Available online at www.sciencedirect.com

ScienceDirect

Mendeleev Commun., 2023, **33**, 252–254

Mendeleev Communications

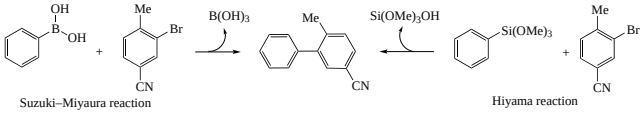
Theoretical study of formation mechanism for 4-methyl-3-phenylbenzonitrile in the course of the Hiyama and Suzuki–Miyaura reactions

Zeinab Ahmadvand and Mehdi Bayat*

Department of Inorganic Chemistry, Faculty of Chemistry, Bu-Ali Sina University, Hamedan 65178-38683, Iran

DOI: 10.1016/j.mencom.2023.02.033

A theoretical study on the mechanism of conversion of 3-bromo-4-methylbenzonitrile into 4-methyl-3-phenylbenzonitrile in the course of the Suzuki–Miyaura and Hiyama−Denmark cross-coupling reactions has been performed at Cam-B3LYP-D3 level of theory. With the use of Pd–NHC type complex as the catalyst, the Hiyama−Denmark cross-coupling is best suited for this process from both thermodynamic and kinetic aspects.



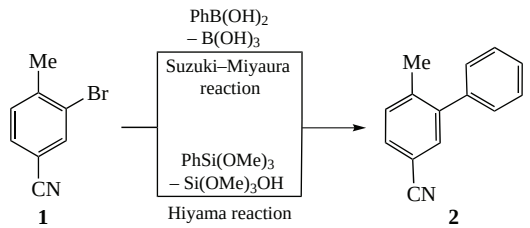
Keywords: cross-coupling, DFT study, Hiyama−Denmark reaction, Suzuki–Miyaura reaction, N-heterocyclic carbenes, mechanism.

Palladium PEPPSI-type (pyridine-enhanced precatalyst preparation stabilization and initiation) complexes containing a tiny N-heterocyclic carbene (NHC) ligand are the good catalyst precursors for the cross-coupling processes yielding a diverse spectrum of non-symmetric biaryls.[1] Compared to other Pd–NHC precursors, the PEPPSI complexes are easily accessible and treatable.[2–4] Various examples of PEPPSI complexes used in the Suzuki–Miyaura reaction demonstrate their exceptional catalytic activity and adaptability.[5–13] However, few investigations have been conducted on using PEPPSI complexes as catalysts in the Hiyama−Denmark cross-coupling.[14,15] These mechanisms are thought[16] to proceed in three basic steps: (1) oxidative addition of R^1X (organohalides) to Pd^0, (2) transmetallation between the resulting complex from the oxidative addition and R^2M (organometallic compounds) and (3) reductive elimination to give the final coupling product R^1–R^2. Recently,[17] we have reported a computational study on competition between the Suzuki–Miyaura and Hiyama reactions leading to benzofuran and quinoxaline derivatives. These results were in good agreement with the experimental data and showed that the Hiyama approach was more suitable for those particular compounds. Herein in continuation of our recent work, a theoretical attempt to analyze and to examine more admissible mechanisms for the transformation of 3-bromo-4-methylbenzonitrile **1** into 4-methyl-3-phenylbenzonitrile **2** was performed, in competition with the abovementioned methods.[17]

The molecular structures of the compounds investigated here, including reactants, transition states, intermediates, and products, were optimized in solution (ethylene glycol as the solvent) by Cam-B3LYP-D3 method in combination with the def2-SVP. Harmonic vibrational frequency measurements were performed at the same theoretical level to ensure that no reactants, intermediates, or products have imaginary frequencies, and that all the transition states have just one imaginary frequency. Single point energies were calculated using the IEF-PCM of the Cam-B3LYP-D3/def2-TZVP/Cam-B3LYP-D3/def2-SVP theoretical level based on the optimized structures produced throughout the solution procedure. The transition states are validated using the intrinsic reaction coordinate (IRC) analysis at the same theoretical level.

