Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 2023, **33**, 153–156

Mendeleev Communications

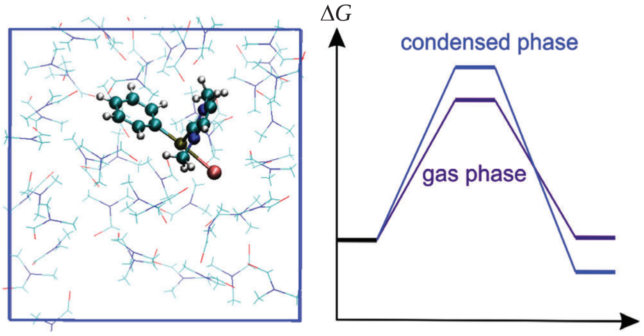
Metadynamics simulations of R–NHC reductive elimination in intermediate palladium complexes of cross-coupling and Mizoroki–Heck reactions

Alexander Yu. Kostyukovich, Evgeniy G. Gordeev and Valentine P. Ananikov*

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences,
119991 Moscow, Russian Federation. E-mail: val@ioc.ac.ru

DOI: 10.1016/j.mencom.2023.02.002

Exploring the free energy surface of the R–NHC coupling reaction in the key intermediates of the Mizoroki–Heck and cross-coupling catalytic cycles has been conducted by the methods of biased and unbiased molecular dynamics. Molecular dynamics simulations were carried out both in vacuum and in a polar solvent, with the following main observations on the influence of the media: (1) the solvent prevents the dissociation of the solvate ligand, so the R–NHC coupling proceeds in a four-coordination complex (rather than in a three-coordination one, as in the case of a gas-phase reaction); (2) in the condensed phase, the potential barrier of the reaction is significantly higher compared to the same process in vacuum (17.7 *vs*. 21.8 kcal mol^{-1}); (3) polar solvent stabilizes the R–NHC coupling product. The reaction in a polar medium is exergonic ($\Delta G = -3.9$ kcal mol^{-1}), in contrast to the in vacuum modeling, where the process is endergonic ($\Delta G = 0.4$ kcal mol^{-1}).



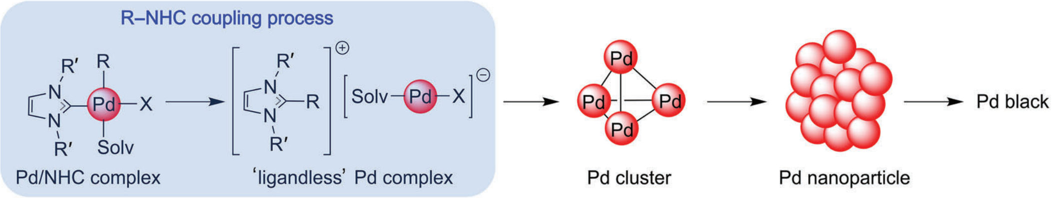
Keywords: R–NHC coupling, molecular dynamics, reaction mechanism, palladium catalysis, catalyst evolution, metadynamics.

The article is dedicated to Prof. Irina Beletskaya for the anniversary and her outstanding contribution on organometallic chemistry and catalysis.

Cross-coupling and Mizoroki–Heck reactions represent a very popular synthetic tool in laboratory practice and are used in industry.[1–3] Progress in the development of these synthetic protocols in recent years is associated with the design of universal catalytic systems.[4,5] In particular, palladium complexes with N-heterocyclic carbene (NHC) ligands have shown high efficiency in catalytic reactions for a wide range of substrates.[6] The design of universal Pd/NHC catalysts requires a deep understanding of the transformation processes of palladium complexes under catalytic reaction conditions. One of the key processes, leading to reversible debonding of the NHC auxiliary ligand from the metal coordination sphere, involves reductive elimination or R–NHC coupling. This reaction is of fundamental importance since it largely determines the structure of catalytically active centers (Scheme 1) and the interplay between molecular and nano-scale catalysis.[7]

Experimental *in situ* study of the evolution of catalytic systems is difficult to perform due to the low concentrations of catalytically active compounds in the reaction system and the short lifetime of the key intermediates of the catalytic cycle. In this regard, quantum chemical modeling is an excellent tool to address this challenge.[8] This is especially useful in the case of biased molecular dynamics methods for exploring free energy landscapes,[9] since they allow one to work with explicit models of condensed matter, which describe chemical processes in solution more reliably than continuum solvent models.[10]

