ABSTRACT: The direct α-arylation of carbonyl compounds emerged over the last two decades as a straightforward method for the formation of C(sp³)–C(sp³) bonds. Mechanistic studies suggested a classical cross-coupling catalytic cycle. This consists of oxidative addition of the aryl halide (ArX) to the Pd(0)-catalyst, transmetallation of the Na- or K-enolate generated in situ, and subsequent reductive elimination. Even though the general reaction mechanism was thoroughly investigated, studies focusing on enantioselective variants of this transformation are rare. Here, the computational study of the [Pd(BINAP)]-catalyzed α-arylation of 2-methyltetralone with bromobenzene is reported. The whole reaction energy profile was computed and several mechanistic scenarios were investigated for the key steps of the reaction, which are the enolate transmetallation and the C–C bond-forming reductive elimination. Among the computed mechanisms, the reductive elimination from the C-bound enolate Pd complex was found to be the most favorable one, providing a good match with the stereoselectivity observed experimentally with different ligands and substrates. Detailed analysis of the stereodetermining transition structures allowed us to establish the origin of the reaction enantioselectivity.

INTRODUCTION

The first examples of direct, Pd-catalyzed α-arylation of carbonyl compounds with aryl halides were first reported by the groups of Buchwald and Hartwig in 1997. Great advances have been made in the field since then. Nowadays, carbonyl compounds ranging from ketones, aldehydes, esters, amides, and nitriles can be coupled with a plethora of aryl halides or pseudohalides with great efficiency. Hartwig and co-workers investigated the reaction mechanism in detail and showed that it follows the cross-coupling catalytic cycle depicted in Figure 1a. The reaction begins with the oxidative addition (OA) of the aryl halide ArX to the Pd(0)-catalyst. The resulting Ar-Pd-X species undergoes transmetallation (TM) with the Na- or K-enolate generated in situ by a suitable base (typically tBuONa or KHMDS). The enolate ligand can bind to the Pd center in three different modes, the C-bound enolate 1 being electronically more favored. The Pd-enolate connectivity is highly dependent on steric, and the O-bound enolate 2 becomes more favored as the hindrance of the ligand and the number of α substituents of the enolate increase. Finally, η³-bound enolates 3 (oxo-η³-allylic enolates) could form upon dissociation of one of the Pd ancillary ligands (Figure 1a). One of the key steps of the reaction is the C–C bond-forming reductive elimination (RE), which could occur via several pathways depicted in Figure 1b. Pathway A is the direct reductive elimination between the aryl C(sp³) and the alkyl C(sp³) of the C-bound enolate 1. B is the vinylogous reductive elimination from the O-bound enolate 2 with the C–C bond forming between the aryl C(sp³) and the alkenyl C(sp³). Pathway C is similar to mechanism A yet occurring from 3 with the enolate bound in a η³ mode. Determining experimentally the actual reductive elimination mechanism is not trivial as pathways A, B, and C could all take place starting from each one of the possible enolates 1–3 by tautomerization from the most stable to the most reactive intermediate prior to the RE step.

Despite the limited knowledge about the key C–C bond-forming step in this transformation, stereoselective variants were also developed. These allow the construction of benzylic stereocenters in the α-position with respect to a carbonyl moiety, supposedly via a stereodetermining RE step. However, in spite of these achievements, this research area still suffers many limitations. In this regard, the computational study of this reaction could greatly improve our understanding of its general mechanism by evaluation of the energetics of
acetals using a BINOL-based monophosphine ligand. The authors proposed a cyclic Pd/Josiphos-catalyzed arylation of silyl ketene acetals in good yields and selectivities.\(^\text{29}\) The authors described a transmetallation to give arylated products via a vinylogous mechanism.\(^\text{115}\) Therefore, the study of the enantioselective Pd-catalyzed arylation of silyl ketene acetals to give arylated products is a well-established transformation that is often used as a benchmark reaction for testing new catalytic systems.\(^\text{34}\)

In order to gain more insights into the reaction mechanism of the enantioselective Pd-catalyzed \(\alpha\)-arylation of carbonyl compounds, we performed a DFT study of the \([\text{Pd}((R)\text{-BINAP})]\) catalyzed coupling between \(2\)-methyltetralone \(4\text{a}\) and bromobenzene \(5\) to give \(6\text{a}\) (Figure 1c).\(^\text{17}\) The arylation of tetralones and indanones is a well-established transformation.\(^\text{34}\) However, because of post-catalytic steps, the arylation of silyl ketene acetals is dependent on the number of \(\alpha\)-substituents of the nucleophile.\(^\text{5,22}\) As \(\alpha\)-disubstituted carbonyl compounds favor the O-bound tautomer \(2\), one might hypothesize this preference to be translated at the TS level differently from previously studied systems.

