Computer-assisted catalyst development via automated modelling of conformationally complex molecules: application to diphosphinoamine ligands

Sibo Lin¹, Jenna C. Fromer², Yagnaseni Ghosh¹, Brian Hanna³, Mohamed Elanany³ & Wei Xu⁴

Simulation of conformationally complicated molecules requires multiple levels of theory to obtain accurate thermodynamics, requiring significant researcher time to implement. We automate this workflow using all open-source code (XTBDFT) and apply it toward a practical challenge: diphosphinoamine (PNP) ligands used for ethylene tetramerization catalysis may isomerize (with deleterious effects) to iminobisphosphines (PPNs), and a computational method to evaluate PNP ligand candidates would save significant experimental effort. We use XTBDFT to calculate the thermodynamic stability of a wide range of conformationally complex PNP ligands against isomeriation to PPN (ΔGPPN), and establish a strong correlation between ΔGPPN and catalyst performance. Finally, we apply our method to screen novel PNP candidates, saving significant time by ruling out candidates with non-trivial synthetic routes and poor expected catalytic performance.

Quantum mechanical methods with high energy accuracy, such as density functional theory (DFT), can optimize molecular input structures to a nearby local minimum, but calculating accurate reaction thermodynamics requires finding global minimum energy structures. For simple molecules, expert intuition can identify a few minima to focus study on, but an alternative approach must be considered for more complex molecules or to eventually fulfill the dream of autonomous catalyst design: the potential energy surface must be first surveyed with a computationally efficient method; then minima from this survey must be refined using slower, more accurate methods; finally, for molecules possessing low-frequency vibrational modes, those modes need to be treated appropriately to obtain accurate thermodynamic energies. This multistep process has a prohibitively steep learning curve for many newcomers, and trained researchers spend significant time monitoring calculations and transferring data from one phase to the next. Various programs have been previously written to automate the workflow between computational chemistry engines. We have constructed our own Python script, XTBDFT, to automate the workflow between (1) GFN-xTB-driven CREST, an accurate and efficient meta-dynamics method for conformational analysis for systems, particularly those with transition-metal atoms and exotic functional groups, (2) conformer refinement with DFT, as implemented in NWChem, and (3) GoodVibes, a script to apply quasi-harmonic treatment of low-frequency vibrational modes. Notably all components of this automated workflow are open-source, allowing for widespread and affordable implementation. Herein we apply XTBDFT toward a practical topic: computational assessment of diphosphinoamine (PNP) ligand candidates.

PNP ligands are extensively studied for Cr-catalyzed ethylene oligomerization to valuable linear alpha olefins. Recent academic and industrial studies continue to show the prominence of PNP ligands. However, reactor fouling, caused by insoluble polyethylene by-product, remains a major impediment to industrial-scale practice. PNP ligands can isomerize to iminobisphosphines (PPN) under catalytic conditions, which has been proposed to lead to increased polyethylene formation. We sought to evaluate that hypothesis by

1Aramco Americas - Boston Research Center, 400 Technology Square, Cambridge, MA 02139, USA. 2Department of Chemical and Biological Engineering, Tufts University, Medford, MA 02155, USA. 3Chemicals R&D Division, Research and Development Center, Saudi Aramco, Dhahran 31311, Saudi Arabia. 4Chemicals R&D Lab at KAUST, Research and Development Center, Saudi Aramco, Thuwal 23955, Saudi Arabia. *email: sibo.lin@aramcoamericas.com
calculating thermodynamic stabilities of PNPs against isomerization to PPN form (ΔGPPN, Fig. 2). Both PNP and PPN molecules possess many conformations, and analysis of the wrong conformer will result in incorrect ΔGPPN. A previous DFT study of PNP ligand conformers found variation of up to 9.9 kcal/mol in calculated Gibbs free energy25, which would drastically impact any thermodynamic comparison with PPN isomer.

In this report, we utilize XTBDFT to automate global optimization and calculation of ΔGPPN of several known PNP/PPN compounds (1–33, Fig. 3), and observe strong agreement with experimental observations. Then a strong inverse relation between PNP stability and polyethylene formation during ethylene oligomerization catalysis is observed. Finally, this method is applied to screen novel PNP ligand candidates, saving significant time by ruling out candidates with non-trivial synthetic routes and poor expected catalytic performance.