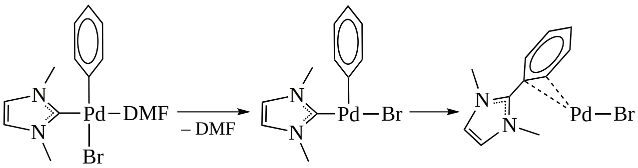
In the present work, for the first time, the process of R–NHC coupling in palladium complexes is evaluated by quantum molecular dynamics methods. The article consists of three parts. The first part presents the results of unbiased DFT molecular dynamics simulations of the Pd/NHC complex at various temperatures in vacuum. The second part is devoted to the



Scheme 1 R–NHC coupling reaction and further transformations of the catalytic system.

metadynamics analysis of the free energy surface (FES) of the R–NHC coupling reaction in vacuum. The third part presents the modeling results of this process in the condensed phase. This article is a continuation of previously performed static computational modeling of R–NHC reductive elimination and makes step forward towards a more realistic description of the process.[11]

Unbiased molecular dynamics simulations in vacuum. The DFT molecular dynamics (MD) method, applied without the use of a biased potential, has the advantage of being able to detect side processes accompanying the main reaction. The complex (IMe)Pd(Ph)(Br)(DMF) (**1**) was chosen as a model compound (Scheme 2), which is an intermediate of the Mizoroki–Heck and cross-coupling catalytic cycles.



1 **2** **3**

Scheme 2 Model R–NHC coupling reaction.

For relatively short trajectories available in DFT calculations and at low temperatures, it is only possible to observe ultrafast processes that have very low activation energies. In this regard, we performed a series of 13 MD simulations with a duration of 10 ps at elevated temperatures from 300 to 1500 K in steps of 100 K. However, the R–NHC coupling reaction was not observed in any of the trajectories during the specified time. Starting from a temperature of 1000 K and higher, dissociation of the solvate ligand occurs in complex **1**. Figure 1 shows the intervals (minimum and maximum values) within which the key interatomic distances change during each MD simulation. According to static calculations, the Ph–NHC interatomic distance in the transition state of the reductive elimination reaction (**TS**) is 1.77 Å.[11] The Ph–NHC distance did not decrease below 2 Å in any of the simulations performed [Figure 1(*a*)]. The values of Pd–NHC and Pd–Ph distances in **TS** are 1.95 and 2.08 Å, respectively, and are within the oscillation intervals in all calculated trajectories [Figures 1(*b*) and 1(*c*)]. As the temperature rises, there is a clear trend towards an increase in the oscillation intervals for Ph–NHC, Pd–NHC and Pd–Ph interatomic distances. For example, at 300 K, the Pd–NHC distance changes in the range of 1.83–2.10 Å, and at 1500 K, the range is 1.73–2.45 Å. The variability of the Pd–Ph bond values is higher than that of the Pd–NHC distance, which indicates a greater 'mobility' of the phenyl ligand. This agrees with the conclusion we made earlier on the basis of static calculations: the mechanism of R–NHC coupling proceeds according to the mechanism of migratory insertion of the phenyl group into the Pd–NHC bond.[11]

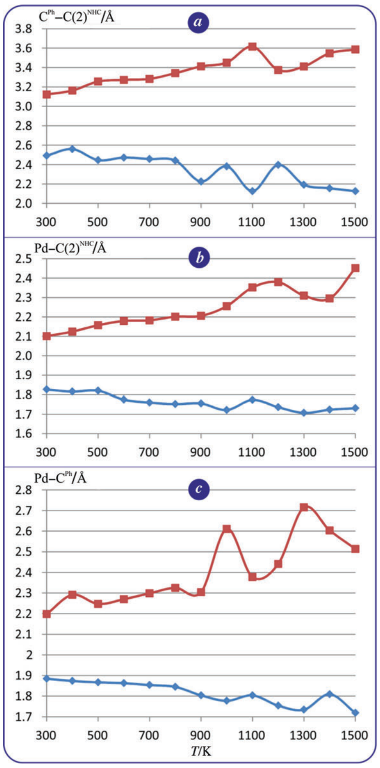


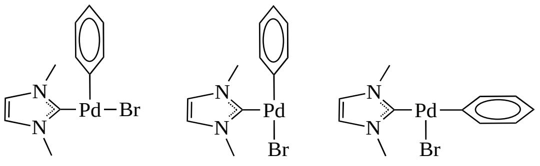
Figure 1 Dependence of (*a*) C^{Ph}–$C(2)^{NHC}$, (*b*) Pd–$C(2)^{NHC}$ and (*c*) Pd–C^{Ph} interatomic distances on temperature. The red curves represent the maximum interatomic distances recorded along the short MD trajectories; the blue curves correspond to the minimum interatomic distances.

