} = R\ln(\sigma_{reac}/\sigma_{prod})$, to the entropy. σ is the total symmetry number of a given state and depends on both internal and external symmetry.[61−63] In simple cases, where σ only depends on rotational symmetry numbers, the change from a C_1 reactant to a C_2 product implies a free energy correction of $-TR\ln(^1/_2)$ = +0.4 kcal/mol at 298 K. As ΔS_{sym} can be complex to determine and is expected to be small (or zero, if $\sigma_{reac} = \sigma_{prod}$), it was omitted here.

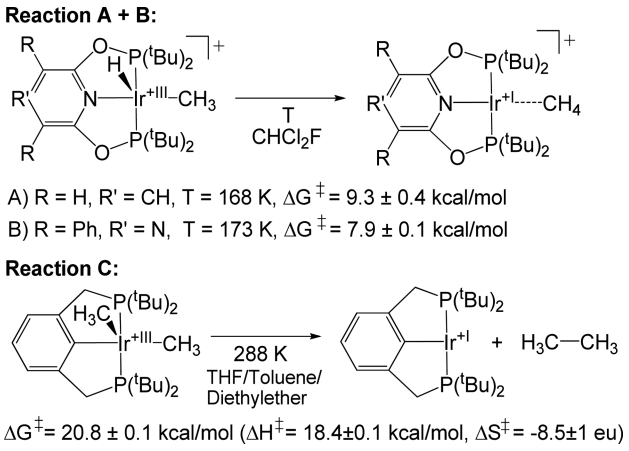
Correction for Multistructural Effects.[56] This implies adding a correction term to the enthalpy, entropy, or free energy to correct for the presence of multiple conformations of similar energy. The free energy correction is $G_{mse} = -RT\ln(\Sigma_{i=1}^{n} e^{-(Gi-G_1)/RT})$, where n is the total number of conformations and $i = 1$ is the conformation with lowest energy.[56] ΔG_{mse} appears to be small (<0.5 kcal/mol in a recent study[56]). It was evaluated here for reaction **G** (PBE-D2, PCM level).

Results and Discussion. The benchmark results for the four reaction types depicted in Scheme 2 are discussed in detail in the following.

C−H and C−C Coupling. C−H bond formation is an elementary step in various Ir-catalyzed reactions, e.g., in hydrogenation of unsaturated substrates (C═C, C═O, and C═N).[24,64] C−C bond formation is relevant for example in Ir-mediated cross-coupling reactions.[25] We have evaluated the ability of DFT to reproduce three experimentally reported C−H and C−C coupling barriers.

Reaction **A** involves iridium-mediated reductive C−H coupling, with a reported barrier of 9.3 ± 0.4 kcal/mol (Scheme 3).[26]

Scheme 3. Evaluated Reductive C−H/C−C Couplings[26−28]



This reaction was evaluated with 13 DFT combinations (B3LYP, B3LYP-D2, B3LYP-D3, B3LYP-D3BJ, PBE, PBE-D2, PBE-D3, PBE-D3BJ, PBE0, PBE0-D3, M06L, M06L-D3, and M11L) and three computational protocols (BS1,PCM; BS2,PCM//BS1,PCM; and BS1,SMD; Table 1). The conformational analysis reveals that the lowest-lying transition state (TS) prefers a H−Ir−C−H dihedral angle of close to 180°, and care must be taken to ensure this angle (e.g., with appropriate starting structures). The *t*-Bu substituents can adopt different conformations (*sym* and *asym*, Figure 1), of which *sym* is preferred. For the computed barriers, the smaller basis set BS1 provides best results for all functionals, except for a small improvement for PBE-D3BJ if BS2 corrections are included (Figure 1). B3LYP-D3BJ fails because it yields first- and second-order saddle points for the minimum and TS optimizations, respectively; this problem was observed repeatedly (calculations are labeled F in the following). PBE-D3BJ converged without problems. If SMD is employed, then all functionals give larger errors (Table 1). For reaction **A**, PBE-D type functionals and M06L perform best (all within or close to the experimental error bar). If the frequencies at the PBE-D2/BS1,PCM level are scaled (factor 0.976), then the barrier increases 0.05 kcal/mol.

DOI: 10.1021/acs.organomet.6b00377
Organometallics 2016, 35, 3795−3807

Table 1. Deviation from Experiment ($\Delta G_{computed} - \Delta G_{experimental}$, kcal/mol) for Reactions A, B (including conformations), and A−B

	B3LYP	B3LYP-D2	B3LYP-D3	B3LYP-D3BJ	PBE0	PBE0-D3	PBE	PBE-D2	PBE-D3	PBE-D3BJ	M06L	M06L-D3	M11L
						Reaction A[a]							
BS1,PCM	+3.2[b]	+1.9	+1.6	F[c]	+0.5	+0.6	+0.3[b]	−0.1	−0.1	−0.5	−0.3[b]	−0.2[b]	+0.8
BS2,PCM//BS1,PCM	+4.2[b]	+3.0	+2.7	F[c]	+1.4	+1.6	+0.9[b]	+0.6	+0.5	+0.1	+0.4[b]	+0.5[b]	+1.6
BS1,SMD	F[c]	+6.7	+5.7	+3.4	+4.7	+4.9	+3.4	+4.6	+3.7	+3.9	+4.5	+4.8	F[c]
						Reaction B[d]							
conformation reac.[e]	d_{asym}	c_{sym}	a_{sym}	F[c]	c_{sym}	c_{sym}	b_{asym}	c_{sym}	c_{sym}	c_{sym}	c_{sym}	c_{sym}	a_{sym}
conformation TS[e]	c_{sym}	c_{sym}	c_{sym}	F[c]	a_{sym}	b_{sym}	a_{sym}	b_{sym}	c_{sym}	b_{sym}	c_{sym}	c_{sym}	c_{sym}
BS1,PCM	+3.9	+3.7	+3.4	F[c]	+3.0	+2.6	+1.2	+2.2	+2.0	+1.9	+1.7	+1.4	+2.9
BS2,PCM//BS1,PCM	+4.6	+4.8	+4.5	F[c]	+3.7	+3.9	+1.3	+2.8	+2.5	+2.4	+2.3	+2.1	+3.6
						Reaction A−B[f]							
BS1,PCM	−0.7	−1.7	−1.7		−2.6	−2.0	−0.9	−2.3	−2.2	−2.4	−2.0	−1.7	−2.0
BS2,PCM//BS1,PCM	−0.4	−1.8	−1.8		−2.2	−2.3	−0.4	−2.3	−2.0	−2.3	−2.0	−1.6	−2.0
reproducing trend?[g]	Y	N	N	N	N	N	Y	N	N	N	N	N	N

[a]Computed with solvent = chloroform, ε = 10, T = 168 K. Exp. barrier =9.3 ± 0.4,[26] [b]TS optimizations were performed with ε = 6, followed by ε = 10 single points.[65] [c]Failed (converged to incorrect state). [d]Computed with solvent = chloroform, ε = 10, T = 173 K. Exp. barrier =7.9 ± 0.1.[27] [e]See Figure 1. [f]$\Delta G_A - \Delta G_B$. Exp. = +1.4 ± 0.5.[26,27] [g]Barrier for **B** below **A**? Yes/No.

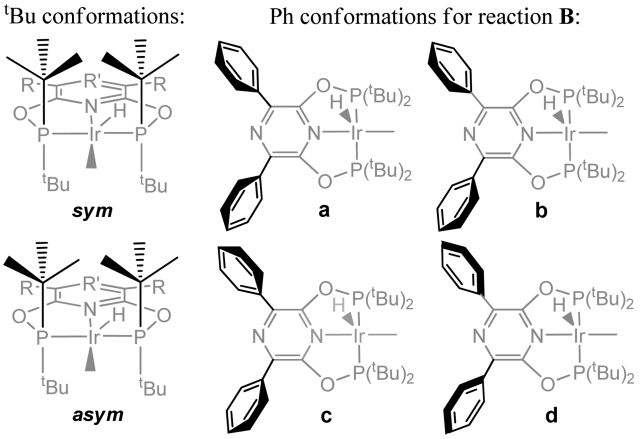


Figure 1. Relevant conformations for reactions **A** and **B**.

Reaction **B** involves reductive methane elimination with a different pincer ligand than in **A** and a lower experimental barrier (7.9 ± 0.1 kcal/mol, Scheme 3).[27] Reaction **B** was evaluated with the 13 DFT combinations and two protocols (Table 1 and Figure 2). Conformational analysis shows that the Ph substituents on the pincer can tilt in different directions (Figure 1a−d), in addition to the conformational freedom of the *tert*-butyl groups (*sym* and *asym*, Figure 1). Different functionals show different preferred conformations (Table 1). Although some *asym* conformations are seen for reactant states, TS's rearrange to *sym*. BS1 shows lower errors than BS2//BS1. For reaction **B**, PBE and M06L, with and without dispersion corrections, perform best, but all overestimate the barrier by 1 to 2 kcal/mol.