Methods

Initial guess geometries for PNP and PPN molecules were conveniently generated with MolView27. These molecules have numerous hindered degrees of rotation, and standard geometry optimization algorithms may yield a relatively high-energy conformer. A previous DFT study of relatively simple (i.e. high substitutional symmetry) PNP molecules found that geometric local minima could differ by 9.9 kcal/mol in Gibbs free energy25. Human-directed generation of conformer ensembles for computational analysis is time-intensive and inconsistent. To ensure identification of a low-energy conformer, an efficient computational method must be utilized to generate and crudely rank a broad conformer ensemble. Conformer sampling algorithms employed in Tinker28, OpenBabel29, and various other molecular modelling programs rely on heavily parameterized classical force fields or semiempirical methods that may not accurately reproduce geometries or energies of exotic molecules or transition-metal complexes, and in some cases researchers have to resort to substituting unparameterized elements with more common elements30. We instead use the meta-dynamics package Conformer Rotamer Ensemble Sampling Tool (CREST2,17) driven by the semi-empirical density functional tight binding theory GFN2-xTB, which, unlike previously developed semi-empirical methods, has been broadly parameterized for all elements H-Rd and benchmarked against diverse chemical databases16, to automate generation of an ensemble of conformers within 2.0 kcal/mol of the minimum energy conformer. As an added benefit of using CREST for conformation searching, its built-in conformer symmetry analysis identifies rotamers that are chemically identical, greatly reducing the size of the conformer ensemble to be processed by higher levels of theory. In one example, CREST identified 35 unique conformers of (Ph2P)2NPh (9) within 6 kcal/mol of the lowest energy conformer. For comparison, the conformer searching procedure built into Spartan ’18 (powered by Merck Molecular Force Field31) returns 225 conformers.

Further geometry optimizations of the conformer ensemble were performed with density functional theory (DFT) as implemented in NWChem18,32 (version 6.8) with the B3LYP functional33,34, def2-SV(P) basis set35, Weigend Coulomb-fitting auxiliary basis set36, Grimme DFT-D3 dispersion corrections37, NWChem medium integration grid, and loose geometric convergence criteria (using NWChem input parameters of gmax 0.002; grms 0.0003; xrms 1; xmax 1). The lowest energy conformer at this intermediate level of theory was then further geometry optimized with tighter convergence criteria (gmax 0.0002; grms 0.00003; xrms 0.0006; xmax 0.001), and thermochemical corrections were calculated, with the def2-SVP basis set36 and the NWChem fine integration grid. Finally, a high-level single-point electronic energy evaluation was performed using the def2-TZVP basis set38.

Because of the hindered degrees of rotation, several optimized geometries possess low-magnitude frequency vibrations, which are inaccurately treated by the harmonic oscillator approximation for thermodynamics. A correction for these vibrations was applied by quasi-harmonically raising all frequencies below 100 cm−1 using the GoodVibes script. Goodvibes code was modified to allow parsing of NWChem output files, and this customization has been merged into the publicly available Goodvibes release.

Taking advantage of the programmable nature of CREST, NWChem, and GoodVibes input files, a Python wrapper script was written to automate all the steps starting from an initial guess geometry (.xyz file). This script (XTBDFIT) communicates data between the various programs, tracks calculations, and automatically triggers the next calculation in the procedure. While code to interface CREST and GFN-xTB with DFT programs

Figure 1. XTBDFT flowchart with example input and output.
such as Orca and Turbomole has been previously published, those programs are not as freely licensed and distributed as NWChem. NWChem is open-source and freely licensable for all users, which has facilitated its implementation in massively distributed cloud-computing solutions. While molecular dynamics has been interfaced with NWChem, the underlying molecular mechanics forcefields are not accurately parameterized for transition metal atoms or exotic functional groups. We believe the portable and lightweight nature of this wrapper script, along with the generous licensing terms of the underlying free chemistry engines, will allow for wide-spread adoption and modification among the chemistry and molecular machine-learning communities. The current version of XTBDFT is available online.

Results

Composite procedure for identifying lowest-energy conformer. To computationally predict the thermodynamics of PNP to PPN isomerization, the minimum-energy conformation of each isomer must be obtained. Conventional geometry optimization algorithms employed by DFT software may identify a relatively high-lying local minimum, especially in systems containing multiple hindered degrees of rotation. Thus, we developed a composite procedure to identify and evaluate a low-energy conformation, consisting of: (a) the semi-empirical quantum chemical meta-dynamics package CREST to generate and crudely rank a diverse ensemble of conformers and (b) a quick, low level of DFT to re-optimize and re-rank the lowest energy conformers. The composite procedure is flexible in the choices of thermochemical recipe for determining the lowest-energy conformation.