Since the R–NHC coupling reaction did not proceed on short trajectories, a series of longer MD simulations was performed at a temperature of 1500 K (Table 1). In all cases, the dissociation of the solvate ligand is observed during the first 1–5 ps of the trajectories. Formed three-coordinated complex **2** has three isomeric structures (Scheme 3), in the most stable of which bromine and NHC ligands are in the *trans* position. In the most unstable isomer, the phenyl and NHC ligands have a *trans* arrangement. After dissociation of DMF and until the moment of R–NHC coupling, the complex rearranged many times from one isomeric structure to another. Most of the time, the system was in the **2a** isomeric configuration. Approximately 41% of the time, the complex existed as isomer **2b**, and only approximately 2% of the time, the system was in the form **2c**. The residence times in various isomeric forms for complex **2** correspond to free energies 0 (**2a**), 1.0 (**2b**) and 10.0 kcal mol^{-1} (**2c**) according to the formula $\Delta G = -RT\ln(K)$. The equilibrium constant K was calculated from the ratio of the total residence times T of isomers **2**. These averaged MD data are in good agreement with the static ΔG calculations (see Scheme 3): 0 (**2a**), 0.4 (**2b**) and 9.2 kcal mol^{-1} (**2c**). The occurrence of R–NHC coupling is possible in both

Table 1 Time characteristics (ps) of MD simulations carried out at a temperature of 1500 K.

Trajectory	t_1[a]	t_2[b]	*T*(**2a**)[c]	*T*(**2b**)	*T*(**2c**)
I	3	292	171	97	6
II	2	374	247	101	2
III	5	281	134	122	3
IV	1	142	61	72	0
V	4	301	132	136	9
VI	2	393	198	158	2
VII	5	125	74	34	3
Combined[d]	3	273	145	103	4

[a] Time of Pd–DMF bond breakage. [b] Time of the Ph–NHC coupling. [c] Total residence time of the system in the isomeric form **2a**. [d] Value averaged over all trajectories.



2a 0 **2b** 0.4 **2c** 9.2

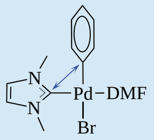
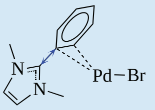
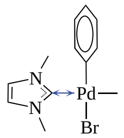
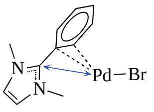
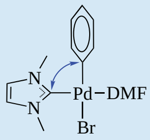
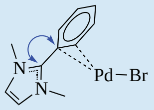
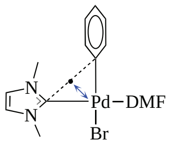
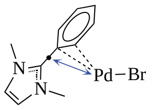
Scheme 3 Free energies of the isomeric structures of the three-coordinated complex **2**. The thermodynamic calculations were carried out for the temperature *T* = 1500 K; PBE1PBE-GD3BJ/Def2-TZVP level of theory.

isomers **2a** and **2b**. In five of the seven simulations performed, the product was formed from **2a** and only in two trajectories from complex **2b**. Atomic rearrangements during MD simulations of R–NHC coupling proceeded as follows: the phenyl group occupied the bridge position between the Pd atom and the NHC ligand, followed by elongation and breakage of the Pd–NHC bond. Thus, the dynamics of the process also confirm that the reaction mechanism corresponds to the insertion of a phenyl substituent in the Pd–NHC bond.

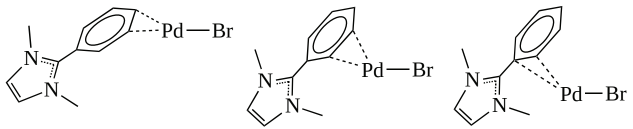
Metadynamics simulations in vacuum. To calculate the free activation energy and the free reaction energy of the R–NHC coupling with a more accurate estimate of the entropy, this process was modeled using the metadynamics method by the PBE-D3/def2SVP level of theory (Orca 5.0.1 software). The method of metadynamics makes it possible to estimate the potential barrier of a reaction by ‘filling’ the energy minima with an additional potential, which pushes the reacting system out of the minimum and allows one to overcome the potential barrier of the reaction. The biased potential effects on the selected collective variables and the impact of the potential on the collective variables should lead to the products of the process under study. The molecular system consisted of one molecule of the complex, placed in a spherical potential to prevent the scattering of fragments of the complex, which may be formed during the simulation. In the case of modeling R–NHC coupling in vacuum, two collective variables were chosen: CV1 is the distance between the carbon atom of the phenyl substituent and the carbon atom of the NHC ligand; CV2 is the distance between the palladium atom and the carbon atom of the NHC ligand (Table 2). During the simulation, a rapid detachment of the DMF molecule from the palladium atom at a temperature of 350 K was observed. The free energy of activation of R–NHC coupling obtained as a result of metadynamics modeling in the gas phase is 17.7 kcal mol^{-1}.