**RESULTS AND DISCUSSION**

**General Reaction Mechanism.** Starting from \(\text{Pd}(0)\), \(\pi\)-coordination of bromobenzene \(5\) and subsequent OA into the C−Br bond lead to the irreversible formation of the intermediate 7 (Figure 2). The OA activation barrier is 8.26 kcal/mol. The subsequent TM step can occur by three different mechanisms: (i) bromide/enolate dissociative anion exchange, (ii) classical 4-membered cyclic transmetallation to give the O-bound Pd-enolate, and (iii) vinylogous 6-membered cyclic transmetallation to give the C-bound Pd-enolate (Figure 2). Because of the low polarity of toluene, the formation of a cationic complex upon bromide dissociation is highly unfavored (ca. 42 kcal/mol, see the Supporting Information). Thus, the TM must occur between 7 and the Na-enolate 8 via cyclic TSs, \(\text{TSTMCR}\) or \(\text{TSTMCS}\), Figure 2). which at the end of the catalytic cycle lead to the formation of the two enantimeric products (\(R\))-6a and (\(S\))-6a. Hence, evaluation of both the activation barrier \(\Delta G^\ddagger\text{TSTM}\) and the reaction Gibbs free energy \(\Delta G^\ddagger\text{TSTMCS}\) associated to the TM step is important. Depending on these values compared to the RE \(\Delta G^\ddagger\text{RE}\), the formation of the Pd-substituted stereocenter can be stereodetermining. The O-bound Pd-enolate forms with \(\Delta G^\ddagger\text{RE}\) = 17.03 kcal/mol via \(\text{TSTMCR}\) to give the intermediate 9 after the loss of NaBr. Formation of the C-bound enolates via \(\text{TSTMCR}\) and \(\text{TSTMCS}\) is much slower, with the enolate eventually leading to (\(S\))-6a being favored (\(\Delta G^\ddagger = 23.26\) and 20.42 kcal/mol, respectively). Additionally, the intermediate 9 was found to be energetically favored over the corresponding C-bound enolates (\(R\))-10 and (\(S\))-10 by ca. 8 kcal/mol. Upon transmetallation, \(\eta^1\)-oxo-allyl Pd-enolates can also be easily accessed from (\(R\))-10 and (\(S\))-10 (\(\Delta G^\ddagger = 5.9\) and 6.1 kcal/mol, respectively, not shown, see the Supporting Information). These were found to be 3−7 kcal/mol lower in energy compared to enolates 10. Nevertheless, they were still less favored than 9. This is consistent with \(\alpha\)-disubstituted Pd-enolates typically being observed in their O-bound form.\(^\text{5}\) A TS directly connecting enolate 9 and (\(R\))-10 was located (4.03