As a prototypical case, we considered the conformer ensembles (ΔE < 6 kcal/mol vs. minimum-energy conformer) of (Ph2P)2NiPr (2) and its PPN isomer 2'. Free energy corrections, G0(RRHO), were calculated using GFN2-xTB vibrational calculations on the GFN2-xTB-optimized structures. A variety of electronic energies were obtained for each conformer, E0-3 (Table 1), of increasing computational cost. For analysis, we consider relative energies:

\[ \Delta E_n = E_n - E_0, \]

where \( E_0 \) is the electronic energy of the minimum conformer in the initial CREST search. \( \Delta E \) is strongly correlated with \( \Delta G \) (Fig. 4) for conformer ensembles of both 2 (\( R^2 = 0.996 \)) and 2' (\( R^2 = 0.978 \)); thus vibrational calculations were not employed in identifying the lowest-energy conformers for other compounds in this study.

Further computational savings could be achieved by using a lower level of theory for geometry optimization and electronic energy evaluation. For the conformer ensembles of 2 and 2', we plotted the \( \Delta E \) of each conformer versus ΔE (Fig. 5). The energy calculations \( \Delta E_0 \) and \( \Delta E_2 \) were highly correlated with \( \Delta E_3 \), indicating that the computational expense of expanding the basis set from def2-SV(P) to def2-SVP is not justified. In contrast, the more affordable energy calculation \( \Delta E_3 \) was accurate for the conformer ensemble of 2 (\( R^2 = 0.98 \)), but not for that of 2' (\( R^2 = 0.75 \)). The most affordable energy calculation, \( \Delta E_{xtb} \) was inaccurate for ordering conformer ensembles of both 2 and 2'. GFN-xTB was developed to produce accurate geometries, frequencies, and non-covalent interactions with remarkable computational efficiency, but for accurate relative energy calculations in this study, higher-level DFT calculations are necessary to determine global minimum energy conformations. Thus, \( \Delta E_1 \) was chosen as an economical yet accurate computational metric by which to identify the lowest energy conformer.

PNP-to-PPN isomerization energy (\( \Delta G_{PPN} \)) of known compounds. The above procedure identified the lowest energy conformer for a wide range of PNP compounds and their PPN isomers. The lowest energy conformer was further optimized with B3LYP-D3/def2-SVP, and electronically evaluated using B3LYP-D3/def2-TZVP (\( E_0 \)). Quasi-harmonic thermochemical corrections were applied to obtain free energies for the lowest energy PNP and PPN conformers, \( G_0(PNP) \) and \( G_0(PPN) \). The free energy of PNP-to-PPN isomerization was then calculated:

\[ \Delta G_{PPN} = G_4(PPN) - G_4(PNP), \]

The \( \Delta G_{PPN} \) of 1–33 are tabulated in Table 2 and found to match experimental observations (see "Discussion" section).
Figure 3. PNP ligands 1–33 or PPN isomers (1′–33′, not shown) that have been reported in the literature. Black structures are calculated to have positive ΔG_{PPN}; red structures have negative ΔG_{PPN}.

Table 1. Thermochemical recipes. a Loose NWChem geometry convergence criteria: gmax 0.002; grms 0.0003; xrms 1; xmax 1. b Tight NWChem geometry convergence criteria: gmax 0.0001; grms 0.00003; xrms 0.0006; xmax 0.001.
Figure 4. Comparison of relative free energies of conformers (ΔG₃) versus relative electronic energies of conformers (ΔE₃) for (a) 2 and (b) 2'.

Figure 5. Comparison of thermochemical recipes against ΔE₃ for conformer ensembles of 2 and 2' (all units are kcal/mol).

Table 2. Calculated PNP-to-PPN isomerization energy (ΔG_{PPN}, kcal/mol).
### Screening novel compounds

Having benchmarked our comprehensive computational method against reported experimental observations, we applied this method to predict the synthetic accessibility of novel PNP ligand candidates. Screening a wide pool of candidates, several were predicted to be thermodynamically stable against isomerization to PPN ($\Delta G_{PPN} > 1$ kcal/mol); synthesis and catalytic testing of these candidates is underway and will be reported in a future publication. Some examples of ligand candidates with $\Delta G_{PPN} < 1$ kcal/mol (Table 1) are shown in Fig. 6 (34–44) and listed in Table 2.