The R–NHC coupling product rearranges, resulting in the removal of the NHC ligand from the metal atom and the coordination of the metal atom to the phenyl substituent. In such a complex, haptotropic rearrangements can easily occur, associated with a change in the coordination of the phenyl group with the metal atom, that is, the binding of the palladium atom to different regions of the phenyl substituent (Scheme 4). The possibility of haptotropic rearrangements leads to the localization of three isomers of the reaction product on the free energy surface, which differ in the region of coordination of the phenyl group with the metal atom (Figure S14). Depending on the chosen isomer, the Gibbs energy of the reaction is 2.5 (**3c**), 1.7 (**3b**), and 0.4 kcal mol^{-1} (**3a**), while the isomer in which the NHC ligand is the most distant from the metal atom is characterized by the lowest energy (**3a**), and the highest energy is characteristic of the product in which the NHC ligand is located closest to a metal atom (**3c**).

Table 2 Collective variables (CVs) used in metadynamics calculations.

No.	Type	1	3
CV1	ID^a Ph–NHC		
CV2	ID Pd–NHC		
CV3	CN^b Ph–NHC		
CV4	distance (GC^c Ph–NHC)–Pd		

^{a} ID – Interatomic Distance. ^{b} CN – Coordination Number. ^{c} GC – Geometric Center.



3a **3b** **3c**

Scheme 4 Isomers of compound **3**.

Thus, in the absence of a solvent medium, the equilibrium is shifted towards the reagent, and to further refine the model, simulations were performed with an explicit solvent medium.

Metadynamics simulations in DMF media. The model for calculating R–NHC coupling in the condensed phase was complex **1** placed in a cube with a volume of (18.57 Å)^3 filled with DMF molecules (Figure 2, snapshot 1). The system contained 50 DMF molecules in addition to the solvate ligand. Periodic boundary conditions were used in all three directions to remove the phase boundary and exclude edge effects. As collective variables, the coordination number between the carbon atoms of the phenyl and NHC rings (CV3, see Table 2) and the distance between the geometric center of the Ph–NHC bond and the Pd atom (CV4) were taken. The well-tempered metadynamics simulation[12] was carried out at a bias temperature of 5000 K to overcome the potential barrier. Since the Pd–Br bond was prone to dissociation under these conditions, it was fixed by applying an external harmonic potential with a constant equal to 0.005 Hartree.

The mechanism of reductive elimination can be illustrated using selected snapshots of structures taken from the metadynamics sampling (Figure 2). The atomic rearrangement begins with the migration of the phenyl group to the bridging position between the palladium atom and the NHC ligand (snapshot 2). The Pd–Ph bond is then broken while the NHC bond to the metal center is maintained (snapshot 3). The R–NHC coupling product is formed when the palladium atom is coordinated to the π-bond of the phenyl group of the Ph–NHC moiety (snapshots 4–6 refer to different isomers of the reaction product).

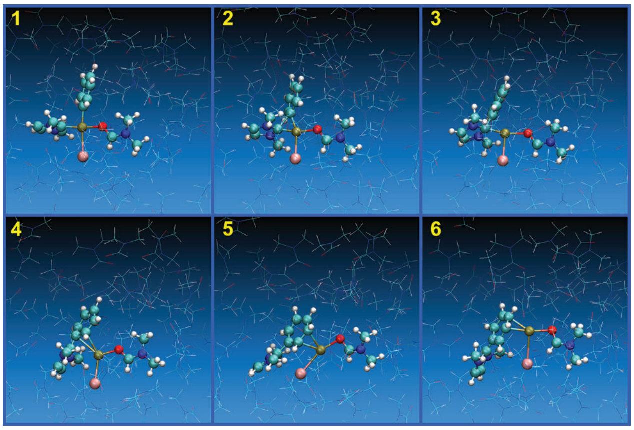


Figure 2 Selected snapshots of structures from the metadynamics sampling of R–NHC coupling.