Figure 1. (a) Catalytic cycle of the \(\alpha\)-arylation of carbonyl compounds. (b) Possible pathways for the reductive elimination step. (c) Benchmark reaction investigated in this study.
The computed relative energy between the TSs $SS_{RECR}$ and $SS_{RECS}$ is $\Delta \Delta G^\ddagger = 1.39$ kcal/mol. This value is slightly reduced to 1.16 kcal/mol when considering NCIs using the PBE-D3 functional (see the Computational Methods section). Considering the irreversibility of the RE step ($\Delta G \text{ ca. } -28$ kcal/mol, Figure 2) and the reversible formation of (R)-10 and (S)-10, the Curtin-Hammett principle can be applied.\cite{40} Therefore, the computed $\Delta \Delta G^\ddagger$ value is in agreement with the enantioselectivity observed experimentally (66% ee, 1.18 kcal/mol).\cite{17} Analysis of the TSs $SS_{RECR}$ and $SS_{RECS}$ gives insights into the observed preference toward the product (R)-6. Previous work by Zhou and co-workers\cite{30,31} on BINOL-based monophosphine ligands showed that C–H···O contacts are key features for accessing high ee levels. Such NCIs are also present in both $SS_{RECR}$ and $SS_{RECS}$, between the carbonyl O atom and ortho-protos of the PPh$_2$ groups (Figure 3a). The more favored $SS_{RECR}$ shows two C–H···O interactions (2.23 and 2.31 Å), while $SS_{RECS}$ shows only one (2.31 Å, Figure 3a). Thus, these NCIs seem to be responsible for the observed selectivity at the first glance. Aiming at a validation of our observations, we computed RE TSs also for a different ligand and substrate. (R)-Difluorophos was shown to be a ligand of choice for this transformation, providing stereoselectivity typically higher than 90% ee for a range of substrates.\cite{20} In the case of the benchmark reaction in Figure 1c with the substrate 4a, (R)-Difluorophos gave the product (R)-6 in 90 or 85% ee (at 60 or 80 °C, respectively) corresponding to a $\Delta \Delta G^\ddagger$ range of 1.76–1.95 kcal/mol. On the other hand, the reaction performance was shown to be generally lower when contracting the substrate ring size from tetralone to indanone derivatives.\cite{20} The ee for the reaction with (R)-BINAP and 4b is 20% under catalytic conditions and 66% under stoichiometric conditions, corresponding to a $\Delta \Delta G^\ddagger$ range of 0.28–1.11 kcal/mol. It should be noted that catalyst decomposition was found to occur under catalytic conditions depending on the ligand, resulting in substantial variability in the observed ee.\cite{20} Nevertheless, our stereochemical model should be able to predict the change in the reaction $\Delta \Delta G^\ddagger$ at least qualitatively,

Figure 2. Reaction Gibbs free energy profile (kcal/mol) of the enantioselective α-phenylation of 2-methyltetralone 4a catalyzed by [Pd((R)-BINAP)] at the [CPCM = toluene]PBE/SDD:6-311+G(d,p)//PBE/lanl2dz:6-31G(d) level of theory. Different reaction pathways are highlighted in different colors (see the pathway color legend).
if correct. The results obtained are shown in Figure 3, with the structures $\text{TS}_{\text{RECR}}^{\text{dif}}$ and $\text{TS}_{\text{RECS}}^{\text{dif}}$ corresponding to the TSs for the pair $(R)$-Difluorphos/4a and $\text{TS}_{\text{RECR}}^{\text{ind}}$ and $\text{TS}_{\text{RECS}}^{\text{ind}}$ for the pair $(R)$-BINAP/4b. Computations correctly describe the increase in $\Delta \Delta \Delta G$ when changing from $(R)$-BINAP to $(R)$-Difluorphos (1.62 kcal/mol Figure 3b). When considering $\text{TS}_{\text{RECR}}^{\text{ind}}$ and $\text{TS}_{\text{RECS}}^{\text{ind}}$, a $\Delta \Delta \Delta G$ value of 0.92 kcal/mol was computed (Figure 3c). This is in agreement with the typical decrement in selectivity associated with this substrate. Analysis of the geometry for these systems shows that the reaction selectivity and the C−H···O distances are not correlated. Despite $(R)$-Difluorphos gives the best selectivity, C−H···O contacts in $\text{TS}_{\text{RECR}}^{\text{dif}}$ (2.28 and 2.28 Å) are longer than those in $\text{TS}_{\text{RECR}}^{\text{ind}}$ and $\text{TS}_{\text{RECS}}^{\text{ind}}$ (2.23 and 2.31 Å, and 2.22 and 2.32 Å, Figure 3). Similarly, there is no trend with the NBO charges of the O and H atoms involved in the interaction (see the Supporting Information). Therefore, additional investigations were undertaken aiming at evaluating the factors affecting the stereochemical outcome. In order to gain more detailed insight into the mode of the interaction between the ligand and the substrate, we turned to an energy decomposition analysis similar to previous studies (Figure 4a).41−44 Several contributions are expected to affect the electronic energy difference between the two diastereomeric TSs ($\Delta \Delta E$): (i) ligand-Pd bonds, (ii) [Pd(Ph)(enolate)] Pd−C breaking bonds, (iii) ligand distortion, (iv) [Ph-enolate] distortion (which includes the forming C−C bond), (v) distortion of the Pd coordination sphere, and (vi) NCIs between the ligand and the substrate/reagent and of these with the metal center.45 The relative contribution due to the NCIs between the ligand and the substrate can be evaluated by considering the TS fragmentation depicted in Figure 4a. $\Delta \Delta \text{Lig} E$ is the electronic energy difference of the sole ligand at the TS and accounts for the relative ligand distortion. Replacing the ligand’s binaphthyl and phenyl groups with H atoms in the TS results in fragments where the relative [Ph-enolate] distortion, Pd coordination sphere, P−Pd bonds, and [Pd(Ph)(enolate)] Pd−C breaking bonds are conserved.46 Therefore, the relative energy of such fragments from the two TSs ($\Delta \Delta \text{Reag} E$) would account for all of these contributions taken together. Subtracting $\Delta \Delta \text{Lig} E$ and $\Delta \Delta \text{Reag} E$ from $\Delta \Delta E$ gives $\Delta \Delta \text{NCI} E$, which accounts for the relative NCIs between