Interestingly, **A** and **B** describe the same transformation but with different pincer ligands (Scheme 3). It is therefore relevant to evaluate if DFT can predict the barrier change between these. The ability to predict barrier changes upon modifications to a ligand is essential for *in silico* guided redesign of catalysts (for a recent successful example on a related iridium-system, see ref 3). Experiment indicates that the barrier of **B** is 1.4 ± 0.5 kcal/mol below that of **A**.[26,27] Surprisingly, only two functionals, B3LYP and PBE, predict **B** to be lower (Table 1). Possible explanations include insufficient conformational sampling for **B** (other conformations might provide lower barriers), or significant errors in the experimental values. It can be noted that previous PBE0 vacuum calculations on significantly truncated models (Me instead of *t*-Bu, Ph ligands omitted) yielded lower barriers, 7.4 (**A**) and 7.2 (**B**) kcal/mol, giving a smaller energy difference of 0.2 kcal/mol.[27]

Reaction **C** involves reductive elimination of two methyl ligands.[28] This reaction was previously studied theoretically by Ghosh et al. with PBE in vacuum,[66] which provided an underestimated barrier ($\Delta G^{\ddagger}_{comp}$ = 18.2 kcal/mol vs $\Delta G^{\ddagger}_{exp}$ = 20.8 kcal/mol).[28] The reported geometries indicate that the models were constrained to point group C_2.[28] Test calculations performed here with PBE/BS1(vacuum) provide a barrier of 17.1 kcal/mol with C_2 constraints but 20.1 kcal/mol without constraints due to a lower reactant geometry. Although symmetry can speed up computations, this example shows that energies can be affected significantly. It is therefore recommended to not include symmetry constraints.

Reaction **C** was here evaluated with three protocols (BS1,PCM; BS2,PCM//BS1,PCM; and BS1,SMD; all without symmetry constraints). Most functionals overestimate the barrier, regardless if dispersion corrections are included and regardless of solvent model (Table 2). Interestingly, for the same protocol, the DFT predictions differ by as much as ∼10 kcal/mol (Figure 2). Single-point BS2 corrections do not improve results, except for a small error reduction for PBE-based functionals. SMD provides larger errors than PCM in all cases, except PBE-D3BJ (Table 2). Overall, PBE and PBE-D type functionals with BS1,PCM perform best for reaction **C**.

Isomerization Reactions. Reactions **D**−**F** concern energy differences between isomers of a given complex (Scheme 4). The ability to reproduce isomer distributions is relevant for establishing the resting state of a system. It is equally important for evaluation of diastereomeric reaction pathways, where the intermediates or transition states only differ in the coordination mode of a ligand.[20] The isomerization of three different iridium-complexes was evaluated here (Scheme 4): an $IrH_2[C_6H_3\text{-}2,6\text{-}(OPt\text{-}Bu_2)_2]$ pincer complex with an imine ligand that can σ-bond in two different orientations,[30] an $[IrClH(\kappa\text{-}P,P,Si\text{-}Si(Me)\{(CH_2)_3PPh_2\}_2)]$ complex with a hydride ligand, which can be in *anti* or *syn* position relative to a methyl substitutent,[29] and an Ir-phosphinooxazoline system with an alkene ligand that π-bonds in a pro-(*R*) or a pro-(*S*) mode.[24]

Reaction **D** concerns a proposed intermediate in the dehydrogenation of isobutylamine, $\{C_6H_3\text{-}2,6\text{-}[OP(t\text{-}Bu)_2]_2\}Ir(HN{=}C(Me)Et)$ (Scheme 4).[30] NMR studies on an equilibrated benzene solution of this complex showed two forms in a 16:10 ratio, of respectively, an (*E*) and a (*Z*) isomer (Scheme 4). This equals an energy difference of ΔG_r° = 0.3 kcal/mol between the two forms. Reaction **D** was here studied with three computational protocols and the 13 DFT combinations (Table 3). With BS1/PCM, all functionals correctly identify the (*E*) isomer as preferred, but overestimate the energy difference between the two species by 0.6−2.0 kcal/mol (Table 3). BS2 corrections provide identical or worse results. BS1,SMD provides slightly better results than PCM (errors ranging from −0.3 to

DOI: 10.1021/acs.organomet.6b00377
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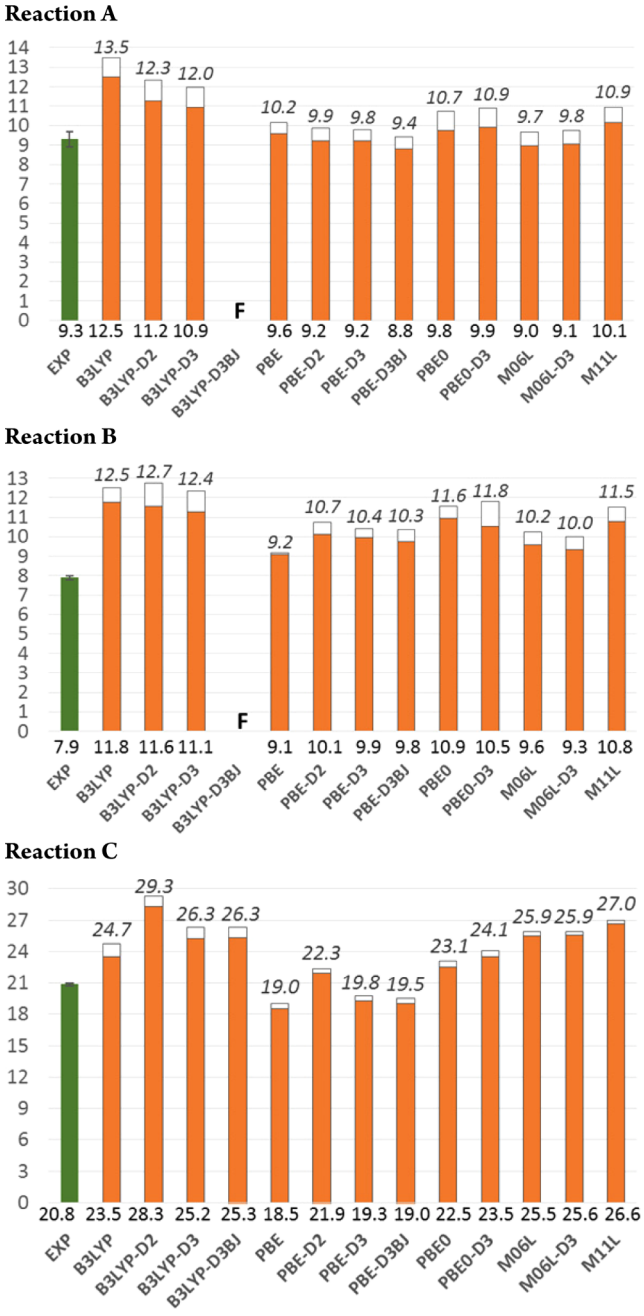
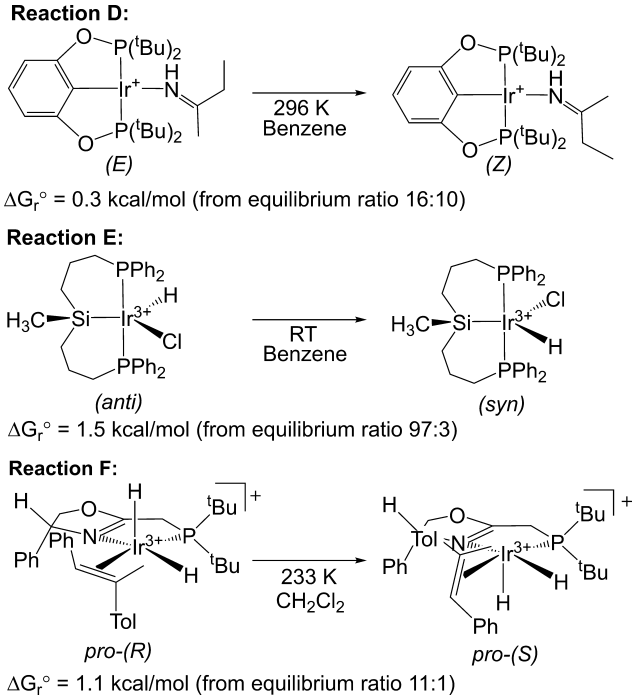


Figure 2. Computed barriers ($\Delta G^{\ddagger}$, kcal/mol) for reactions **A**,[26] **B**,[27] and **C**[28] with BS1,PCM (orange bars, nonitalic numbers) or BS2,PCM//BS1,PCM (white bars, italic numbers, *F* = failed).

+1.8 kcal/mol). Of the dispersion corrections, only D2 consistently improves results; D3 and D3BJ yield identical or worse errors. For all protocols tested, PBE-D2 performs best.