### Discussion

To assess the accuracy of our computational method, we compared $\Delta G_{PPN}$ for 1–33 to previously reported experimental observations. PNP/PPN isomers can be kinetically trapped during synthesis from lithiated aminophosphine and chlorophosphine; however, in some cases the kinetic products can be observed converting to the thermodynamic product in the presence of excess chlorophosphine, which acts as an isomerization catalyst42,43. Alternatively, synthesis from primary amine, two equivalents of chlorophosphine, and triethylamine in dichloromethane solvent is proposed to yield the thermodynamic product because PNP-PPN isomerization is catalyzed by triethylammonium chloride42. We expected the calculated $\Delta G_{PPN}$ values (Table 1) to correspond with previously reported experimental observations.

The PNP derived from alkylamines (1–4) have been isolated via the triethylamine route32,42,44, and accordingly have positive calculated $\Delta G_{PPN}$. N-trimethylsilylamine-derived PNP 5 has only been synthesized with the lithiation route45,46, even in studies where other PNP compounds were made via the triethylamine route48; this observation is consistent with the calculated $\Delta G_{PPN}$ of $\sim 2.6$ kcal/mol. With bulkier N-trisopropylsilylamine, 6 has never been isolated. Using the same synthetic procedure as for 5, only the PPN isomer 6a was observed, which is consistent with the much more negative $\Delta G_{PPN}$ of $\sim 10.4$ kcal/mol. With bis(dicyclohexylphosphino)amines, $\Delta G_{PPN}$ values match previously isolated isomers and 7 and 844. For aniline-based molecules, $\Delta G_{PPN}$ agrees with experimentally observed isomers from triethylamine syntheses: 9, 10, 11, 1245, and 1346. Depending on the synthetic conditions, different PNP/PPN product mixtures have been reported for 14 and 1547, and accordingly these compounds have relatively small but positive $\Delta G_{PPN}$. The N-aryl compounds 16–18 were all isolated from triethylamine syntheses, and they all exhibit positive $\Delta G_{PPN}$. Their reported isomerization to PPN species upon protonation48 is matched by the negative $\Delta G_{PPN}$ for 19–21. Tris(diphenylphosphino)amine 22 has been synthesized in only 8% yield from lithiated bis(diphenylphosphino)amine and chlorophosphine49, although other reports have reported exclusive formation of the PPN isomer 2245. $\Delta G_{PPN}$ is small (0.6 kcal/mol), reflecting the accessibility of both isomers.

23-(n-C$_3$H$_7$)$_2$N$_2$ and 24-(n-C$_3$H$_7$)$_3$N$_2$ have both been isolated from triethylamine-based syntheses50. While $\Delta G_{PPN}$ of 23-CH$_3$ has a small negative value, that of 24-CH$_3$ is quite positive and large, leading to the novel observation: *electron-withdrawing P-substituents favour the PNP isomer*. We expect this to be a useful design strategy for novel PNP ligands.

Conversely, N-substitution follows the opposite pattern, as shown by NO$_2$-substituted 25 and OMe-substituted 26 with $\Delta G_{PPN}$ of $\sim 0.9$ and 4.7 kcal/mol, respectively. The negative $\Delta G_{PPN}$ of 23-CH$_3$ and 25 conflicts with the reported isolated PNP compounds, and perhaps indicate that the error of this computational thermodynamic method is ca. 1 kcal/mol. Compounds 27–32 have all been isolated in the PNP form from triethylamine syntheses, and accordingly they all have $\Delta G_{PPN} > 0$. These similarly sized compounds clearly show that $\Delta G_{PPN}$ is higher with N-aryl substitution instead of N-aryl substitution.

As a strategy to disfavour PPN isomerization, the N-substituent can be covalently tethered to a P-substituent. Synthesis of 33 was reported to yield no detectable amounts of 3348, and accordingly 33 has a $\Delta G_{PPN}$ of 6.1 kcal/mol (c.f. 3.5 kcal/mol for 9).

