▌ **Organic & Supramolecular Chemistry**

Experimental and Mechanistic Exploration of Zn-Catalyzed Sonogashira–type Cross-Coupling Reactions

Amrutha P. Thankachan,[a] Thoppilan G. Abi,*[b] Kallikkakam S. Sindhu,[a] and Gopinathan Anilkumar *[a, c]

Dedicated with great respect to Dr. Vijay Nair on the occasion of his 75th birthday

One of the most straightforward methods for the synthesis of disubstituted alkynes is the transition metal catalyzed Sonogashira-type cross-coupling reactions. Herein we report a detailed study of our recent research on the first Zn-catalyzed protocol for C(sp^2)–C(sp) cross-coupling reaction of aryl iodides with terminal alkynes. A wide range of functional groups were tolerated in the reaction and both functionally and structurally diverse diaryl acetylenes were prepared efficiently using this protocol. The reaction mechanism for the Zn-catalyzed Sonogashira-type coupling reaction was investigated by means of density functional theory (DFT) methods on a model system. The calculations were performed using hybrid Becke Perdew Functional (BPV86) in conjugation with LANL-2DZ basis set and found that the reaction pathway involves oxidative addition and reductive elimination mechanism.

Introduction

The transition metal catalyzed Sonogashira cross-coupling reaction has been one of the most powerful and straightforward strategies for the synthesis of diversely substituted acetylene moieties.[1] These acetylenic products are exceptionally important intermediates in organic synthesis as well as vital skeletons found in a range of natural products and bioactive molecules.[2] The original Sonogashira coupling procedures require the use of palladium-phosphine complexes and CuI co-catalyst in organic solvents using an amine base.[3] The first palladium-catalyzed Sonogashira reaction has been reported independently by the groups of Cassar,[4] Heck[5] and Sonogashira[6] in 1975. Among these methods the copper-palladium combination was used only in Sonogashira's report, which can also be considered as an extension of Castro's report of 1963.[7] But the addition of copper(I) salt under the reaction conditions may sometimes cause Glaser type oxidative homo-coupling of the terminal alkynes to yield the diynes.[8] Development of competent catalyst system and prevention of the homo-coupling are the major challenges faced by Sonogashira (C(sp^2)–C(sp)) cross-coupling reactions.

Aiming at the suppression of all these drawbacks, an impressive variety of modifications have been developed in the field of typical Sonogashira cross-coupling reactions. Among these the two promising protocols are performing the reaction in the absence of either palladium[9] or copper.[10] Other noteworthy modifications are carrying out the reactions at room temperature,[11] using aqueous solvents,[10f, 11a, 12] under aerobic atmosphere[10b, 10f, 13] and solvent free conditions.[9m] Fu introduced N-heterocyclic carbene (NHC) ligands into the field of Sonogashira reaction in 2003.[14] Later Hierso and co-workers reported the extreme catalytic ability of ferrocenyl triphosphine ligands in the Sonogashira reaction of a variety of aryl halides.[15] Recently Metin *et al.* demonstrated an efficient graphene oxide-supported Cu—Pd alloy nanoparticles-based catalyst for Sonogashira cross-coupling reactions under aerobic conditions.[16] Some specially designed reactants such as ynamides,[17] tetrazines[18] and functionalized cyclopropane halides[19] as well as metabolically encoded alkyne containing protein in *E. Coli*.[20] were also used for this purpose. Recently new protocols were introduced for bio-orthogonal transition metal catalyzed Sonogashira coupling with functionalized alkynes in protein level.[21] It posses great application in the treatment of breast cancer.[22] Yang and Wu developed the first and smooth method for the deacetonative Sonogashira cross-coupling of aryl substituted propargyl alcohols and aryl or heteroaryl chlorides.[23] Tobe and co-workers introduced a successful Pd-catalyzed route for the synthesis of poly-ethynyl substituted ar-