Reaction **E** concerns iridium-hydrides (Scheme 4), which are found as intermediates in for example hydrogenation and C−H

Scheme 4. Evaluated Isomerization Reactions[24,29,30]



activation reactions.[3,24,67] They often form multiple isomers,[24,67] which might exhibit different reactivities.[29] NMR studies on [IrClH(κ-*P*,*P*,*Si*−Si(Me){$(CH_2)_3PPh_2$}$_2$)] in benzene showed two monohydrides, with the hydride and a methyl-substituent on Si *anti* or *syn* to each other.[29] The equilibrium ratio is 97:3 *anti*/*syn*, equaling an energy difference of 1.5 kcal/mol at 298 K. With BS1,PCM, all functionals underestimate the energy difference (by 0.2−2.0 kcal/mol), and half the functionals incorrectly predict the *syn* form to be the preferred species (Table 4). It can be noted that previous computational studies by Sola et al. established that the *anti* form is electronically preferred, while the *syn* form is sterically preferred.[29] Large basis set corrections to the electronic energy (BS2,PCM//BS1,PCM) therefore enhance the preference for the *anti* form, reducing the absolute error to 0.3−1.1 kcal/mol, with correct prediction of *anti* as preferred for all functionals (Table 4). Optimizations with BS2 provide similar results, with slight improvement for PBE and M06L. A clear advantage of including dispersion corrections is not evident and no clearly best functional is identified.

Reaction **F** describes the isomerization of an iridium-dihydride with a coordinated alkene (Scheme 4). The coordination mode of a prochiral alkene in a hydrogenation reaction determines which product configuration can be formed.[23] Although the enantioselectivity will be dependent on the barrier, not the intermediate distribution, there is a strong interest to determine if the major or the minor intermediate forms the product.[24,68] NMR studies in CH_2Cl_2 at 233 K established a ratio of 11:1 between a pro-(*R*) and a pro-(*S*) species of an alkene-coordinated iridium-dihydride (Scheme 5),[24] which corresponds to an energy difference of 1.1 kcal/mol. We have attempted to reproduce this value with 3 computational protocols and the 13 DFT combinations. At the BS1,PCM level, all Minnesota functionals incorrectly predict the pro-(*S*) form to be the major species (Table 5).

Table 2. Deviation from Experiment ($\Delta G_{computed} - \Delta G_{experimental}$, kcal/mol) for Reaction C[a]

	B3LYP	B3LYP-D2	B3LYP-D3	B3LYP-D3BJ	PBE0	PBE0-D3	PBE	PBE-D2	PBE-D3	PBE-D3BJ	M06L	M06L-D3	M11L
BS1,PCM	+2.7	+7.4	+4.4	+4.4	+1.6	+2.6	−2.3	+1.0	−1.6	−1.8	+4.7	+4.7	+5.7
BS2,PCM//BS1,PCM	+3.8	+8.5	+5.5	+5.5	+2.3	+3.3	−1.9	+1.4	−1.1	−1.4	+5.0	+5.1	+6.2
BS1,SMD	+7.7	+10.2	+7.1	F[b]	+5.6	+5.6	+2.6	+3.2	+1.8	+1.1	+5.9	+5.9	+9.0

[a]Computed with solvent = diethyl ether, ε = 4.24, *T* = 293 K. Exp. barrier =20.8 ± 0.1 kcal/mol.[28] [b]Failed (converged to incorrect state).

DOI: 10.1021/acs.organomet.6b00377
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Table 3. Deviation from Experiment ($\Delta G_{computed} - \Delta G_{experimental}$, kcal/mol) for Reaction D[a]

	B3LYP	B3LYP-D2	B3LYP-D3	B3LYP-D3BJ	PBE0	PBE0-D3	PBE	PBE-D2	PBE-D3	PBE-D3BJ	M06L	M06L-D3	M11L
BS1,PCM	+1.2	+0.9	+1.2	+1.6	+1.5	+1.9	+1.4	+0.6	+1.5	+1.5	+1.7	+1.6	+2.0
BS2,PCM//BS1,PCM	+1.2	+0.9	+1.2	+1.7	+1.6	+2.0	+1.4	+0.8	+1.6	+1.6	+1.8	+1.7	+2.1
BS1,SMD	+1.2	−0.3	+0.3	F[b]	+0.8	+0.3	+1.5	+0.1	+1.7	+1.4	+1.8	+1.8	+1.4
reproducing trend?[c]	Y	Y/N[d]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

[a]Computed with solvent = benzene, ε = 2.27, T = 298 K. Exp. energy = +0.3 kcal/mol,[30] [b]Failed. [c]*E* should be below *Z*. [d]N with SMD.

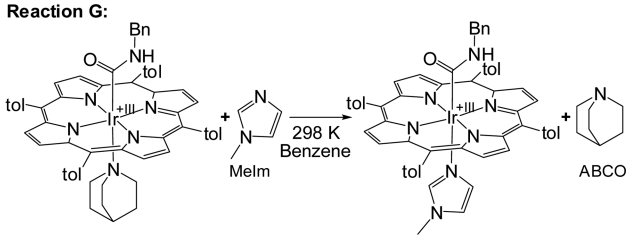
Table 4. Deviation from Experiment ($\Delta G_{computed} - \Delta G_{experimental}$, kcal/mol) for Reaction E[a]

	B3LYP	B3LYP-D2	B3LYP-D3	B3LYP-D3BJ	PBE0	PBE0-D3	PBE	PBE-D2	PBE-D3	PBE-D3BJ	M06L	M06L-D3	M11L
BS1,PCM	−0.5	−1.8	−2.0	F[b]	−0.5	−1.6	−1.4	−1.7	−0.2	−1.3	−2.0	−1.5	−1.6
BS2,PCM//BS1,PCM	+0.3	−0.7	−0.9	F[b]	+0.3	−0.4	−0.4	−0.7	+0.8	−0.2	−1.1	−0.7	−0.8
BS2,PCM	−1.3	−0.6	−0.8	F[b]	+0.4	F[b]	−0.0	−0.7	−0.2	−0.3	−0.3	+0.8	−0.6
reproducing trend?[c]	Y	Y/N[d]	Y/N[d]		Y	Y/N[d]	Y	Y/N[d]	Y	Y	Y/N[d]	Y/N[d]	Y/N[d]

[a]Computed with solvent = benzene, ε = 2.27, T = 298 K. Exp. energy = +1.5 kcal/mol,[29] [b]Failed. [c]*anti* should be below *syn*. [d]N for BS1.

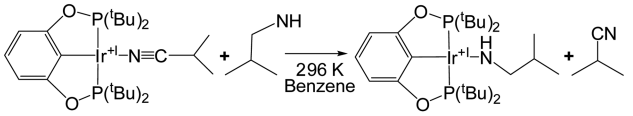
Scheme 5. Evaluated Ligand Exchange Reactions[30−32]

Reaction G:



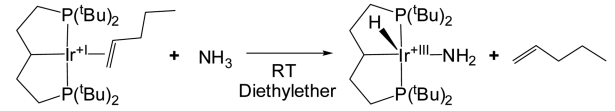
ΔG° = -0.38 ± 0.03 kcal/mol (from K_{eq} = 1.9 ± 0.1)

Reaction H:



ΔG° = 3.7 ± 0.4 kcal/mol (from K_{eq} = 552 ± 27 for reverse reaction)

Reaction I (oxidative):



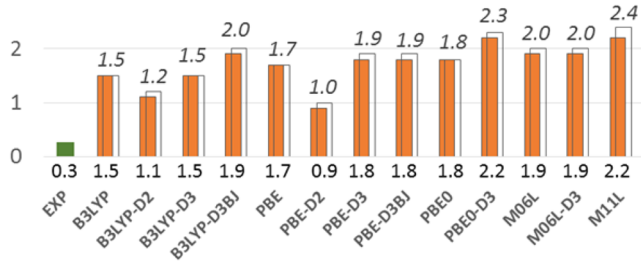
ΔG° = -1.3 kcal/mol (from K_{eq} = 9)

BS2 corrections do not change results. DFT-D type functionals, in particular with the D3 correction, perform best (Figure 3). SMD gives slightly worse results and fails for several of the functionals.

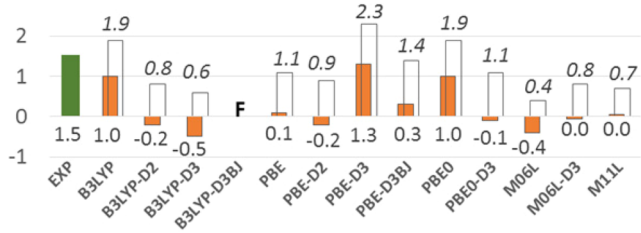
Ligand Exchange Reactions. Many organometallic reactions involve exchange of a ligand as part of the catalytic cycle. Three such reactions are analyzed here,[30−32] with exchange of typical ligands, such as imidazole, nitrile, amine, and alkene (Scheme 5).