Summarizing the results for our computational method, with $|\Delta G_{PPN}| > 0.9$ the predicted PNP/PPN isomer matches experimentally reported isomers synthesized with triethylamine. With $|\Delta G_{PPN}| < 0.9$ kcal/mol, the experimentally isolated isomers depend on exact experimental conditions. Compare this accuracy with conventional DFT geometry optimization to a single nearest minimum: for PNP molecules, conformers at polyethylene by-product formation during Cr-catalyzed ethylene oligomerization24. These catalytic reactions are known to be highly sensitive to air, moisture, temperature, and various experimental parameters, and so we selected experimental data previously published by Sasol that were all collected under similar conditions44,46,51. There is a notable correlation between $\Delta G_{PPN}$ and lower polyethylene formation (Table 3). As a simplified model, if PNP and PPN isomers are in thermodynamic equilibrium ($[PNP]_0/[PPN]_0 = e^{-\Delta G_{PPN}/RT}$), initial PNP concentration is directly correlated with ethylene oligomerization productivity (oligomerization productivity = $a[PPN]_0$), initial PNP concentration is directly correlated with polymerization productivity (polymerization productivity = $b[PNP]_0$), and $a$ and $b$ are constant across the range of PNP and PPN compounds, then the following relation should be observed:

$$\ln \left( \frac{\text{polyethylene wt%}}{\text{a}} \right) = \ln \left( \frac{b}{a} \right) - \frac{\Delta G_{PPN}}{RT} \quad (3)$$

In agreement, there is an inverse linear relationship between the logarithm of polyethylene wt% and $\Delta G_{PPN}$ (Fig. 7), supporting the proposal that polyethylene formation proceeds through PPN-derived catalytic species. Scatter results from $a$ and $b$ varying across the range of ligands (experimental catalytic activities, listed in Table 3, span two orders of magnitude between the various ligands). However, there is still remarkable correlation using this simplified model ($R^2 = 0.72$), indicating that PNP stability against isomerization to PPN is a useful design criterion for novel ligands.
As a qualitative summary of Fig. 7, the best-performing (meaning, in this case, the least polyethylene-producing) PNP ligands are those with ΔGPPN > 6 kcal/mol, and we are heeding that in design and development of novel PNP-based catalysts. While unstable PNP ligands have been pre-coordinated to Cr to resist PPN isomerization46, we have chosen to only pursue the ligands with ΔGPPN > 1 kcal/mol. Candidates 34–44, ruled out by this criterion, are shown in Fig. 6, and their ΔGPPN values are tabulated in Table 1. Significant researcher time will be saved by ruling out these candidates with non-trivial synthetic routes and poor expected catalytic performance.

Machine learning from quantum chemical computational models is a powerful tool that has often been brought to bear on ethylene oligomerization catalysts52–56. The scriptable and automated nature of our composite computational procedure is poised to contribute to catalyst discovery driven by machine learning and artificial intelligence. Unlike conventionally used molecular mechanics-based conformational searching algorithms, the extended tight binding theory used in our procedure is parameterized out-of-the-box for transition metals; an area of ongoing research is the application of XTBDFT toward the analysis of conformationally complex organometallic intermediates and transition states, perhaps using more computationally expensive DFT or coupled cluster methods.

Conclusions
We have developed XTBDFT, an automated workflow to efficiently screen and evaluate conformationally complex molecules. We have applied this composite method to known PNP/PPN compounds to determine their relative thermodynamic stability and shown excellent agreement with the experimentally observed isomers. Furthermore, we show that thermodynamic stability of PNP ligands against isomerization to PPN is strongly correlated with lower undesired polyethylene formation. This procedure can be applied generally to other conformationally

| ΔGPPN (kcal/mol) | Polyethylene wt% | Ligand | Activity (kg/(gCrh)) |
|------------------|------------------|--------|---------------------|
| −2.6             | 12.9             | 5      | 20.1                |
| −0.9             | 16.2             | 25     | 932.8               |
| 0.5              | 3.4              | 28     | 516.9               |
| 2.5              | 1.2              | 4      | 1550                |
| 3.5              | 3.3              | 9      | 765.9               |
| 3.8              | 7.8              | 27     | 159.6               |
| 4.7              | 4.6              | 26     | 385.9               |
| 6.7              | 0.6              | 31     | 1001.6              |
| 7.5              | 0.6              | 32     | 3200                |
| 8.6              | 1.3              | 1      | 1070                |
| 8.9              | 0.8              | 29     | 145.5               |
| 9.0              | 0.8              | 30     | 2150                |
| 9.5              | 0.9              | 2      | 1950                |
| 9.5              | 0.8              | 3      | 614.7               |

Table 3. Reported polyethylene production (wt.%) versus ΔGPPN (kcal/mol). *Catalytic data were obtained under similar conditions from three papers from Sasol researchers: 1, 2, 4, 5, 30, 32 from ref.46, 3 from ref.44, and 9, 25–29, and 31 from ref.44; 300 mL Parr reactor using 100 mL methylcyclohexane at 60 °C, 45–50 barg ethylene, 2.5–10 μmol Cr(acac)₃, 1–1.5 eq. ligand, 270–480 eq. MMAO-3A.