[a] A. P. Thankachan, K. S. Sindhu, Dr. G. Anilkumar
     School of Chemical Sciences
     Mahatma Gandhi University
     P. D. Hills P O, Kottayam, INDIA-68656
     Fax: +91-481-2731036
     E-mail: anilgi1@yahoo.com
[b] Dr. T. G. Abi
     Department of Chemistry
     Sacred Heart College
     Thevara, Kochi-682013, INDIA
     E-mail: abitg@shcollege.ac.in
[c] Dr. G. Anilkumar
     Advanced Molecular Materials Research Centre (AMMRC)
     Mahatma Gandhi University
     P. D. Hills, Kottayam, INDIA-686560
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omatic compounds.[24] Very recently Sun and Mei synthesized a pair of chiral alkyne appended Ru(II)-complexes *via* Sonogashira cross-coupling under microwave irradiation.[25] Among these chiral pair, the *leavo* isomer has been effectively used as a probe for targeting nuclei of living cell. Some other transition metals are also now utilized in this field.[26]

All these modifications were based upon the assumption of a hypothetical reaction mechanism, since very little is known about the mechanism of the transition metal catalyzed Sonogashira cross-coupling reactions. The recent progress in computational chemistry provided an insight into the mechanism of these reactions and the mechanistic pathway of some of the diversely modified Sonogashira reactions were explored recently.[27] Herein we report a detailed experimental study of our recent finding on the zinc-catalyzed C(sp²)-C(sp) Sonogashira-type cross-coupling reaction of terminal alkynes with aryl halides[28] and the first computational study of the proposed catalytic cycle using transition state theory. The purpose of this work is to evaluate the feasibility of the proposed mechanism for zinc-catalyzed Sonogashira-type reaction using experimental and theoretical analysis.
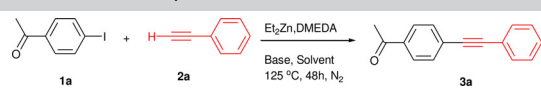
Results and Discussion

Experimental analysis: We initiated the optimization of reaction conditions by the coupling of 4-iodoacetophenone **1 a** with phenylacetylene **2 a** as model substrate in the presence of various ligands and bases in different solvents at 125 °C under nitrogen atmosphere (Table 1). The progress of the reaction
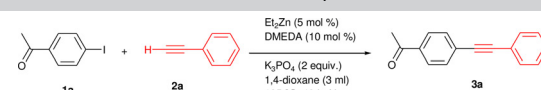
was monitored by thin layer chromatography (TLC). After 48 h of stirring, the solvent was removed under reduced pressure in a rotary evaporator and the product **3 a** was isolated from the crude reaction mixture by column chromatography on silicagel using EtOAc-hexane as the eluent.

The structure of the product **3 a** was established by nuclear magnetic resonance, mass spectrometric analyses and analytical methods, and all the spectral data were in good agreement with the reported values.[29]

To our delight, the reaction in the presence of N,N'-dimethylethylenediamine (DMEDA) as ligand gave the required product 1-(4-(Phenylethynyl)phenyl)ethanone **3 a** in 75 % yield (Table 1, entry 4). With *trans*-1,2-diaminocyclohexane, moderate but promising yield of 66 % was observed (Table 1, entry 3). When L-proline and ethylenediamine were used as ligands, very small amount of the target product **3 a** was obtained (Table 1, entries 1 and 2). The C2-bridged O—O ligands were found to be ineffective for this reaction protocol. Next, the effect of bases were evaluated. Among the different bases used, only K_3PO_4 gave the highest yield of 75 % (Table 1, entry 4). The bases such as K_2CO_3 and Cs_2CO_3 also worked but the yields were less compared to that of K_3PO_4 (Table 1, entries 5 and 6). The organic base Et_3N gave only trace amount of the product **3 a** which was detected in GCMS (Table 1, entry 7). Subsequently stronger bases such as NaO^tBu, KO^tBu, NaOH and KOH were also screened; but unfortunately no products were observed (Table 1, entries 8–11). Screening of solvents revealed that the suitable solvent for this zinc-catalyzed reaction was 1,4-dioxane (Table 1, entry 4). Performing the reaction in solvents such as *t*-BuOH, THF and CH_3CN afforded the target product in low yields. (Table 1, entries 13–16). Polar solvents such as DMF, DMSO and NMP showed no effect on the reaction (Table 1, entries 17–19). After these optimization studies, we conducted a set of control experiments to find out the control of individual additives in the reaction and the results are summarized in Table 2.