Recently, Pd–PEPPSI-type complex with NHC ligands was used as the catalyst for formation of a wide range of non-symmetrical biaryls in high yields.[1] In particular, the reactions between phenylboronic acid or trimethoxy(phenyl)silane and 2-bromotoluene in the course of the Hiyama or Suzuki–Miyaura reactions led to the same 2-phenyltoluene with 75 and 94% yields, respectively.[1] In view of this, with the DFT calculations we have studied herein the formation mechanism for 4-methyl-3-phenylbenzonitrile **2** from 3-bromo-4-methylbenzonitrile **1** and the abovementioned phenylating nucleophiles in ethylene glycol as solvent (Scheme 1).

Figure 1 depicts the profile of the mechanism for the **1** → **2** transformation *via* the Hiyama and Suzuki–Miyaura cross-coupling reactions, as well as their relative Gibbs energy in ethylene glycol. The initializing reactants, Pd^0–NHC and 3-bromo-4-methylbenzonitrile **1**, are situated at 0.0 kcal mol^{-1}. The reaction starts by the interaction of bromide **1** with NHC–Pd^0, which results in creation of Int1 (–9.54 kcal mol^{-1}). In this step, the oxidative addition of the C-Br bond of bromoarene **1** to NHC–Pd^0 results in the cleavage of the mentioned bond and the production of the C–Pd and Br–Pd bonds. This step involves passing *via* three-center type transition state, TS1 (–2.05 kcal mol^{-1}) and forming the Int2 (–41.05 kcal mol^{-1}). The creation of Int2 from initializing reactants is thought to be the common point of mechanisms for both Hiyama and Suzuki–