Reaction **G** describes a porphyrin complex with a carbamoyl ligand.[32] For this complex, binding of methylimidazole (MeIm) in the other axial position is slightly favored over binding of 1-azabi-cyclo[2.2.2]octane

Reaction D



Reaction E



Reaction F

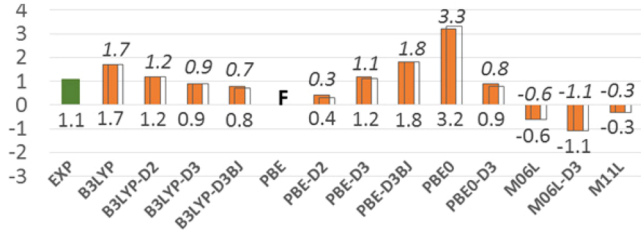


Figure 3. Computed energies (ΔG°, kcal/mol) for reactions **D**,[30] **E**,[29] and **F**[24] with BS1,PCM (orange bars, nonitalic numbers), or BS2, PCM//BS1,PCM (white bars, italic numbers, F = failed).

Table 5. Deviation from Experimental Barriers ($\Delta G_{computed} - \Delta G_{experimental}$) for Reaction F[a]

	B3LYP	B3LYP-D2	B3LYP-D3	B3LYP-D3BJ	PBE0	PBE0-D3	PBE	PBE-D2	PBE-D3	PBE-D3BJ	M06L	M06L-D3	M11L
BS1,PCM	+0.5	+0.1	−0.2	−0.3	+2.1	−0.2	F[b]	−0.7	+0.0	+0.7	−1.7	−2.2	−1.4
BS2,PCM//BS1,PCM	+0.6	+0.1	−0.2	−0.4	+2.1	−0.3	F[b]	−0.8	+0.0	+0.7	−1.7	−2.2	−1.4
BS1,SMD	−1.7	F[b]	F[b]	+0.5	+1.8	−0.9	−0.4	−0.2	−0.4	+0.9	−0.7	F[b]	F[b]
reproducing trend?[c]	Y/N[d]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y/N[e]	N	N

[a]Computed with CH_2Cl_2, ε = 12.1, T = 233 K. Exp. energy = +1.1 kcal/mol.[24] [b]Failed. [c]*pro*-(*R*) should be below *pro*-(*S*). [d]N for SMD. [e]N for PCM.

DOI: 10.1021/acs.organomet.6b00377
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(ABCO, Scheme 5). This porphyrin complex shows high flexibility, with a large number of close-lying conformations. A constant feature of these is a CH/π interaction between the benzyl group of the carbamoyl ligand and one of the tolyl groups (Figure 4). The other

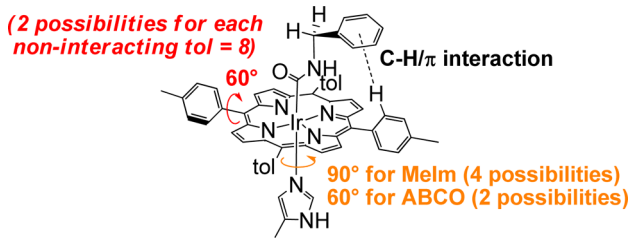

Figure 4. Conformational freedom of complexes in Reaction **G**.

tolyl groups can tilt in two directions, whereas the lower axial ligand can have two conformations for ABCO and at least four for MeIm. This requires evaluation of 16 distinct conformers for Ir-ABCO and 32 for Ir-MeIm (see Supporting Information).

Reaction **G** was studied with two protocols and the 13 DFT functionals (Table 6). A pronounced sensitivity to dispersion is found. B3LYP, PBE, and PBE0 give errors of 10.7−12.3 kcal/mol, as does M11L. B3LYP-D and PBE-D type functionals perform much better, with absolute errors of 1.0−6.6 kcal/mol (BS1,PCM; Table 6 and Figure 5). BS2 corrections do not improve results. The dependence on dispersion is rationalized from the optimized geometries: With PBE and PBE-D2 (BS1,PCM), the Ir−MeIm bond lengths are 2.28 and 2.24 Å, respectively, whereas Ir−ABCO shows bond lengths of 2.49 and 2.38 Å, respectively. Thus, ABCO binding requires more pronounced dispersion interactions and functionals unable to describe these overestimate the preference for MeIm.

For reaction **G**, it is relevant to evaluate the corrections arising from multistructural effects (G_{mse}), due the presence of many close-lying conformers. With PBE-D2/BS1,PCM, the 16 analyzed Ir-ABCO conformers are within 1.5 kcal/mol and the 32 analyzed Ir-MeIm conformers are within 1.9 kcal/mol. Although the corrections to each state are significant (G_{mse} = −1.24 and −0.98 kcal/mol, respectively), they largely cancel out to give ΔG_{mse} = −0.26 kcal/mol, which slightly worsens the PBE-D2 error to −1.7 kcal/mol. This is in line with Plata and Singleton's G_{mse} values.[56] Due to the flexibility of this system, additional low-lying conformers might exist, but their effect will be negligible, as long as the lowest conformer was identified.

Reaction **H** is proposed to occur in catalytic amine dehydrogenation and concerns exchange of a nitrile with an amine, with an estimated cost of 3.7 ± 0.4 kcal/mol (Scheme 5).[30] The free amine shows several low-lying conformations (within 1 kcal/mol), but different functionals analyzed (M06L, PBE-D2, and B3LYP-D2 and -D3) provide the same preferred conformer, which was employed as input geometry for all functionals. For the bound amine, energy differences between conformers are larger (>1 kcal/mol, analyzed with B3LYP-D2 and -D3), with one preferred geometry that was employed as input geometry. With BS1,PCM, absolute errors for reaction **H** range from 0.2 to 4.1 kcal/mol (Table 7). PBE-D2 performs best (Figure 5). BS2 corrections reduce the error for some functionals but increase it for

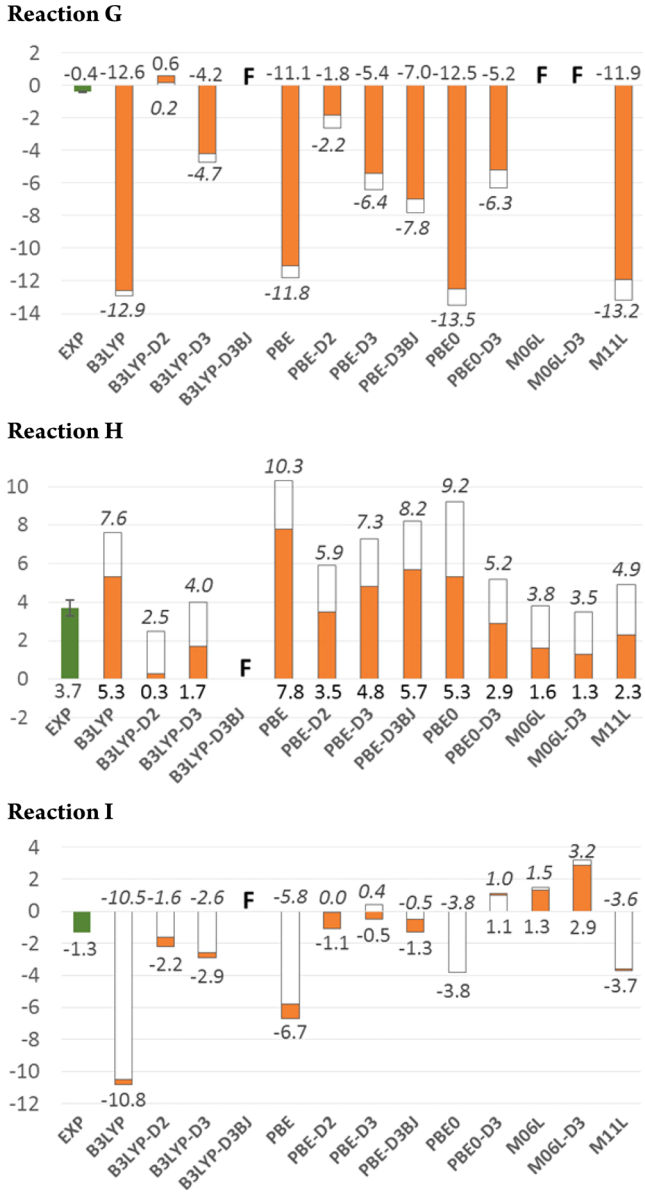

Figure 5. Computed energies (ΔG°, kcal/mol) for reactions **G**,[32] **H**,[30] and **I**[31] with BS1,PCM (orange bars, nonitalic numbers) or BS2, PCM//BS1,PCM (white bars, italic numbers, *F* = failed).

most. Satisfyingly, all functionals correctly predict that nitrile coordination is favored.