Table 1. Optimization of reaction conditions[a]

Entry	Base	Solvent (3 ml)	Yield (%)[b]
1[c]	K_3PO_4	1,4-dioxane	8
2[d]	K_3PO_4	1,4-dioxane	12
3[e]	K_3PO_4	1,4-dioxane	66
4	K_3PO_4	1,4-dioxane	75
5	K_2CO_3	1,4-dioxane	60
6	Cs_2CO_3	1,4-dioxane	35
7	Et_3N	1,4-dioxane	Trace
8	NaO^tBu	1,4-dioxane	nd[f]
9	KO^tBu	1,4-dioxane	nd
10		1,4-dioxane	nd
11	NaOH	1,4-dioxane	nd
12	KOH	DME	44
13	K_3PO_4	THF	38
14	K_3PO_4	Toluene	Trace
15	K_3PO_4	^tBuOH	30
16	K_3PO_4	^tBuOH	20
17	K_3PO_4	DMF	nd
18	K_3PO_4	DMSO	nd
19	K_3PO_4	NMP	nd

[a] Reaction conditions: phenyl acetylene (1.0 mmol), 4-iodoacetophenone (1.1 mmol), base (2 equiv.), Et_2Zn (5 mol %), Ligand (10 mol %), solvent (3 ml), 125 °C. [b] Isolated yield, [c] L-proline was used as ligand, [d] ethylenediamine was used as ligand, [e] *trans*-1,2-diaminocyclohexane was used as ligand, [f] Not detected.

Table 2. Control experiments

Entry	K_3PO_4 (2 equiv.)	Et_2Zn (5 mol%)	DMEDA (10 mol%)	Yield (%)[a]
1	✓	✓	✓	75
2	–	✓	✓	nd[b]
3	1 equiv.	✓	✓	52
4	✓	–	✓	18
5	✓	✓	–	34
6	✓	–	–	nd
7	✓	✓	5 mol %	28
8	✓	2 mol %	4 mol %	43
9[c]	✓	✓	✓	Trace
10[d]	✓	✓	✓	40
11[e]	✓	✓	✓	72

[a] Isolated yield, [b] not detected, [c] Absence of N_2 atmosphere, [d] Temperature was 80 °C, [e] The reaction was done in presence of TEMPO.

First we investigated the ideal stoichiometry of the base. In the absence of the base, no product was detected and on decreasing its equivalence, the yield of **3a** also get decreased (Table 2, entries 2–3). Subsequently the reactions were performed either in the absence of Et_2Zn or DMEDA. In the absence of Et_2Zn, the required product was obtained only in 18% yield, while in the absence of DMEDA, 34% of the target product **3a** was detected (Table 2, entries 4–5). It is worth underlining that in the absence of both Et_2Zn and DMEDA, no reaction took place and the starting materials were recovered intact (Table 2, entry 6). Performing the reaction in 1:1 combination of Et_2Zn and DMEDA resulted in low yield of the product (Table 2, entry 7). Similarly with lower catalyst loading, the yield also decreased (Table 2, entry 8). Repeating the reaction in air or at low temperature, the yield also get lowered (Table 2, entries 9–10). Finally the involvement of radicals in the reaction path way was analyzed by performing the reaction in the presence of TEMPO which gave the expected product with 72% yield (Table 2, entry 11). We also analyzed the metal impurities in Et_2Zn by using ICP-MASS spectrometry, which showed that the metal salt contained only 66.22 ppm of Zn. Other trace metal impurities were found below the detection levels. Gratifyingly, the optimized condition for the zinc-catalyzed Sonogahira-type cross-coupling reaction was found to be 5 mol % of Et_2Zn, 10 mol % of DMEDA, and 2 equiv of K_3PO_4 at 125 °C in 1,4-dioxane under nitrogen atmosphere (Table 2, entry 1).