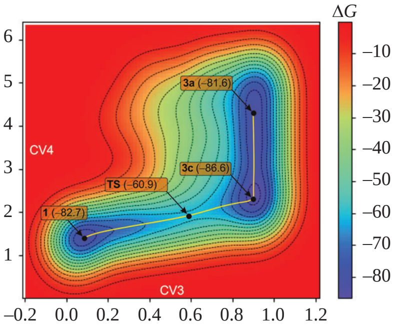


Figure 3 Two-dimensional free energy profile (kcal mol^{-1}) of the R–NHC coupling reaction.

Figure 3 shows a two-dimensional profile of the reconstructed FES. The activation energy of the R–NHC coupling is 21.8 kcal mol^{-1}, which is 4.1 kcal mol^{-1} higher than the potential barrier of this reaction calculated in vacuum. Only two minima of the three possible isomers of product were localized on FES, which belong to **3a** and **3c** (see Figure 3). According to the obtained data, the R–NHC coupling reaction in DMF is exergonic ($\Delta G = -3.9$ kcal mol^{-1}). Comparing the results of the metadynamics simulations in the gaseous and condensed phases, several differences can be identified. First, in DMF media, the solvate ligand remained coordinated to the palladium atom while the system was in the reagent valley. Three-coordinated structure **2** was not formed, which led to the absence of *cis*/*trans* isomerization of the reagent. Second, the reaction is thermodynamically allowed in a polar medium, which is associated with significant stabilization of product **3**. Third, the potential barrier of R–NHC coupling in the gas phase is lower than that in the condensed phase. The last point is apparently related to the fact that in the gas phase, the reaction proceeds in the three-coordination complex of palladium.

In summary, to evaluate the behavior of the key intermediates of Mizoroki–Heck and cross-coupling reactions, molecular dynamics modeling of the catalyst transforming process was carried out.[†] In vacuum, this process is preceded by the dissociation of the most weakly bound solvate ligand with the formation of a three-coordination complex (NHC)Pd(Ph)(Br), which is prone to dynamic isomerization. Reductive elimination occurs in two isomers with a probability ratio of 29/71%. The activation energy of the process was calculated to be 17.7 kcal mol^{-1}. The phenyl ligand of the (NHC)Pd(Ph)(Br) complex is more mobile than NHC, as evidenced by the greater range of Pd–Ph bond variability. This is an additional argument in favor of the mechanism of insertion of the phenyl ligand into the Pd–NHC bond. In the condensed media of DMF, the R–NHC coupling proceeds in a four-coordination complex with a higher potential barrier (21.8 kcal mol^{-1}), however, in contrast to the gas-phase reaction, is exergonic ($\Delta G = -3.9$ kcal mol^{-1}). Thus, there is significant stabilization of the reaction product in a polar solvent medium.

This work was supported by Russian Science Foundation (RSF grant 22-13-00247).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.02.002.