1 **2**

Scheme 1

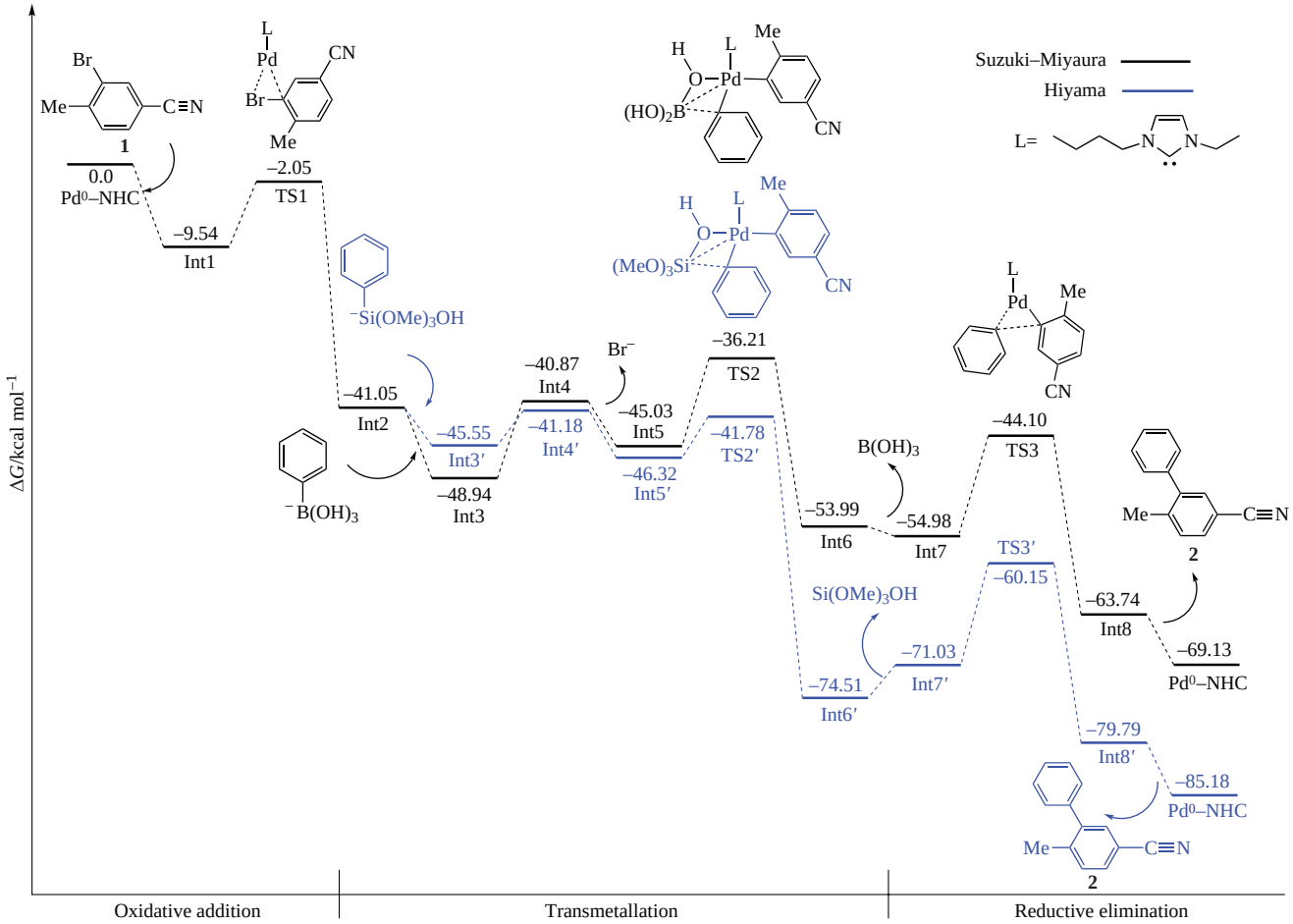


Figure 1 Energetic profile (Gibbs energy in kcal mol^{-1}) of reaction mechanism for formation of 4-methyl-3-phenylbenzonitrile **2** at the Cam-B3LYP-D3/def2-TZVP//Cam-B3LYP-D3/def2-SVP level of theory in ethylene glycol as solvent.

Miyaura reactions (see Figure 1). In the following step, the base first would strike boronic acid and form the anionic arylboronate, then it hits the NHC–Pd^0 complex and produces the Int3 (–48.94 kcal mol^{-1}). The agglomerated compound is generated by releasing Br$^-$ anion and then rearranging of the organoborate species in the Pd^0 center assigned with Int4 (–40.87 kcal mol^{-1}). This stage is followed by creation of Int5 (–45.03 kcal mol^{-1}). Phenyl migration from arylboronate to the metal center leads to the production of Int6 (–53.99 kcal mol^{-1}). This step is followed by formation of TS2 (–36.21 kcal mol^{-1}) which requires an activation barrier of 8.82 kcal mol^{-1} compared to Int5. As a result, the release of B(OH)$_3$ from Int6 aids in growth of Int7 (–54.98 kcal mol^{-1}). The final step (reductive elimination) leads to production of Int8 (–63.74 kcal mol^{-1}) by the formation of a C(Ar)–C(Ph) bond among the aryl moieties on Pd metal. This stage proceeds *via* the production of TS3 (–44.10 kcal mol^{-1}) and involves an activation barrier of 10.88 kcal mol^{-1} compared to Int7. When Int8 is formed, the NHC–Pd^0 (–69.13 kcal mol^{-1}) is introduced into the catalytic cycle, releasing the required biphenyl molecule (see Figure 1).