Next, with these optimized reaction conditions in hand, the scope and generality of the reaction was investigated with a range of alkynes and aryl halide derivatives. First we checked the substrate group compatibility of various aryl halides with phenyl acetylene. Aryl iodide with electron withdrawing substituent at *p*-position afforded the respective diaryl acetylenes in good yields (Table 3, entries 1 and 4). The electron rich aryl iodides such as 4-methoxy and 4-methyl substituted moieties gave moderate yield of the required product (Table 3, entries 5 and 10). The coupling of 4-iodo aniline and phenyl acetylene resulted in the corresponding product **3e** with 79% yield (Table 3, entry 9). Gratifyingly, the protocol worked well in the case of reaction between unsubstituted aryl iodide and phenyl acetylene, affording the corresponding product in comparatively good yield (Table 3, entry 7). The aryl iodides with sterically hindered *o*-methyl substituent generated small amount of product **3i**, while similar reaction using *o*-iodo aniline as the reactant gave the respective product in good yield (Table 3, entries 14 and 15). Apart from *ortho*-substituted aryl iodides, the *meta*-substituted derivatives also worked smoothly (Table 3, entry 13). Under the optimized conditions, the coupling of *m*-xylene derivative afforded the corresponding diaryl acetylene **3g** in good yield (Table 3, entry 12). To our delight, the present zinc-catalyzed Sonogashira type cross-coupling reaction proceeded well in the case of heterocyclic iodides also (Table 3, entry 16). Apart from substituted aryl iodides, aryl bromides also underwent coupling with phenyl acetylene affording the required products, *albeit* in low yields (Table 3, entries 2, 6, 8 and 11).

We then extended the protocol for the coupling between substituted terminal alkynes and aryl iodides. From Table 4, it is

Table 3. Substrate scope of zinc-catalyzed Sonogashira type cross-coupling reactions for substituted aryl halides.

Entry	Aryl halide	Product	Yield (%)[a]
1		**3a**	75
2		**3a**	23
3		**3a**	0
4		**3b**	66
5		**3c**	45
6		**3c**	12
7		**3d**	54
8		**3d**	20
9			79
10		**3f**	52
11		**3f**	21
12		**3g**	78
13		**3h**	66
14		**3i**	23
15[b]		**3j**	59
16		**3k**	73

[a] Isolated yield, [b] 34% of cyclized product was also obtained.

clear that the newly introduced methodology is tolerant towards a number of terminal alkynes. The phenyl acetylene bearing electron-rich methyl and methoxy groups at the *para*-position afforded the product in moderate yields (Table 4, entries 1 and 2). Notably, under the optimized conditions, we obtained the *para*-disubstituted diaryl alkynes in 54%, 61% and 70% yields when reacted between electron rich *para*-substituted aryl iodides and aryl acetylenes. (Table 4, entries 3, 5 and 6) It is noteworthy that the *meta*-substituted aryl iodides coupled smoothly with substituted terminal alkynes affording the corresponding products in good yields (Table 4, entries 7). Both heterocyclic iodide and heterocyclic alkyne reacted well under the reaction conditions and produced the respective diaryl alkynes in comparatively good yields (Table 4, entries 8 and 9).

In order to get an insight into the reaction mechanism, we carried out some computational analysis and found that the re-

Table 4. Substrate scope of zinc-catalyzed Sonogashira type cross-coupling reactions of substituted terminal alkynes with aryl halides.

X = Br, I
R[1] = 4-NO$_2$, 4-NH$_2$, 3-CF$_3$, 4-CH$_3$, 2-CH$_3$..
R[2] = aryl

Entry	Aryl halide	Alkyne	Product	Yield (%)[a]
1			3c	43
2			3f	48
3			3l	54
4			3l	24
5			3l	61
6			3m	70
7			3n	49
8			3o	53
9			3p	60

[a] Isolated yield

action pathway involves oxidative addition (OA) and reductive elimination (RE) mechanism.

Computational Calculations and Analysis: The recent progress in computational quantum calculations makes it a reliable method for the study of reaction mechanisms.[30] However, for describing the reaction mechanism; all possible reaction paths should be included. But, such a complete description is challenging because of the need to map out a multidimensional potential energy surface. Instead of using conventional methods of optimized point geometries reported earlier[31] here we employed a simplified approach, termed the transition state theory.[32] The mechanism of the Pd-catalyzed Sonogashira-type cross-coupling with aryl halides has been recently investigated using computational methods of TS optimization.[33] Here we report the first computational chemistry study of the catalytic cycle of the Zn-catalyzed Sonogashira-type cross-coupling reaction based on transition state theory with 4-iodoacetophenone and phenyl acetylene as model system which we used for the experimental optimization studies. We performed the studies using density functional theory (DFT) methods,[34] by determining the structures corresponding to reactant states, product states and transition states along the reaction pathway. All calculations were performed using the Gaussian 09 program package[35] with hybrid Becke Perdew Functional in combination with Vosco's correlation functions (BPV86)[36] and LANL-2DZ basis set.[37] We generated the structures corresponding to different states using gauss view software and subjected to geometry optimization. Transition state optimizations were