Figure 3. Computed $\Delta \Delta \Delta G$ values in kcal/mol and geometric features for the reaction with different ligand/substrate combinations at the [CPCM = toluene]PBE-D3/SDD:6-311+G(d,p)/PBE/lanl2dz:6-31G(d) level of theory. (a) $(R)$-BINAP/4a, (b) $(R)$-Difluorphos/4a, and (c) $(R)$-BINAP/4b. The phenyl and enolate ligands undergoing C−C bond formation are highlighted in green. C−H···O NCIs are highlighted as black dotted lines and their values are reported in Å. All of the hydrogen atoms not involved in highlighted interactions are omitted for clarity.
The values of the computed contributions for each one of the ligand/substrate combinations included in this study are reported in Figure 4. As expected, because of the rigidity of this class of bidentate ligands, \( \Delta \Delta L_{\text{NCI}} \) was found to be small. Moreover, it was found to be always negative, that is, in favor of the minor (S)-product (−0.07 to −0.31 kcal/mol). The contribution due to the distortion of the [(PH\(_3\))\(_2\)Pd(PPh)](enolate) fragment \( \Delta \Delta R_{\text{NCI}} \) impacts the selectivity to a slightly larger extent, even though in opposite directions depending on the substrate. \( \Delta \Delta R_{\text{NCI}} \) is positive in the case of the tetralone derivative 4a and negative for 2-methylindanone 4b, suggesting a more favorable arrangement of the former substrate at the TS. The most important contribution to the computed \( \Delta \Delta E^T \) is \( \Delta \Delta R_{\text{NCI}} \). This was computed to be positive and bigger in magnitude compared to \( \Delta \Delta L_{\text{NCI}} \) and \( \Delta \Delta R_{\text{NCI}} \) in all the cases, indicating that the selectivity is mainly due to attractive \( \pi \) interactions between the ligand and the substrate at the TS. Such NCIs are maximized when (R)-Difluorophos is the ligand, providing \( \Delta \Delta R_{\text{NCI}} = +4.08 \) kcal/mol. A value of +3.05 kcal/mol was computed for the (R)-BINAP/4a combination, which further decreased for (R)-BINAP/4b (+2.28 kcal/mol).