Figure 6. Novel ligand candidates with ΔGPPN < 1 kcal/mol. Black structures are calculated to have positive ΔGPPN; red structures have negative ΔGPPN.
complex systems. This research leverages entirely open-source software, which we envision can be utilized by the greater computational chemistry and machine learning communities.

Data availability
Electronic Supplementary Information available: DFT-optimized Cartesian coordinates of molecules (.xyz) and table of calculated energies (.xlsx). Correspondence and other requests should be directed to S.L.

Received: 20 October 2020; Accepted: 25 January 2021

References
1. Ryu, H. et al. Pitfalls in computational modeling of chemical reactions and how to avoid them. Organometallics 37, 3228–3239 (2018).
2. Pracht, P., Bohle, F. & Grimme, S. Automated exploration of the low-energy chemical space with fast quantum chemical methods. Phys. Chem. Chem. Phys. 22, 7169–7192 (2020).
3. dos Passos Gomes, G., Pollice, R. & Aspuru-Guzik, A. Navigating through the maze of homogeneous catalyst design with machine learning. Trends Chem. 3, 96–110 (2021).
4. Foscato, M. & Jensen, V. R. Automated in silico design of homogeneous catalysts. ACS Catal. 10, 2354–2377 (2020).
5. Ribeiro, R. F., Marenich, A. V., Cramer, C. J. & Truhlar, D. G. Use of solution-phase vibrational frequencies in continuum models for the free energy of salvation. J. Phys. Chem. B 115, 14556–14562 (2011).
6. Luchini, G., Alegre-Requena, J., Funes-Ardoiz, I. & Paton, R. GoodVibes: automated thermochemistry for heterogeneous computational chemistry data. F1000Research 9, 291 (2020).
7. Grimme, S. Supramolecular binding thermodynamics by dispersion-corrected density functional theory. Chem. Eur. J. 18, 9955–9964 (2012).
8. Jacob, C. R. et al. PyADF—a scripting framework for multiscale quantum chemistry. J. Comput. Chem. 32, 2238–2338 (2011).
9. Zapata, F. et al. QMflows: a tool kit for interoperable parallel workflows in quantum chemistry. J. Chem. Inf. Model. 59, 3191–3197 (2019).
10. Larsen, A. H. et al. The atomic simulation environment—a Python library for working with atoms. J. Phys. Condens. Matter 29(27), 273002 (2017).
11. Yesiltepe, Y. et al. An automated framework for NMR chemical shift calculations of small organic molecules. J. Cheminf. 10, 52 (2018).
12. Grimme, S. et al. Fully automated quantum-chemistry-based computation of spin–spin-coupled nuclear magnetic resonance spectra. Angew. Chem. Int. Ed. 56, 14763–14769 (2017).
13. T. Lu, Molclus program, (accessed on January 4, 2021) http://www.keinsci.com/research/molclus.html.
14. Mu, X. & Sun, M. The linear and non-linear optical absorption and asymmetrical electromagnetic interaction in chiral twisted bilayer graphene with hybrid edges. Mater. Today Phys. 14, 100222 (2020).
15. Wang, J., Wang, J. & Mu, X. Physical mechanism of concentration-dependent fluorescence resonance energy transfer. Spectrochim. Acta Part A Mol. Biomol. Spectrosc. 231, 118143 (2020).
16. Banworth, C., Ehler, S. & Grimme, S. GFN2-xTB—An accurate and broadly parametrized self-consistent tight-binding quantum chemical method with multipole electrostatics and density-dependent dispersion contributions. J. Chem. Theory Comput. 15, 1652–1671 (2019).
17. Grimme, S. Exploration of chemical compound, conformer, and reaction space with meta-dynamics simulations based on tight-binding quantum chemical calculations. J. Chem. Theory Comput. 15, 2847–2862 (2019).
18. Aprà, E. et al. NWChem: past, present, and future. J. Chem. Phys. 152, 184102 (2020).
19. Fiedel, C., Ghisolfi, A. & Braunstein, P. Functional short-bite ligands: synthesis, coordination chemistry, and applications of N-functionalized bis(diaryl/dialkylphosphino) amine-type ligands. Chem. Rev. 116, 9237–9304 (2016).
20. Agapie, T. Selective ethylene oligomerization: recent advances in chromium catalysis and mechanic investigations. Coord. Chem. Rev. 255, 861–880 (2011).
21. Carter, A. et al. High activity ethylene trimerisation catalysts based on diphenoxime ligand. Chem. Commun., 858–859 (2002). https://pubs.rsc.org/en/content/articlelanding/2002/CC/b201335e#divAbstract
22. Bollmann, A. et al. GFN2-xTB—an accurate and broadly parametrized self-consistent tight-binding quantum chemical method with multipole electrostatics and density-dependent dispersion contributions. J. Am. Chem. Soc. 126, 14712–14713 (2004).
23. Hirscher, N. A., Perez Sierra, D. & Agapie, T. Robust chromium precursors for catalysis: isolation and structure of a single-component ethylene tetramerization precatalyst. J. Am. Chem. Soc. 141, 6022–6029 (2019).
24. Lifschitz, A. M., Hirscher, N. A., Lee, H. B., Buss, J. A. & Agapie, T. Ethylene Tetramerization catalysis: effects of aluminum-induced isomerization of PNP to PPN ligands. Organometallics 36, 1640–1648 (2017).
25. Kim, T. H. et al. MAO-free and extremely active catalytic system for ethylene tetramerization. Appl. Organomet. Chem. 33, e4829 (2019).
Boelter, S. D. et al. Evaluation of bis (phosphine) ligands for ethylene oligomerization: discovery of alkyl phosphines as effective ligands for ethylene tri- and tetramerization. Organometallics 39, 967–975 (2020).