carried out using QST3 calculations.[38] Harmonic frequency analysis was carried out to find the structures corresponding to the minima or transition state geometry. For energy minimum geometry, the number of imaginary frequencies will be equal to zero and for a high energy transition state geometry, the number of imaginary frequencies (negative value of frequency) will be equal to one. The unscaled frequencies from vibrational analysis were also used to find the other stationary points on the potential energy surface (PES). Intrinsic reaction coordinate (IRC) analysis[39] was also carried out to confirm the credibility of the obtained transition state which connects reactants and products in both directions. Once the optimized gas phase point geometries were obtained, we incorporated the 1,4-dioxane solvent used in the experimental procedure by CPCM solvent model[40] to perform single point energy and frequency calculations. During the frequency calculation we set the temperature as 398 K in order to maintain the optimized reaction temperature and the corresponding thermal correction to Gibbs free energies is achieved. The Gibbs free energies obtained from these calculations were used to explain the reaction pathway and the feasibility of the reaction.

The two key steps in this catalytic cycle were found to be the oxidative addition (OA) and reductive elimination (RE) and these paths have been investigated carefully for the reaction involving a variety of substrates. The reported Gibbs free energies in solution involve thermal corrections to Gibbs free energy and solvation free energy corrections computed by singlet point CPCM calculations on gas-phase optimized geometries. We present two distinct energy profiles corresponding to oxidative addition (OA) and reductive elimination (RE) for the ease of analysis.

Previous studies suggested that Zn exists in different coordinated states. Zn (II) can form tetra coordinated complexes as observed in Zn-Carbonic anhydrase catalytic cycle.[41] The formation of tri coordinated Zn is also reported on treatment of bis(trimethyl (silyl)methyl)Zn with 2,4,6 tri-*tert*-butyl thiophenol in Et$_2$O.

The average coordinate bond length between metal and ligands in Zn complexes is found to be 2 to 2.75 Å.[42] Our results are also concordant with the previous reports and Zn is coordinated with 4 atoms/groups throughout the reaction path and the fourth coordination lies between 2.5 to 3.0 Å unit. The variation in bond lengths between Zn and its coordinated groups/atoms throughout the catalytic cycle is depicted in Table 5.

Oxidative Addition: Figures 1 and 2 depict the free energy profile and the pictorial representation of optimized geometries of oxidative addition process respectively. The geometries correspond to panel a, b and c in Figure 2 represents the reactant minima, transition state and product minima respectively. In order to obtain a simplified free energy profile, we choose reactant state as our reference state and fixed its Gibbs free energy as 0 k cal/mol. The crucial step involved in the oxidative addition reaction is the dissociation of C—I bond followed by the formation of C—Zn bond. The earlier reports suggested that the ligand exchange occurs during the oxidative addition process is a feasible process with low free energy barrier.[43] Here also, a low barrier height was observed for this cat-

Table 5. Variation of coordinate bond lengths between Zn and coordinated atoms in the reaction pathway. All bond lengths reported in Å units

State	Zn—N1	Zn—N2	Zn—C4(1a)	Zn-I	Zn—A A=O,C1-2a
Oxidative Addition					
Reactant	2.403	2.350			2.085 A=O
TS1	2.530	2.472	2.698	3.71	
Product	2.216	2.207	2.050	2.755	
Reductive Elimination					
Reactant	2.181	2.357	2.066	2.836	2.863 A≡C1-2a
TS1	2.256	2.168	2.073 Zn-C	2.833	2.622 A≡C1-2a
Intermediate1	2.177	2.264	2.074 Zn-C	3.021	2.941 A≡C1-2a
Product	2.232	2.239	2.018 Zn-O		
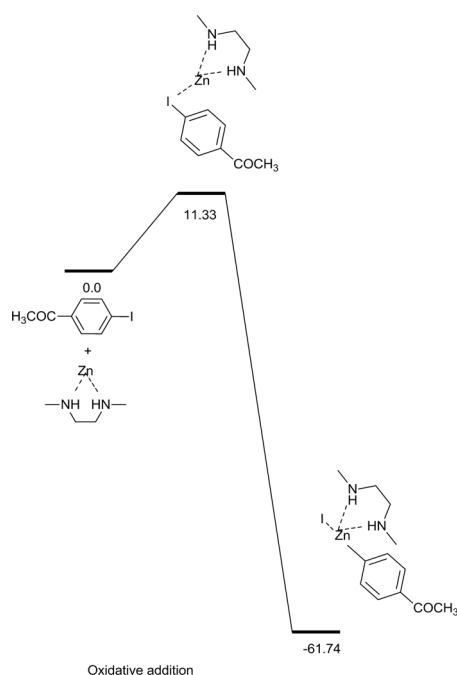
Figure 1. Free energy profile for the optimized geometries of oxidative addition process.
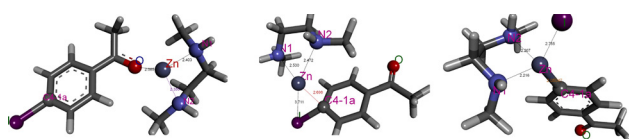
Figure 2. Pictorial representations of optimized geometries of oxidative addition process.