Reaction **I** describes replacement of an alkene through oxidative addition of an amine (Scheme 5).[31] The equilibrium constant translates to a reaction energy of −1.3 kcal/mol.[31] Reaction **I** was studied with 13 DFT combinations and 3 computational protocols

Table 6. Deviation from Experiment ($\Delta G_{computed} - \Delta G_{experimental}$, kcal/mol) for Reaction G[a]

	B3LYP	B3LYP-D2	B3LYP-D3	B3LYP-D3BJ	PBE0	PBE0-D3	PBE	PBE-D2	PBE-D3	PBE-D3BJ	M06L	M06L-D3	M11L
confor. Ir-ABCO[b]	A11	A13	A13	F[c]	A9	A9	A13	A13	A3	A10	F[c]	F[c]	A12
confor. Ir-MeIm[b]	M12	M7	M15	F[c]	M16	M31	M4	M4	M16	M4	F[c]	F[c]	M20
BS1,PCM	−12.3	+1.0	−3.8	F[c]	−12.2	−4.9	−10.7	−1.4	−5.0	−6.6	F[c]	F[c]	−11.5
BS2,PCM//BS1,PCM	−12.5	+0.6	−4.4	F[c]	−13.1	−5.9	−11.4	−2.2	−6.0	−7.4	F[c]	F[c]	−12.8
reproducing trend?[d]	Y	N[e]	Y		Y	Y	Y	Y	Y	Y			Y

[a]Computed with solvent = benzene, ε = 2.27, T = 298 K. Experim. energy = −0.38 ± 0.05 kcal/mol.[32] [b]Lowest conformation, see Supporting Information. [c]Many conformations failed, reliable analysis not possible. [d]Ir-MeIm should be preferred over Ir-ABCO. [e]Ir-ABCO is preferred.

DOI: 10.1021/acs.organomet.6b00377
Organometallics 2016, 35, 3795−3807

Table 7. Deviation from Experiment ($\Delta G_{computed} - \Delta G_{experimental}$, kcal/mol) for Reaction H[a]

	B3LYP	B3LYP-D2	B3LYP-D3	B3LYP-D3BJ	PBE0	PBE0-D3	PBE	PBE-D2	PBE-D3	PBE-D3BJ	M06L	M06L-D3	M11L
BS1,PCM	+1.6	−3.4	−2.0	F[b]	+1.6	−0.8	+4.1	−0.2	+1.1	+2.0	−2.1	−2.4	−1.4
BS2,PCM//BS1,PCM	+3.9	−1.2	+0.3	F[b]	+3.9	−1.5	+6.6	+2.2	+3.6	+4.5	+0.1	−0.2	+1.2
reproducing trend?[c]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

[a]Computed with benzene, ε = 2.27, T = 298 K. Exp. energy = +3.7 ± 0.4 kcal/mol.[30] [b]Fails. [c]Ir-nitrile should be preferred over Ir-amine.

Table 8. Deviation from Experiment ($\Delta G_{computed} - \Delta G_{experimental}$, kcal/mol) for Reaction I[a]

	B3LYP	B3LYP-D2	B3LYP-D3	B3LYP-D3BJ	PBE0	PBE0-D3	PBE	PBE-D2	PBE-D3	PBE-D3BJ	M06L	M06L-D3	M11L
BS1,PCM	−9.5	−0.9	−1.6	F[b]	−2.5	+2.4	−5.4	+0.2	+0.8	0.0	+2.6	+4.2	−2.4
BS2,PCM//BS1,PCM	−9.2	−0.3	−1.3	F[b]	−2.5	+2.3	−4.5	+1.3	+1.7	+0.8	+2.8	+4.5	−2.3
BS1,SMD	−10.7	−1.2	−3.6	−2.2	−5.0	−0.3	−6.4	−0.5	−0.7	−0.9	+1.1	+2.5	−4.9
reproducing trend?[c]	Y	Y	Y	Y	Y	Y/N[d]	Y	Y	Y/N[e]	Y	Y/N[d]	N[f]	Y/N[g]
def2-TZVP,SMD[h]	−11.6		−4.5[i]	−3.6[i]			−6.8		−1.7[i]	−1.2[i]	−0.1	+1.3[i]	

[a]Computed with diethyl ether, ε = 4.24, T = 298 K. Exp. energy = −1.3 kcal/mol.[31] [b]Fails. [c]Expected free energy ordering on the basis of experiment:[31] $G_{[Ir-alkene]} > G_{[Ir(H)(NH_2)]}$ and $G_{[Ir(NH3)]} > G_{[Ir(H)(NH_2)]}$. [d]N with PCM, $G_{[Ir(H)(NH_2)]} > G_{[Ir-alkene]}$. [e]N with BS2//BS1, $G_{[Ir(H)(NH_2)]} > G_{[Ir-alkene]}$. [f]$G_{[Ir(H)(NH_2)]} > G_{[Ir-alkene]}$. [g]N at BS1,PCM level, $G_{[Ir(H)(NH_2)]} > G_{[Ir(NH3)]}$. [h]From ref 19, given for comparison. [i]Dispersion correction to energy not geometry.

Table 9. Deviation from Experiment ($\Delta G_{computed} - \Delta G_{experimental}$, kcal/mol) for Reaction J[a]

	B3LYP	B3LYP-D2	B3LYP-D3	B3LYP-D3BJ	PBE0	PBE0-D3	PBE	PBE-D2	PBE-D3	PBE-D3BJ	M06L	M06L-D3	M11L
BS1,PCM+SS (1 atm)	+8.7	−3.6	−3.1	−5.3	+2.6	−5.0	+0.9	−6.9	−3.6	−5.3	−1.5	−2.7	−2.4
BS1,PCM+SS+CP (1 atm)	+12.6	+0.3	+0.9	−1.3	+6.5	−1.1	+5.2	−2.6	+0.7	−1.1	+1.4	+0.2	+1.1
BS1,PCM+SS+CP (229 atm)	+9.4	−2.9	−2.3	−4.5	+3.6	−4.3	+2.0	−5.8	−2.6	−4.3	−1.8	−3.0	−2.1
BS1,SMD+SS+CP (1 atm)	+12.9	+0.7	+1.6	F[b]	+5.8	−0.2	+7.0	−1.7	+0.1	−1.5	−0.5	−1.3	F[b]
BS2,PCM+SS+CP//BS1,PCM (1 atm)	+10.5	−1.8	−1.2	−3.4	+4.7	−2.9	+3.2	−4.7	−1.3	−3.0	+0.3	−0.8	+0.3
BS2,PCM+SS+CP//BS1,PCM (229 atm)	+7.3	−5.0	−4.4	−6.6	+1.5	−6.1	+0.0	−7.9	−4.5	−6.3	−2.9	−4.1	−2.9

[a]Computed with solvent = toluene, ε = 2.37, T = 298 K. Exp. energy =0.05 ± 1 kcal/mol.[29] SS = standard state conversion, CP = counterpoise corrections, computed at basis set employed for electronic energies. 229 atm is an entropy modification, see computational details. [b]Failed.

(Table 8 and Figure 5). With BS1,PCM, functionals lacking dispersion have the largest errors. For PBE-D and B3LYP-D functionals, errors are below 1.6 kcal/mol, whereas PBE0-D3, M06L, M06L-D3, and M11L give errors of up to 4.2 kcal/mol (Table 8). BS2 corrections provide negligible improvements. BS1,SMD shows either similar or worse errors, except for M06L, M06L-D3, and PBE0-D3.

The experimental results indicate that formation of the oxidative product, $Ir(H)(NH_2)$, should be preferred over formation of $Ir(NH_3)$. Although reaction **I** has been studied previously in the literature,[14,19] this aspect has to our knowledge not been addressed earlier. Interestingly, most DFT combinations correctly predict the expected trend. However, at the BS1,PCM level, M11L incorrectly predicts that $Ir(NH_3)$ is favored over $Ir(H)(NH_2)$ by 1.5 kcal/mol, whereas M06L, M06L-D3, and PBE0-D3 incorrectly predict that alkene coordination is favored over $Ir(H)(NH_2)$ formation. With SMD, PBE0-D3 and M06L instead show the correct trend and reasonable errors (Table 8). Note that the M06L result (+1.1 kcal/mol) differs from a previous study,[14] which for reaction **I** reported an error of −0.1 kcal/mol with M06L,SMD (and a somewhat different computational protocol).[69] Application of the previous protocol here gives an error of +0.8 kcal/mol,[69] and the discrepancy to earlier results cannot be explained.