Bergwerf, H. MolView. http://molview.org. Accessed May 19, 2020. ([for ref 13, 27, and 41, these reference softwares from websites. I am not sure if the correct format for your journal is "[FirstInitial]. [Lastname]" or "[Lastname], [FirstInitial]."—please use whichever your journal prefers.])

Rackers, J. A. et al. Tinker 8: software tools for molecular design. J. Chem. Theory Comput. 14, 5273–5289 (2018).

O’Boyle, N. M. et al. Open Babel: an open chemical toolbox. J. Cheminf. 3, 33 (2011).

Liu, L. et al. What triggered the switching from ethylene-selective trimerization into tetramerization over the Cr(2,2'-dipicolylamine) catalysts?. ACS Catal. 9, 10519–10527 (2019).

Halgren, T. A. Merck molecular force field. J. Basis, form, scope, parameterization, and performance of MMFF94. J. Comput. Chem. 17, 490–519 (1996).

Valiev, M. et al. NWChem: a comprehensive and scalable open-source solution for large scale molecular simulations. Comput. Phys. Commun. 181, 1477–1489 (2010).

Becke, A. D. Density-functional thermochemistry. III. The role of exact exchange. J. Chem. Phys. 98, 5648–5652 (1993).

Stephens, P. J., Devlin, F. J., Chabalowski, C. F. & Frisch, M. J. Ab initio calculation of vibrational absorption and circular dichroism spectra using density functional force fields. J. Phys. Chem. 98, 11623–11627 (1994).

Weigend, F. & Ahrlicks, R. Balanced basis sets of split valence, triple zeta valence and quadruple zeta valence quality for H to Rn: design and assessment of accuracy. Phys. Chem. Phys. 7, 3297–3305 (2005).

Weigend, F. Accurate Coulomb-fitting basis sets for H to Rn. Phys. Chem. Chem. Phys. 8, 1057–1065 (2006).

Grime, S., Antony, J., Ehrlich, S. & Krieg, H. A consistent and accurate ab initio parameterization of density functional dispersion correction (DFT-D) for the 94 elements H–Pu. J. Chem. Phys. 132, 154104 (2010).

Jorissen, K., Vila, F. D. & Rehr, J. J. A high performance scientific cloud computing environment for materials simulations. Comput. Phys. Commun. 183, 1911–1919 (2012).