alytic cycle. The transition state TS1 had a Gibbs free energy of 11.3 kcal/mol which is quite higher than the reactant state involving the starting compounds. Moreover, a larger value of −61.74 kcal/mol was obtained as the Gibbs free energy of the reaction.

The reaction pathway involved the formation of a transition state where Zn is surrounded by two Nitrogen atoms of the ligand, C4 of 4-iodoacetophenone and the Iodine atom. The single imaginary frequency of this transition state indicated the increase of the C—I bond length (from 2.154 A to 2.224), and the decrease of C—Zn bond length to 2.698 Å. The stereochemistry of the reaction obtained from the optimized geometries depicted an inversion in the geometry from reactant to TS state with a stable C—Zn bond formation at a distance of 2.05 Å. The final product of the oxidative addition was obtained through the dissociation of the C—I bond followed by the formation of a tetra coordinated complex with Zn metal. In the tetra coordinated complex the longest and weakest bond corresponds to Zn—I bond with bond length 2.75 Å. The enthalpy change of oxidative addition was found to be −63.94 kcal/mol, which indicates the exergonic nature of the process.

The free energy profile and pictorial representation of reactant-TS2-Int1-product states involved in the reductive elimination process is shown in Figure 3 and 4 respectively. The path of reductive elimination was started with tetra coordinated oxidative addition product and potassium phenyl acetylene. The potassium phenyl acetylene involved in this process was expected to be obtained from K_3PO_4 and phenyl acetylene used in the synthetic procedure. The reactant minimum obtained from these starting compounds was a tetra coordinated Zn complex as shown in panel a of Figure 4. Zn has coordination with C4 of 4-iodo acetophenone at a bond distance of 2.07 Å and acetylenic carbon of phenyl acetylene at a bond length of 2.86 Å. The two nitrogen atoms of DMEDA are bonded to the Zn at bond distances of 2.18 and 2.36 Å units respectively. The occurrence of transition state of reductive elimination was confirmed by an imaginary frequency of vibration (-235.35 cm-1), which corresponds to a decrease of bond length between C4 of 4-iodoacetophenone and acetylenic carbon from 3.024 Å to 1.918 Å.

In the TS2 state, the Zn—C4—C≡ bond angle is 133.9 0 and a strong interaction was observed between coupling carbons present in different planes at a shorter bond distance. Another significant process in the reaction pathway was the formation of a minimum energy intermediate in between the TS2 and the coupling product. A slight decrease in Zn—C4—C≡ bond angle was observed in the intermediate 1 where it changes from 133.9 0 to 131.3 0. The subsequent elimination of KI led to a stable coupling product with a linear geometry with C—C≡C bond angle 179.6 0. And the Zn catalytic system was regenerated in the RE process. The occurrence of a stable intermediate and a slightly higher barrier than the oxidative addition are the noticeable aspects in the RE pathway. The barrier of 14.48 kcal/mol for RE process may be attributed to the reaction condition with a higher temperature of 398 K. The net Gibbs free energy of the reaction was found to be −33.55 kcal/mol and the net enthalpy change was 0.32 kcal/mol. The RE reaction pathway obtained from the TS optimization method is further confirmed by IRC analysis in forward and reverse direction from the transition state geometry.