Averkiev and Truhlar have also studied reaction **I** with SMD and different functionals, with a somewhat more elaborate computational protocol (def2-TZVP, scaling of frequencies, raising of low-lying frequencies, and separate computation of the components contributing to solvation energies).[19,70] Interestingly, our results and those by Averkiev et al. are similar, but the latter are all ∼1 kcal/mol more negative (for a comparison, see Table 8). Thus, the previous study has larger errors for all functionals that here have a negative error with SMD and smaller errors only for the functionals that here have a positive error, M06L and M06L-D3 (Table 8). In order to evaluate the effect of scaling, we have scaled the M06L,SMD frequencies with 0.976, which changes the error by 0.06 kcal/mol. Differences to earlier results thus are not due to scaling.

In summary, ligand exchange is highly sensitive to dispersion corrections. This is particularly clear if exchanging ligands differ substantially: For reaction **G** and **I**, the reactant has a larger ligand, which can make more pronounced dispersion interactions. Inability to describe these leads to large overestimation of the exergonicity. For **H**, the exchanging ligands are more similar, and the effect of dispersion corrections is less pronounced.

Ligand Association Reactions. Many iridium-mediated reactions are proposed to involve steps where ligands associate in free coordination sites.[25,33,64] However, ligand association is challenging to compute. A major source of error arises from the fact that the reactant state is composed of two molecules that typically are computed separately. This gives rise to errors related to solvation of the separate species, likely overestimation of individual entropies and basis set superposition errors (BSSEs). Also, dispersion interactions contribute significantly to ligand binding and need to be described adequately.[11]

Reaction **J** involves acetonitrile association to an iridium-pincer complex (Scheme 6).[29] Similar transformations might take place in many systems involving a solvent with coordinating ability. Reaction **J** was studied with BS1,PCM and BS2,PCM//BS1,PCM. Standard state (SS) conversions, amounting to −1.89 kcal/mol, were included at all levels, as these are essential for converting the computed energies from

DOI: 10.1021/acs.organomet.6b00377
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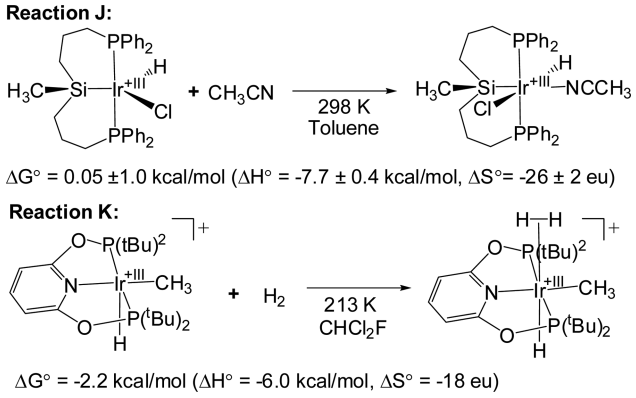
Scheme 6. Evaluated Ligand Association Reactions[29,33]



a 1 atm to a 1 M standard state for reactions, where the number of moles change. The conformational analysis reveals that the energy of the 6-coordinated species is very sensitive to the orientation of the phenyl groups (energy differences of >10 kcal/mol between conformers). With BS1,PCM+SS, B3LYP performs worst (error of +8.7 kcal/mol), whereas PBE actually performs best (+0.8 kcal/mol, Table 9 and Figure 6). After inclusion of counterpoise (CP) corrections (to correct

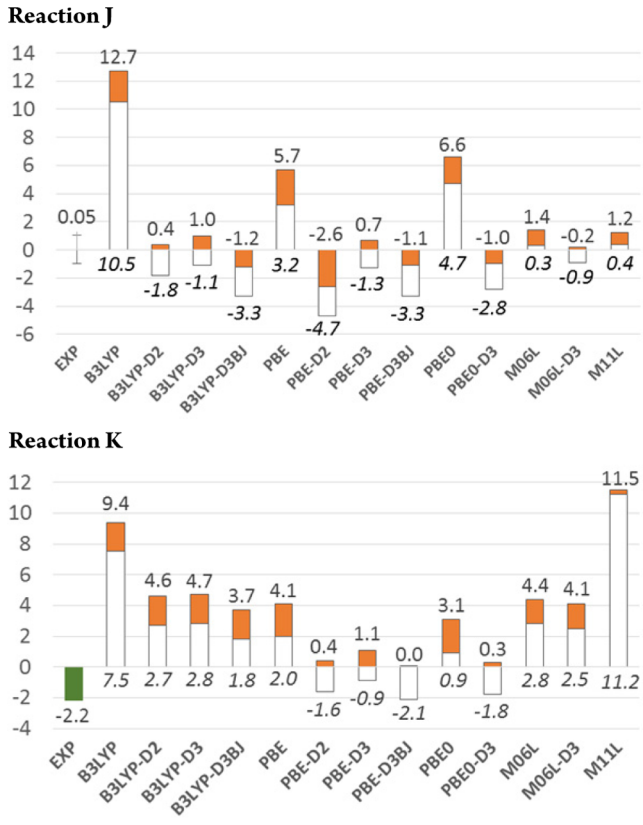


Figure 6. Computed energies (ΔG°, kcal/mol) for reactions **J**[29] and **K**[33] with BS1,PCM+SS+CP (orange bars, nonitalic numbers), and BS2,PCM+SS+CP//BS1,PCM (white bars, italic numbers).

for BSSEs), a more typical profile is observed, where all the functionals lacking dispersion corrections show large errors (Figure 6), whereas DFT-D type functionals have more moderate absolute errors of 0.3−2.6 kcal/mol (Table 9). As the error bar for this reaction is rather large (±1 kcal/mol), several results fall within the experimental range.

Comparison of PCM and SMD shows that the former performs better for essentially all functionals. Martin[57] entropy modifications involving an artificial pressure increase to 229 atm (see computational

Table 10. Deviation from Experiment ($\Delta G_{computed} - \Delta G_{experimental}$, kcal/mol) for Reaction K[a]

	B3LYP	B3LYP-D2	B3LYP-D3	B3LYP-D3BJ	PBE0	PBE0-D3	PBE	PBE-D2	PBE-D3	PBE-D3BJ	M06L	M06L-D3	M11L
BS1,PCM+SS (1 atm)	+10.9	+6.1	+6.2	+5.2	+4.5	+1.7	+5.5	+1.8	+2.5	+1.4	+5.8	+5.5	+12.9
BS1,PCM+SS+CP (1 atm)	+11.5	+6.7	+6.8	+5.8	+5.3	+2.5	+6.3	+2.6	+3.3	+2.1	+6.6	+6.3	+13.7
BS1,PCM+SS+CP (334 [475] atm)	+9.1 [+8.9]	+4.3 [+4.1]	+4.4 [+4.2]	+3.4 [+3.2]	+2.8 [+2.7]	0.0 [-0.1]	+3.8 [+3.6]	+0.1 [0.0]	+0.8 [+0.7]	−0.3 [-0.5]	+4.1 [+3.9]	+3.8 [+3.7]	+11.2 [+11.0]
BS1,SMD+SS+CP (1 atm)	+16.5	+11.4	+12.9	+12.8	+11.3	+7.9	+11.3	+8.7	+8.8	+8.3	+13.4	13.4	F[b]
reproducing trend?[c]	N	N	N	N	N	Y/N[d]	N	Y/N[d]	Y/N[e]	Y/N[f]	N	N	N
BS2,PCM+SS+CP//BS1,PCM (1 atm)	+9.5	+4.7	+4.8	+3.8	+2.8	+0.1	+4.0	+0.3	+1.1	−0.1	+5.3	+5.0	+13.9
BS2,PCM+SS+CP//BS1,PCM (334 [475] atm)	+7.0 [+6.9]	+2.2 [+2.0]	+2.4 [+2.2]	+1.3 [+1.2]	+0.4 [+0.2]	−2.4 [-2.6]	+1.6 [+1.4]	−2.1 [-2.3]	−1.4 [-1.6]	−2.5 [-2.7]	+2.8 [+2.7]	+2.5 [+2.4]	+11.4 [+11.2]
reproducing trend?[c]	N	N	N	N	Y/N[e]	Y	Y/N[e]	Y	Y	Y	N	N	Y/N[e]

[a]Computed with solvent = chloroform, ε = 8, T = 213 K. Exp. energy = −2.2 kcal/mol.[33] SS = standard state conversion, CP = counterpoise correction, computed at basis set employed for electronic energies. 334 and 475 atm are entropy modifications, see computational details. [b]Failed. [c]H_2 binding should be exergonic. [d]N for BS1,PCM+SS+CP (1 atm) and SMD. [e]Y with entropy modification. [f]N with BS1,SMD.

DOI: 10.1021/acs.organomet.6b00377
Organometallics 2016, 35, 3795−3807

details),[57] amount to −3.2 kcal/mol, and reduce the error for functionals that are strongly endergonic (B3LYP, PBE0, and PBE) but worsen results for all others (Table 9). The Singleton[56] entropy modification was evaluated at the PBE-D2/BS1,PCM level, resulting in an error of −8.6 kcal/mol (Table S2), i.e., worse than the unmodified (−2.6 kcal/mol) and the 229 atm modified (−5.8 kcal/mol) result (Table 9).