\( \Delta \Delta E^T \) and \( \Delta \Delta R_{\text{NCI}} \) correlate, giving further support to the role of NCIs in the enantiodiscrimination process. Additional detail regarding such NCIs and the groups involved in the recognition event is desirable. This would provide the basis for a more rational design of improved ligands by harnessing NCIs. The effect of a specific group on the computed selectivity can be investigated by removing this from the (R) and (S)-TSs and by evaluating the change in \( \Delta \Delta E^T \) associated to this perturbation. Therefore, following the same approach described in Figure 4a, we performed an energy decomposition analysis of the TSs depicted in Figure 3 by systematically removing the Ph groups of the ligand ([R]-BINAP or (R)-Difluorophos). The results obtained are reported in Figure 4b. \( \Delta \Delta R_{\text{NCI}} \) is the relative distortion energy of the truncated TS and of the PhPH\(_2\), residue summed. \( \Delta \Delta R_{\text{NCI}} \) is the relative interaction energy due to NCIs involving the removed Ph group and is calculated as \( \Delta \Delta R_{\text{NCI}} = \Delta \Delta E^T - \Delta \Delta R_{\text{NCI}} \). The previously highlighted C–H···O interactions are present in the favored TS of all of the systems examined (vide infra). Therefore, it is not surprising that Ph2 and Ph3 are the groups contributing the most to the selectivity, as these are the groups involved in the C–H···O contacts highlighted before. Specifically, the interactions due to these groups account for \( \Delta \Delta R_{\text{NCI}} \) (Ph2) = 1.45, 2.60, and 1.18 kcal/mol and \( \Delta \Delta R_{\text{NCI}} \) (Ph3) = 0.85, 1.61, and 0.47 kcal/mol for (R)-BINAP/4a, (R)-Difluorophos/4a, and (R)-BINAP/4b, respectively (Figure 4b). However, as the geometric and electronic features of these interactions do not account for the trend observed across the three systems (vide infra), other effects should be considered to justify the higher \( \Delta \Delta R_{\text{NCI}} \) (Ph2) and \( \Delta \Delta R_{\text{NCI}} \) (Ph3) calculated for (R)-Difluorophos/4a. We reasoned that a destabilizing interaction involving Ph2 and Ph3 could be in place in the (S)-TSs.

In both TS\(_{\text{Re,CS}}\) and TS\(_{\text{Ra,CS}}\), the tetralone \( \gamma \)-methylene moiety is engaged in a CH⋯Pd interaction with the Pd occupied d\(_{z^2}\) orbital (Figure 5), which is shorter in the case of (R)-Difluorophos (2.53 Å) than for (R)-BINAP (2.63 Å). This interaction causes the substrate to be in an area occupied by Ph2 and Ph3. However, in TS\(_{\text{Re,CS}}\), the distance between the
explored; due to stabilization of the enolates. The reaction major product was correctly computed the reaction energy pro-

The phenyl and enolate portions undergoing C–C bond formation are highlighted in green. H···H distances are highlighted as black dotted lines and their values are reported in Å. Hydrogen atoms not involved in highlighted interactions are omitted for clarity.

Figure 5. Detail of the structures TS_{RE}CS and TS_{RE}CS^{def}, showing steric repulsion between the γ-methylene group of 4a and Ph2/Ph3 in the ligand. The phenyl and enolate portions undergoing C–C bond formation are highlighted in green. H···H distances are highlighted as black dotted lines and their values are reported in Å. Hydrogen atoms not involved in highlighted interactions are omitted for clarity.

**CONCLUSIONS**

The Pd-catalyzed α-arylation of carbonyl compounds is a fundamental reaction in transition metal catalysis. Extensive mechanistic analyses disclosed the general reaction mechanism. However, only limited information was available regarding the actual mechanism governing the formation of the product C–C bond. It was hypothesized that this could proceed via three possible mechanisms: (i) RE via a classic three-membered cyclic TS from a C-bound enolate; (ii) vinylogous RE from an O-bound enolate via a five-membered cyclic TS; and (iii) RE from a nη²-bound o xo-allyl Pd-enolate. To the best of our knowledge, there were no computational studies aiming at distinguishing between these. In this work, we have computed the reaction energy profile for the general mechanism initially hypothesized by Buchwald and Hartwig (Figure 1a). Computations show that the benchmark [Pd((R)-BINAP)]-catalyzed coupling between 2-methyltetralone and bromobenzene proceeds via facile OA followed by TM to give C-bound enolates. Formation of the O-bound enolate is also possible and more favored, but this is shown to be an unproductive off-cycle species. RE is computed to be the stereo- and rate-determining step of the reaction, which proceeds via direct C–C bond formation from the C-bound enolates. The reaction major product was correctly computed to have (R)-configuration when a (R)-ligand is used. This is due to stabilization of the (R)-TS by electrostatic C–H···O contacts and destabilization of the (S)-TS by specific steric repulsion. Even though the attractive NCIs are similar in strength across the different ligand–substrate combinations explored; (R)-Difluorophos optimizes repulsive interactions, leading to higher enantioselectivity. The formulation of such a detailed stereochemical model was possible thanks to the use of an energy decomposition analysis aimed at evaluating the contribution of each ligand’s Ph substituent to the reaction selectivity. This approach was previously reported by Wheeler in the context of chiral Brønsted acid-catalyzed reactions. However, to the best of our knowledge, this is the first time it is applied to the rationalization of an enantioselective reaction with biaryl phosphine ligands, for which a quadrant visual analysis is most often used. As the development of stereo-selective versions of the α-arylation of carbonyl compounds still suffers limitations, we envision that this work will allow a more rational design of catalytic systems for this class of transformations in the future.