The mechanism of cross coupling reaction involving the reaction pathways other than OA-RE pathways were also re-
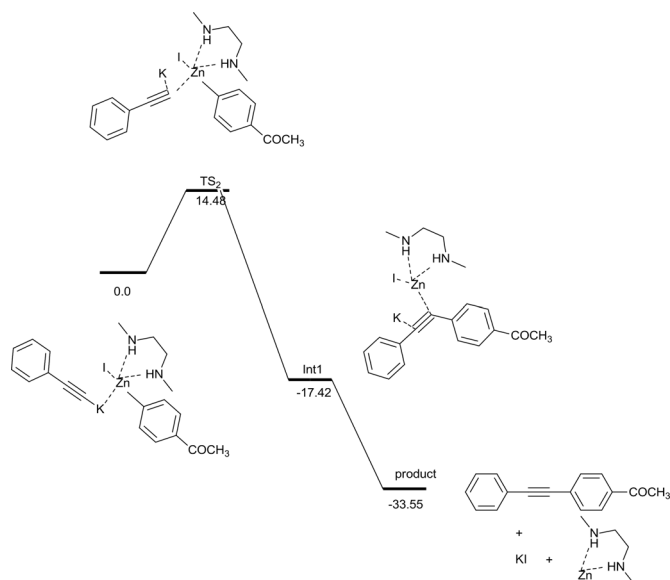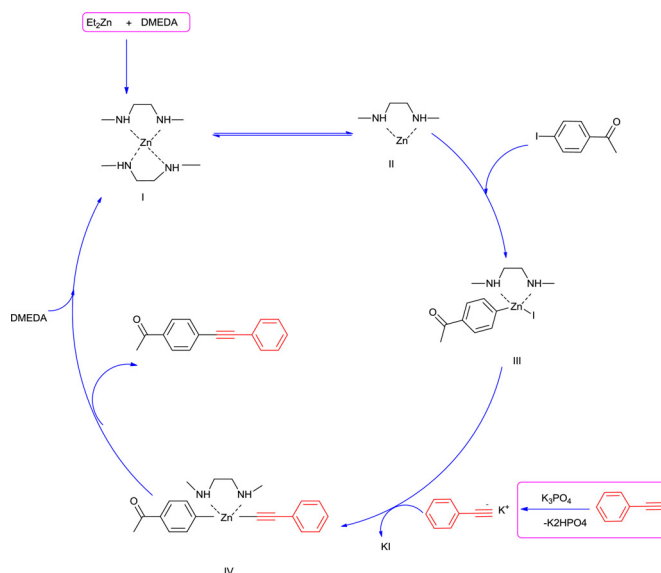
Figure 3. Free energy profile for optimized geometries of reductive elimination process.

Figure 4. Pictorial representation of optimized geometries of reductive elimination process.

Scheme 1. Proposed catalytic cycle.

ported in the literature. Some electron transfer or free radical mechanisms are suggested on the basis of electron donating ability of the ligand and nucleophile. The electronic structure and nature of transition metal, halides and base are very crucial in this regard. The chance of any free radical mechanism is ignored in the current study since a closed shell electronic calculation is maintained throughout the computational calculations and all the states involved in computational calculations are electronically singlet states. It strongly supports our experimental observation of performing the reaction in the presence of TEMPO as additive.

Based on the experimental observations and mechanistic studies, we present a catalytic cycle for the novel zinc-catalyzed Sonogashira-type cross-coupling reaction as shown below (Scheme 1).

Conclusions

In summary, we have presented the experimental and computational studies of Zn-catalyzed Sonogashira-type cross-coupling reaction and provided the detailed potential energy profiles of all mechanistic steps involved in this reaction. The cross-coupling reaction is actually preceded by an in situ generated Et_2Zn-DMEDA complex. Our protocol can effectively tolerate wide range of functional groups and can also be used for the synthesis of heterocyclic alkynes. The present method is efficient in terms yield, catalyst toxicity, reaction conditions and catalyst loading. This synthetic route excludes the utilization of both palladium and copper. The smoother conditions employed make this protocol a feasible alternative to the traditional Sonogahira cross-coupling reactions. We performed the mechanistic study through computational scheme of transition state optimization. A minimum energy path which proceeds through OA-RE mechanism is obtained from our calculations which are in correlation with previous theoretical studies.

Supporting Information

Experimental procedure and spectroscopic data for various compounds are available online as supporting information

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