Reaction **K** describes association of H_2 to an Ir(III) complex (Scheme 6).[33] H_2 coordination is an elementary step in for example iridium-mediated hydrogenation reactions.[23] For the system studied here, the equilibrium constants measured over the range of 163−213 K provided an enthalpy of −6.0 kcal/mol and an entropy of −18 e.u.[33] This gives a reaction energy of −2.2 kcal/mol at 213 K. Reaction **K** was investigated with BS1,PCM; BS2,PCM//BS1,PCM; and BS1,SMD with the 13 DFT combinations (Table 10). All reported energies include the standard state conversion amounting to −1.21 kcal/mol at 213 K. We further evaluated the effect of counterpoise and entropy corrections. For the Martin entropy modification, the density of $CHCl_2F$ at 213 K is not known; therefore, we tested both 1409 kg/m^3 (corresponding to 282 K) and, assuming that the density increases at lower temperature, an arbitrary value of 2000 kg/m^3. The two densities result in corrections of −2.5 and −2.6 kcal/mol, respectively (identical for all functionals), showing that the exact choice of density is not critical.

With BS1,PCM+SS, B3LYP and M11L functionals deviate from experiment by >10 kcal/mol (Table 10 and Figure 6). PBE and PBE0 errors are similar to those of B3LYP-D functionals and M06L (4.5−6.2 kcal/mol). The best results are obtained with PBE0-D3 and PBE-D type functionals (1.4−2.5 kcal/mol). CP corrections are 0.6−0.8 kcal/mol and do not provide improvements. The Martin entropy modification of −2.5 kcal/mol (334 atm) provides lower errors for most functionals. However, even with this correction, essentially all functionals incorrectly predict H_2 binding to be endergonic, except the PBE-D and PBE0-D type functionals. BS2 corrections lower energies by ∼2 kcal/mol for all (Table 10). Applying both BS2 corrections and entropy modifications therefore worsen the results for PBE-D and PBE0-D-type functionals. SMD provides significantly worse results than PCM (Table 10).

Summary. The combined results for the 11 reactions analyzed here show, not surprisingly, that functionals lacking dispersion corrections (B3LYP, PBE, and PBE0) have the largest absolute average errors (AAEs) of 3.4−5.4 kcal/mol (Table 11; BS1,PCM). Also, M11L shows a similar AAE (4.0 kcal/mol). These functionals are not recommended for iridium-mediated chemistry.

Inclusion of dispersion corrections provides remarkable improvements. B3LYP-D2, -D3, and -D3BJ as well as M06L, in combination with PCM, show reasonable AAEs of 2.5−2.7 kcal/mol (Table 11). The best results are clearly obtained with PBE-D and PBE0-D type functionals, whose AAEs are only 1.2−1.9 kcal/mol (BS1,PCM; Table 11). There is no advantage to employing D3BJ over D2 or D3. For PBE-D2 with BS1,PCM, the raw free energies for the 9 reactions where the number of moles do not change (**A**−**I**), have an AAE of only 0.9 kcal/mol, with a maximum error of 2.2 kcal/mol (Table 11). For all 11 reactions, the AAE is 1.2 kcal/mol with PBE-D2/BS1,PCM, with a maximum error of 2.6 kcal/mol (Table 11). BS2 corrections provide insignificant effects, changing the average error by ±0.0 to 0.2 kcal/mol for most of the functionals. The SMD model was tested on seven reactions and appears to perform significantly worse than PCM but still shows a dominant preference for PBE-D type functionals. Based on these results, PBE-D2/BS1,PCM is recommended for iridium-mediated chemistry, without any corrections to the free energies, except SS and CP corrections for association or dissociation steps, i.e., steps where the number of moles change. This protocol should allow for reliable discrimination between mechanistic proposals that differ in energy by a few kcal/mol.

Enthalpy and Entropy. For the reactions **C**, **J**, and **K**, the experimental enthalpies and entropies are known (Schemes 1 and 6).[28,29,33] For each of these, we have analyzed the errors in the computed entropies and enthalpies at the PBE-D2/BS1,PCM level to evaluate which of these contributes more to the errors in free energies (Table 12). Also, the effect of entropy modifications is considered.

For reaction **C**, the enthalpy error is +4.9 kcal/mol, and the entropy error is +13.5 e.u., which equals −3.9 kcal/mol at 288 K. The reasonable ΔG error at this level (+1.0 kcal/mol, Table 12) thus appears to originate from a favorable error cancelation. If the raw entropy is halved (Singleton modification[56]), then the ΔG error increases to +1.7 kcal/mol (Table 12).

For reaction **J**, the enthalpy error is −5.0 kcal/mol, and the entropy error is −7.8 e.u, which equals +2.4 kcal/mol at 298 K (Table 12). The enthalpy and entropy errors partially cancel out, resulting in a ΔG

Table 11. Deviation from Experiment ($\Delta G_{computed} - \Delta G_{experimental}$, kcal/mol) for Reactions A−K and Average Absolute Errors (AAEs)[a,b]

reaction	B3LYP	B3LYP-D2	B3LYP-D3	B3LYP-D3BJ	PBE0	PBE0-D3	PBE	PBE-D2	PBE-D3	PBE-D3BJ	M06L	M06L-D3	M11L
A	+3.2	+1.9	+1.6	F[c]	+0.5	+0.6	+0.3	−0.1	−0.1	−0.5	−0.3	−0.2	+0.8
B	+3.9	+3.7	+3.4	F[c]	+3.0	+2.6	+1.2	+2.2	+2.0	+1.9	+1.7	+1.4	+2.9
C	+2.7	+7.4	+4.4	+4.4	+1.6	+2.6	−2.3	+1.0	−1.6	−1.8	+4.7	+4.7	+5.7
D	+1.2	+0.9	+1.2	+1.6	+1.5	+1.9	+1.4	+0.6	+1.5	+1.5	+1.7	+1.6	+2.0
E	−0.5	−1.8	−2.0	F[c]	−0.5	−1.6	−1.4	−1.7	−0.2	−1.3	−2.0	−1.5	−1.6
F	+0.5	+0.1	−0.2	−0.3	+2.1	−0.2	F[c]	−0.7	+0.0	+0.7	−1.7	−2.2	−1.4
G	−12.3	+1.0	−3.8	F[c]	−12.2	−4.9	−10.7	−1.4	−5.0	−6.6	F[c]	F[c]	−11.5
H	+1.6	−3.4	−2.0	F[c]	+1.6	−0.8	+4.1	−0.2	+1.1	+2.0	−2.1	−2.4	−1.4
I	−9.5	−0.9	−1.6	F[c]	−2.5	+2.4	−5.4	+0.2	+0.8	0.0	+2.6	+4.2	−2.4
J	+12.6	+0.3	+0.9	−1.3	+6.5	−1.1	+5.2	−2.6	+0.7	−1.1	+1.4	+0.2	+1.1
K	+11.5	+6.7	+6.8	+5.8	+5.3	+2.5	+6.3	+2.6	+3.3	+2.1	+6.6	+6.3	+13.7
$AAE_{BS1,PCM,11}$[d]	5.4	2.6	2.5	2.7	3.4	1.9	3.8	**1.2**	1.5	1.8	2.5	2.5	4.0
$[AAE_{BS1,PCM,9}]$[e]	[3.9]	[2.3]	[2.2]	[2.1]	[2.8]	[2.0]	[3.4]	[**0.9**]	[1.4]	[1.8]	[2.1]	[2.3]	[3.3]
Other Protocols													
$AAE_{BS2,PCM//BS1,PCM,11}$[d]	5.5	2.4	2.4	2.8	3.5	2.2	3.6	1.6	1.8	2.0	2.1	2.3	4.2
$AAE_{BS1,SMD,7}$[f]	8.1	5.1	5.2	6.1	5.0	2.9	4.7	2.6	2.5	2.6	4.7	5.0	5.1

[a]BS1,PCM for **A**-**I**, BS1,PCM+SS+CP for **J**-**K**. [b]AAEs shown for BS1,PCM; BS2,PCM//BS1,PCM; and BS1,SMD (including CP and SS for reaction **J** and **K**). [c]Fails, unable to converge to correct state. [d]AAE based on 11 reactions (**A**−**K**) except B3-D3BJ (**C**, **D**, **F**, **J**, **K**), PBE (**A**−**E**, **G**−**K**), M06L and M06L-D3 (**A**−**F**, **H**−**K**). [e]AAE based on 9 reactions (**A**−**I**) except B3-D3BJ (**C**, **D**, **F**), PBE (**A**−**E**, **G**−**I**), M06L and M06L-D3 (**A**−**F**, **H**, **I**). [f]AAE based on 7 reactions (**A**, **C**, **D**, **F**, **I**, **J**, **K**) except B3LYP (**C**, **D**, **I**, **J**), B3LYP-D2, B3LYP-D3, M06L-D3 (**A**, **C**, **D**, **I**-**K**), B3LYP-D3BJ (**A**, **I**, **K**), and M11L (**C**, **D**, **I**).