Hanwell, M. D., de Jong, W. A. & Harris, C. J. Open chemistry: RESTful web APIs, JSON, NWChem and the modern web application. J. Cheminf. 9, 55 (2017).

Tech-X Corporation, Chemistream. https://txcorp.com/images/docs/chemistream/latest/index.html. Accessed January 4th 2021.

Maumel, M. C. et al. Efficient synthesis of novel N-substituted bulky diphosphinoamines. Synthesis 2007, 3863–3867 (2007).

Haddow, M. F. et al. Aminophobanes: hydrolytic stability, tautomerism and application in Cr-catalysed ethene oligomerisation. Dalton Trans. 45, 2294–2307 (2016).

Kuhlmann, S. et al. N-substituted diphosphinoamines: toward rational ligand design for the efficient tetramerization of ethylene. J. Catal. 245, 279–284 (2007).

Schmidibaur, H., Lauteschläger, S. & Kohler, F. H. Isomerism and conformation of (N-silyl)(bis(diphenylphosphino)amines and bis(N-silylidiphenylphosphino)amines. J. Organomet. Chem. 271, 173–180 (1984).

Blann, K. et al. Ethylene tetramerisation: subtle effects exhibited by N-substituted diphosphinoamine ligands. J. Catal. 249, 244–249 (2007).

Fei, Z., Scopelliti, R. & Dyson, P. J. Influence of the functional group on the synthesis of aminophosphines, diphosphinoamines and iminobiphosphines. Dalton Trans. https://doi.org/10.1039/B303645F (2003).

Fei, Z., Bircik, N., Zhao, D., Scopelliti, R. & Dyson, P. J. Transformation between diphosphinoamines and iminobiphosphines: a reversible PNP ↔ NP→P rearrangement triggered by protonation/deprotonation. Inorg. Chem. 43, 2228–2230 (2004).

Ellermann, J. & Wend, W. Chemie polyfunktioneller moleküle: LXXV. Die synthese von tris (diphenylphosphino) amin am metall und auf direktem wege. J. Organomet. Chem. 281, c29–c32 (1985).

Nifant’ev, I. E. et al. 5,6-Dihydrolodibenzo[c, e][1,2]azaphosphinine-based PNP ligands, Cr(0) coordination, and Cr(III) precatalysts for ethylene oligomerization. Organometallics 37, 2660–2664 (2018).

Killian, E. et al. The use of bis(diphenylphosphino)amines with N-aryl functionalities in selective ethylene tri- and tetramerisation. J. Mol. Catal. A: Chem. 270, 214–218 (2007).

Tang, S. et al. 2D-QSPR/DFT studies of aryl-substituted PNP-Cr-based catalyst systems for highly selective ethylene oligomerization. J. Mol. Model. 20, 2129 (2014).

Ahn, S., Hong, M., Sundararajan, M., Ess, D. H. & Baik, M.-H. Design and optimization of catalysts based on mechanistic insights derived from quantum chemical reaction modeling. Chem. Rev. 119, 6509–6560 (2019).

Kwon, D.-H. et al. Computational transition-state design provides experimentally verified Cr(PN) catalysts for control of ethylene trimerization and tetramerization. ACS Catal. 8, 1138–1142 (2018).

Kwon, D.-H., Small, B. L., Sydora, O. L., Bischof, S. M. & Ess, D. H. Challenge of using practical DFT to model Fe pendant donor diimine catalyzed ethylene oligomerization. J. Phys. Chem. C 123, 3727–3739 (2019).

Kwon, D.-H. et al. Why Less Coordination Provides Higher Reactivity Chromium Phosphinoamidine Ethylene Trimerization Catalysts. ACS Catal. 10, 9674–9683 (2020).

Acknowledgements
The authors acknowledge Sivakumar Nanjundan for setting up and maintaining Aramco America’s computing cluster; and Prof. Stefan Grime for providing CREST and GFN-xTB troubleshooting advice.

Author contributions
S.L.: Conceptualization, J.C.F. and S.L.: Methodology; J.C.F. and S.L.: Software; S.L.: Investigation; S.L., Y.G., B.H. M.E., W.X.: Resources; S.L.: Writing—Original Draft; All authors: Writing—review & editing; B.H. and W.X.: Supervision.

Competing interests
The authors declare no competing interests.

Additional information
Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-021-82816-x.

Correspondence and requests for materials should be addressed to S.L.

Reprints and permissions information is available at www.nature.com/reprints.
Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

© The Author(s) 2021