**EXPERIMENTAL SECTION**

**Computational Methods.** The selection of a suitable computational method capable of describing sensitive equilibria between Pd-enolate species is crucial for the success of this study. Therefore, preliminary work aiming at the identification of an appropriate functional was undertaken and is reported in the Supporting Information. The results reported were obtained by geometry optimization at the BP86/Lanl2dz:6-31G(d) level of theory (Lanl2dz pseudopotential for Pd, Na, and Br atoms). Stationary points on the potential energy surface were determined to be minima (no vibrational modes with imaginary frequency) or TSs (TS, only one mode with imaginary vibrational frequency) by vibrational analysis at the same level. Finer single point energy (SPE) calculations were performed at the PBE/SDD:6-311+(d,p) level with the polarizable continuum model (PCM) to toluene, which is the solvent used experimentally. Thermal corrections were calculated from the vibrational analysis at the BP86/Lanl2dz:6-31G(d) level of theory on the optimized geometries. We arbitrarily report in the text the results obtained with PBE, as these provide a better fit to the experimental data. However, other DFT methods including hybrid functionals were evaluated and found to reproduce the results obtained with the PBE functional (see the Supporting Information). It is well-recognized that dispersion corrections are normally needed to account for NCIs. In this specific study, we found that functionals including long-range dispersion failed in reproducing the experimental distribution between the two Pd-enolate tautomeric forms (see the Supporting Information). We posit this to be due to an overestimation of the NCIs between the C-bound enolate and the Pd-complex α-Disubstituted enolates are found in solution as O-bound tautomers most likely because of steric repulsion, which seems to be underestimated in the case of long-range-corrected functionals. On the other hand, NCIs are likely to be involved in the molecular recognition process, leading to the enantiodiscrimination of the products. Indeed, we computed the diastereomeric TSs of the reaction stereodetermining step, and adding the Grimme long-range dispersion correction (G3) to the PBE functional (PBE-D3/SDD:6-311+(d,p)). This provided a better fit with the experimental enantioselectivity trend for the catalyst/substrate combinations explored, suggesting the requirement for specific computational tools for the investigation of different aspects of this reaction.

**ASSOCIATED CONTENT**

**Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c01768.

Computational methods, coordinates of located structures, and corresponding thermochemical data (PDF)
Electronic Properties on Structure, Stability, and Reactivity. Functionalized Alkyl Groups. Influence of Ligand Steric and Reactivity

Complete contact information is available at:
https://pubs.acs.org/10.1021/jacs-joc.0c01768

Notes
The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Computations were performed at the HPC facility of the Department of Chemical Sciences, University of Padova (C3P). The Department of Chemical Sciences of the University of Padova is thankfully acknowledged for the grant P-DisC#08-BIRD2019. We thank Prof. Zonta C. and Dr. Ruchti J. for helpful discussions.

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(46) Here we make an approximation by assuming that the (relative) interactions between the added H atoms and the reagents is negligible.

(47) Evaluation of ΔNCEE between different TSs does not provide any insight about whether the energy difference is due to attractive or repulsive interactions. In order to prove that the NCIs in place are attractive, we performed the same energy decomposition analysis of Figure 4a between TS_{SECR} and (R)10 (ref 50). This allowed us to establish that NCIs contribute to the activation barrier by lowering its value with ΔNCEE = −5.66 kcal/mol.

(48) We chose to evaluate the distortion energy of the PhPH group rather than PhH in order to include the C--P distortion energy into consideration. However, the results were shown to change only by hundreds of kcal/mol when compared to the use of the PhH truncation or even when neglecting the Ph portion distortion.

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