DOI: 10.1021/acs.organomet.6b00377
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Table 12. PBE-D2,PCM errors (δ) on Enthalpies (H), Entropies (S) and Free Energies (G) for reactions C, J, and K

reaction	δH (kcal/mol)	δS (e.u.)	$-T_{exp} \times \delta S$ (kcal/mol)	δG (kcal/mol)
		Raw Values[a]		
C	+4.9	+13.5	−3.9	+1.0
J	−5.0	−7.8	+2.4	−2.6
K	+2.4	−0.9	+0.2	+2.6
average $\lvert\delta\rvert$	4.1	7.4	2.2	2.1
		Values with Martin Entropy Modification[b]		
C	+4.9	+13.5	−3.9	+1.0
J	−5.0	+3.0	−0.9	−5.8
K	+2.4	+10.7	−2.3	+0.1
average $\lvert\delta\rvert$	4.1	9.1	2.4	2.3
		Values with Singleton Entropy Modification[c]		
C	+4.9	+11.0	−3.2	+1.7
J	−5.0	+12.3	−3.7	−8.6
K	+2.4	+11.4	−2.4	+0.0
average $\lvert\delta\rvert$	4.1	11.6	3.1	3.5

[a]BS1,PCM for **C** and BS1,PCM+SS+CP for **J** and **K**. For **J** and **K**, δH includes CP, δS includes SS conversion ($[R \times \ln(24.5)] = 6.4$ e.u. at 298 K, $[R \times \ln(17.5)] = 5.7$ e.u. at 213 K). [b]Entropies computed with $P = 235$ for **C**, $P = 229$ for **J**, $P = 334$ for **K**.[57] [c]Raw entropies multiplied by 0.5 (prior to SS conversion).[56]

error of −2.6 kcal/mol (Table 12). Hence, modifications to the entropy of reaction **J** make the ΔG error worse (−5.8 and −8.6 kcal/mol for the Martin and Singleton modifications, respectively, Table 12).

For reaction **K**, the enthalpy error is +2.4 kcal/mol, and the entropy error is −0.9 e.u, which equals +0.2 kcal/mol at 213 K (Table 12). The errors do not cancel out, and the ΔG error becomes +2.6 kcal/mol. The Martin and Singleton entropy modifications both increase the entropy error by ∼10 e.u. (Table 12), which ironically cancels out the enthalpy error and leads to excellent ΔG values, with errors of 0.1 and 0.0 kcal/mol, respectively (Table 12).

The three examples evaluated here allow for several tentative conclusions. First, the errors of computed enthalpies appear to be significantly larger than those of entropies. This is in contrast to widespread assumptions but is in line with Plata and Singleton's recent conclusions.[56] Second, entropy modifications (as proposed by Martin[57] or Singleton[56]) either have little effect on entropies or lead to significantly increased errors (Table 12). Third, the effect of these entropy modifications on the free energies is random and depends on the sign and the magnitude of the enthalpy error. Based on these results, there is no foundation to recommend entropy modifications when computing entropies or free energies of iridium-mediated transformations.

CONCLUSIONS

Experimental research on iridium-mediated reactions is often combined with computational studies in order to gain insights into the mechanistic details. Such knowledge can be employed to predict modifications that might improve the performance of a given system.[3] However, the accuracy of theoretical results can vary widely, and the number of putative corrections to be included is large,[56] making it difficult to decide on a computational protocol that is adequate. Although DFT benchmarks on organometallic systems have been reported, they often include very different catalysts (involving different metals)[9,14] or focus on a single property only.[11,19−21,49]

Here we have explicitly chosen 11 transformations in solution corresponding to typical reaction steps encountered in iridium-mediated chemistry (bond formation, isomerization, and ligand exchange or association, Scheme 2). Thirteen DFT combinations (B3LYP, B3LYP-D2, B3LYP-D3, B3LYP-D3BJ, PBE, PBE-D2, PBE-D3, PBE-D3BJ, PBE0, PBE0-D3, M06L, M06L-D3, and M11L) were evaluated with respect to energies and prediction of experimental trends. Full models were employed and geometries were optimized at each level, including a solvent model. Best results are obtained for PBE-D2 (AAE = 1.2 kcal/mol, BS1,PCM), followed by PBE-D3, PBE-D3BJ, and PBE0-D3 (AAEs of 1.5 to 1.9 kcal/mol, Table 11). Functionals lacking dispersion corrections (B3LYP, PBE, and PBE0) and M11L provide poorest results (AAEs of 3.4 to 5.4 kcal/mol) and are not recommended. M06L and B3LYP-D type functionals provide reasonable results (AAEs of ∼2.5 kcal/mol), but their error is twice as large as that of PBE-D2.

A number of putative corrections were evaluated, but the majority of these either have no effect or increase errors in free energies: Big basis set corrections do not improve results, and the triple-ζ basis set BS1 (ECP + double-ζ on Ir) appears fully adequate. Scaling of frequencies has no effect for the two cases where it was evaluated. Corrections for multistructural effects were evaluated for reaction **G**, where they were found to be small (−0.26 kcal/mol) despite the large number of low-lying conformations. Counterpoise corrections can be large (several kcal/mol) and are recommended to be included on the basis of the results for reaction **J**. Entropy modifications employing the Singleton[56] scheme, involving halving of the raw entropy, can be very large (>6 kcal/mol) but do not improve the entropies (Table 12) or the average ΔG error (Table S2). Entropy modifications according to Martin,[57] involving inclusion of an artificial pressure term, only affect reactions were the number of moles change, where they can amount to several kcal/mol. Although they improve errors in free energies for one reaction (**K**), their effect appears random and is dependent on the sign of the enthalpy error (Table 12). The Martin modification does not improve agreements with experimental entropies (Table 12). On basis of the results obtained here, inclusion of the Martin or Singelton entropy modifications in free energy calculations of iridium-systems is not recommended.

The most accurate computational protocol identified here for computing free energies of iridium-catalyzed reactions in solution, PBE-D2/BS1,PCM, is simple to apply and does not include any corrections for reactions with a constant number of moles. For association and dissocation reactions only, a standard state conversion (involving addition of a constant) is required, and it is recommended to also include a counterpoise correction (which requires one additional calculation). This protocol shows excellent average errors of 1.2 kcal/mol for all reaction types (maximum error of 2.6 kcal/mol), allowing for reliable discrimination between different reaction pathways. The benchmark set studied here includes diverse types of iridium complexes; however, it should be noted that the majority are formally pincer complexes. Therefore, it cannot be excluded that for ligand types deviating significantly from those studied here different results might be obtained. Furthermore, our evaluation shows that the very good results obtained for free energies at the PBE-D2/BS1,PCM level might be due to favorable cancellations of larger enthalpy and entropy errors (Table 12). Hence, this computational protocol is only recommended for free energies and not for computations of enthalpies or entropies alone. The results shown here make it clear that future efforts for improving DFT free energies require balanced correction efforts that will improve both entropies and enthalpies.

DOI: 10.1021/acs.organomet.6b00377
Organometallics 2016, 35, 3795−3807

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.6b00377.

Conformations evaluated in reaction **G**, evaluation of Singleton entropy modifications and sample inputs (PDF)

Coordinates for all iridium-complexes and the free amine in reaction **H**, optimized at the BS1,PCM level (XYZ)

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Notes

The author declares no competing financial interest.

■ ACKNOWLEDGMENTS

This work has been supported by the Research Council of Norway through a FRIPRO grant (No. 231706/F20) to K.H.H., through a Centre of Excellence Grant (No. 179568/V30) and by Notur - The Norwegian Metacenter for Computational Science through a grant of computer time (No. nn9330k). The High Performance Computing group at UiT-The Artic University of Norway is gratefully acknowledged. I thank Dr. L. Frediani for fruitful discussions on entropy. I am also indebted to a reviewer of this paper for commenting on the temperature dependence of the dielectric constant.

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DOI: 10.1021/acs.organomet.6b00377
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(70) The protocol in ref 19 included basis set def2-TZVP, scaling of frequencies with functional dependent scaling factor, raising of low-lying frequencies to above 100 cm^{-1}, and computation of free energies in solution as $G°sol = G°(gas) + \Delta G°_S$, where $\Delta G°_S = \Delta G_{ENP} + G_{CDS} + \Delta G°_{conc} + \Delta G_{vib}$. ΔG_{vib} was computed as the change in vibrational free energy on passing from the gas-phase to solution (implying that both gas phase and solution geometries and vibrational frequencies are computed), $\Delta G_{ENP} + \Delta G_{CDS}$ are terms computed via SMD, and $\Delta G°_{conc}$ is the standard state conversion term.

DOI: 10.1021/acs.organomet.6b00377
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