References

1 *The Mizoroki–Heck Reaction*, ed. M. Oestreich, Wiley, Chichester, 2009.
2 A. Biffis, P. Centomo, A. Del Zotto and M. Zecca, *Chem. Rev.*, 2018, **118**, 2249.
3 T. W. J. Cooper, I. B. Campbell and S. J. Macdonald, *Angew. Chem., Int. Ed.*, 2010, **49**, 8082.
4 S. L. Buchwald and D. Milstein, in *Ligand Design in Metal Chemistry: Reactivity and Catalysis*, eds. M. Stradiotto and R. J. Lundgren, John Wiley & Sons, 2016.
5 *Ligand Design in Metal Chemistry*, eds. M. Stradiotto and R. J. Lundgren, Wiley Online Library, 2016.
6 E. Peris, *Chem. Rev.*, 2017, **118**, 9988.
7 V. M. Chernyshev, E. A. Denisova, D. B. Eremin and V. P. Ananikov, *Chem. Sci.*, 2020, **11**, 6957.
8 D. Ess, L. Gagliardi and S. Hammes-Schiffer, *Chem. Rev.*, 2019, **119**, 6507.
9 A. Barducci, M. Bonomi and M. Parrinello, *Wiley Interdiscip. Rev.: Comput. Mol. Sci.*, 2011, **1**, 826.
10 G. Norjmaa, G. Ujaque and A. Lledós, *Top. Catal.*, 2022, **65**, 118.
11 A. Yu. Kostyukovich, E. G. Gordeev and V. P. Ananikov, *Mendeleev Commun.*, 2022, **32**, 571.
12 A. Barducci, G. Bussi and M. Parrinello, *Phys. Rev. Lett.*, 2008, **100**, 020603.
13 (*a*) I. S. Ufimtsev and T. J. Martinez, *J. Chem. Theory Comput.*, 2009, **5**, 2619; (*b*) A. V. Titov, I. S. Ufimtsev, N. Luehr and T. J. Martinez, *J. Chem. Theory Comput.*, 2013, **9**, 213.
14 P. J. Hay and R. W. Wadt, *J. Chem. Phys.*, 1985, **82**, 299.
15 (*a*) F. Neese, *Wiley Interdiscip. Rev.: Comput. Mol. Sci.*, 2012, **2**, 73; (*b*) F. Neese, *Wiley Interdiscip. Rev. Comput. Mol. Sci.*, 2018, **8**, e1327.
16 T. D. Kühne, M. Iannuzzi, M. Del Ben, V. V. Rybkin, P. Seewald, F. Stein, T. Laino, R. Z. Khaliullin, O. Schütt, F. Schiffmann, D. Golze, J. Wilhelm, S. Chulkov, M. H. Bani-Hashemian, V. Weber, U. Borštnik, M. Taillefumier, A. S. Jakobovits, A. Lazzaro, H. Pabst, T. Müller, R. Schade, M. Guidon, S. Andermatt, N. Holmberg, G. K. Schenter, A. Hehn, A. Bussy, F. Belleflamme, G. Tabacchi, A. Glöß, M. Lass, I. Bethune, C. J. Mundy, C. Plessl, M. Watkins, J. VandeVondele, M. Krack and J. Hutter, *J. Chem. Phys.*, 2020, **152**, 194103.
17 L. Martínez, R. Andrade, E. G. Birgin and J. M. Martínez, *J. Comput. Chem.*, 2009, **30**, 2157.
18 S. Grimme, C. Bannwarth and P. Shushkov, *J. Chem. Theory Comput.*, 2017, **13**, 1989.
19 W. Humphrey, A. Dalke and K. Schulten, *J. Mol. Graph.*, 1996, **14**, 33.

Received: 3rd November 2022; Com. 22/7039

[†] *Computational details*. Unbiased molecular dynamics calculations were performed by the TeraChem program for a single palladium complex in vacuum.[13] The molecular structure of the complex was preliminarily optimized by the PBE D3 method using the LanL2DZ basis set[14] for the palladium atom and the def2-SVP basis set for all other atoms. Furthermore, the optimized structure of the complex was used for molecular dynamics modeling at various temperatures and the same level of theory. For MD simulation, the NVT ensemble was used (Langevin thermostat; the Langevin damping time was 20.0 fs; timestep was 0.5 fs).

Metadynamics calculations in vacuum were performed using the Orca 5.0.1 software package.[15] Before MD simulation, the molecular structure of the complex was optimized by the RI PBE D3 def2-SVP def2/J method. The optimized structure was used as a starting point for MD simulations at the same level of theory using the NVT ensemble (Nosé–Hoover chain thermostat and temperature was 350 K). The value of the integration timestep was 0.5 fs. The high of the biased Gaussian hill potential was 0.239 kcal mol^{-1} (1 kJ mol^{-1}), the width of the Gaussian hill was 0.1 Å and the spawning frequency was 20 steps.

MD calculations in a condensed medium were carried out in CP2K version 7.1.[16] The model system was complex **1** placed in a medium consisting of 50 DMF molecules, which corresponds to a concentration of approximately 0.26 mol dm^{-3}. The model system was built in the Packmol program.[17] Then, the system was equilibrated by the XTB method[18] in the NPT_I ensemble (constant temperature and pressure using an isotropic cell) for 40 ps with a step of 1 fs. The resulting cell with a volume of (18.57 Å)^3 was equilibrated using the pure PBE functional in the NVT ensemble for 7 ps with a step of 1 fs. Productive metadynamics simulations were performed using the PBE functional with Grimme's dispersion correction. The DZVP-MOLOPT-SR-GTH basis set and corresponding GTH-PBE pseudopotentials were taken for Pd and atoms of NHC, Ph and Br ligands. The SZV-MOLOPT-SR-GTH basis set was taken for atoms of solvate molecules. Simulations were carried out in the NVT ensemble with a time step of 1 fs. The temperature was kept constant at 300 K by a Nosé–Hoover chain thermostat (timeconstant = 100 fs).

Visualization and analysis of molecular dynamics trajectories were performed using the VMD software package.[19]