In the Hiyama−Denmark cross-coupling process (see Figure 1), Int3′ (–45.55 kcal mol^{-1}) is produced by reaction of organosilane species (*via* the O atom of OH group) with Int2′, which is 4.50 kcal mol^{-1} more stable than Int2. Following the release of Br$^-$ and subsequent rearrangement of the organosilane species at the Pd^0 center, an agglomerated compound is produced, which is ascribed to Int4′ (–41.18 kcal mol^{-1}) followed by production of Int5′ (–46.32 kcal mol^{-1}). Transfer of phenyl from silicon to metal center affords Int6′ (–74.51 kcal mol^{-1}). The transformation proceeds *via* the formation of TS2' (–41.78 kcal mol^{-1}) and requires the activation barrier of 4.54 kcal mol^{-1} compared to Int5′. Subsequently, Int7′ (–71.03 kcal mol^{-1}) is produced *via* the release of Si(OMe)$_3$OH. The last step (reductive elimination) is associated with creation of the C(Ar)–C(Ph) bond among aryl moieties on metal, as well as in the Suzuki–Miyaura reaction, which results in production of Int8′ (–79.79 kcal mol^{-1}). The process is followed by formation of TS3′ (–60.15 kcal mol^{-1}) and necessitates an activation barrier of 10.88 kcal mol^{-1} compared to Int7′. Following production of Int8′ and the release of the biaryl product, the NHC–Pd^0 (–85.18 kcal mol^{-1}) is introduced into the catalytic cycle (see Figure 1).

Thus, at the Cam-B3LYP-D3 level of theory, a competition between Suzuki–Miyaura and reaction mechanisms for the production of 4-methyl-3-phenylbenzonitrile **2** from two potential reactions has been explored. The results obtained are consistent with the experimental data showing that the Hiyama procedire is suitable thermodynamically and kinetically for the transformation in question.

The authors acknowledge the Bu-Ali Sina University Research Councils for financial support of this work.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.02.033.

References

1 M. Osińska, A. Gniewek and A. M. Trzeciak, *J. Mol. Catal. A: Chem.*, 2016, **418**–**419**, 9.
2 Y.-C. Lin, H.-H. Hsueh, S. Kanne, L.-K. Chang, F.-C. Liu, I. J. B. Lin, G.-H. Lee and S.-M. Peng, *Organometallics*, 2013, **32**, 3859.

3 A. Chartoire, X. Frogneux, A. Boreux, A. M. Z. Slawin and S. P. Nolan, *Organometallics*, 2012, **31**, 6947.
4 V. Colombel, F. Rombouts, D. Oehlrich and G. A. Molander, *J. Org. Chem.*, 2012, **77**, 2966.
5 R. D. J. Froese, C. Lombardi, M. Pompeo, R. P. Rucker and M. G. Organ, *Acc. Chem. Res.*, 2017, **50**, 2244.
6 J. L. Farmer, H. N. Hunter and M. G. Organ, *J. Am. Chem. Soc*., 2012, **134**, 17470.
7 P. Lei, G. Meng, Y. Ling, J. An and M. Szostak, *J. Org. Chem.*, 2017, **82**, 6638.
8 S. Shi, P. Lei and M. Szostak, *Organometallics*, 2017, **36**, 3784.
9 F. Rajabi and W. R. Thiel, *Adv. Synth. Catal.*, 2014, **356**, 1873.
10 H. Baier, A. Kelling and H.-J. Holdt, *Eur. J. Inorg. Chem.*, 2015, 1950.
11 J. J. Dunsford and K. J. Cavell, *Organometallics*, 2014, **33**, 2902.
12 L. Benhamou, C. Besnard and E. P. Kündig, *Organometallics*, 2014, **33**, 260.
13 S. Yaşar, Ç. Şahin, M. Arslan and İ. Özdemir, *J. Organomet. Chem.*, 2015, **776**, 107.
14 S. Modak, M. K. Gangwar, M. Nageswar Rao, M. Madasu, A. C. Kalita, V. Dorcet, M. A. Shejale, R. J. Butcher and P. Ghosh, *Dalton Trans.*, 2015, **44**, 17617.
15 T. Mitsui, M. Sugihara, Y. Tokoro and S.-I. Fukuzawa, *Tetrahedron*, 2015, **71**, 1509.
16 L. Xue and Z. Lin, *Chem. Soc. Rev.*, 2010, **39**, 1692.
17 Z. Ahmadvand and M. Bayat, *J. Mol. Liq.*, 2021, **325**, 115174.

Received: 28th September 2022; Com. 22/7007