New Ways of Diamondoid Functionalization – A Synthetic Method for the Incorporation of Dispersion Energy Donors into Catalysts and Molecular Balances

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Damit das Mögliche entsteht, muss immer wieder das Unmögliche versucht werden.

Hermann Hesse

Für meine Familie.

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Abstract

This thesis deals with the selective functionalization of diamondoids and their incorporation in existing catalytic systems as well as molecular balances to quantify London dispersion interactions.

In the first part, we present a new substitution reaction based on the Mitsunobu reaction. This sequence works particularly well for lower diamondoids, like adamantane and diamantane, with high yields and good reaction control. Abundant alcohols react to diphenylphosphinite structures. The corresponding diamondoid based trivalent phosphorous compounds are insensitive towards air and moisture and therefore ideal storable precursors. The reaction of the phosphinites with diisopropylazodicarboxylate as activating agent leads to an intermediate betaine structure. The latter collapses upon protonation by a mildly acidic nucleophile, to a carbocation. This cation is trapped by the deprotonated nucleophile leading to the desired target compound. The reaction sequence is universal for all structures that can form a stabilized carbocation intermediate and works well for a broad variety of pronucleophiles. Therefore it offers the possibility of nearly every C−C or C−heteroatom bond formation reaction. Mechanistic studies underline the formation of a carbocation intermediate, which has not been reported in all redox condensation reactions published so far.

The second part of this thesis deals with a new uniform synthesis concept towards all-*meta* substituted iodobenzenes and anilines. 3,5-Disubstituted catechols serve as starting materials and were synthesized *via* formylation of the corresponding 2,4-disubstituted phenols and subsequent Dakin reaction. After oxidation of the dihydroxybenzenes, the *o*-quinones react in a [4+2] cycloaddition with an alkyne to a bicyclic 1,2-diketone. Final photodecarbonylation with visible light yield the 1,3,5-trisubstituted scaffold which is further manipulated to the desired targets *via* known reactions, e.g., Schmidt reaction. The new type of substitution reaction from the first part of this thesis was crucial for the generation of the 3,5-disubstituted diamondoid precursors since the corresponding phenol structure was not available and the sequence described before was not applicable to adamantane and diamantane substituted compounds. This underlines the importance of suitable reaction sequences that also enable the incorporation of diamondoids into existing structures.

We applied our new scalable reaction pathway in the synthesis of chiral BINOL-based phosphoric acid catalysts, substituted with all-*meta* adamantyl and diamantyl arenes. In a comparative study, this new bulky catalyst performed equally well in comparison to existing catalysts in the reductive amination reaction of acetophenone and delivers enantiomeric excesses of up to 84% without optimization of the reaction conditions.

Zusammenfassung

Die vorliegende Arbeit beschäftigt sich mit der selektiven Funktionalisierung von Diamantoiden und deren Einarbeitung in bestehende Katalysatorsysteme und Strukturen, die zur Untersuchung von London'schen Dispersionwechselwirkungen genutzt werden.

Im ersten Teil wird eine neuartige Substitutionsreaktion aufbauend auf der bekannten Mitsunobu-Reaktion beschrieben, die vor allem an niederen Diamantoiden hohe Ausbeuten bei einfacher Reaktionsführung bietet. Dabei werden einfach zugängliche Hydroxyverbindungen in eine Diphenylphosphinitstruktur umgewandelt. Ausgehend von Diamantoidalkoholen sind diese trivalenten Phosphorverbindungen nicht oxidationsempfindlich und sind lagerbare universelle Vorstufen. Durch die Reaktion der Phosphinite mit Diisopropylazodicarboxylat als Aktivierungsreagenz bildet sich eine intermediäre Betainstruktur. Diese wird anschließend von einem wenig aziden Nukleophil protoniert. Die protonierte Struktur dissoziiert zum Carbokation, welches vom deprotonierten Nukleophil abgefangen wird und so zur Zielstruktur führt. Die Reaktion ist auf Strukturen anwendbar, die ein stabilisiertes intermediäres Carbokation ausbilden können und funktioniert mit einer Vielzahl an Nukleophilen, sodass nahezu alle Formen einer C−C oder C−Heteroatom Bindungsknüpfung durchgeführt werden können. Mechanistische Studien unterstreichen die Bildung einer kationischen Zwischenstufe, die in allen bisherig veröffentlichten Redoxkondensationsreaktionen nicht berichtet worden ist.

Im zweiten Teil dieser Arbeit wird ein neues Konzept für die universelle Synthese von all-*meta* substituierten Iodbenzolen sowie Anilinen beschrieben. Als Ausgangsverbindungen dienen hierbei 3,5-substituierte 1,2-Dihydroxybenzole, die über eine Formylierung aus den 2,4-substituierten Phenolen zugänglich sind. Eine anschließende Dakin-Reaktion liefert die Zielausgangsverbindung, welche nach Oxidation in einer [4+2] Cycloaddition mit einem Alkinbaustein zu einer bizyklischen 1,2-Dicarbonylstruktur reagiert. Anschließende Photodecarbonylierung mit Licht im sichtbaren Wellenlängenbereich führen zum 1,3,5-trisubstituierten Grundgerüst, welches durch literaturbekannte Reaktionen, wie z.B. der Schmidt-Reaktion, in die Zielverbindung überführt wird. Das neue Reaktionskonzept aus dem ersten Teil dieser Arbeit war dabei für die Bildung der 3,5-disubstituierten Diamantoidvorstufen unerlässlich, da hier mangels Phenolvorstufe der oben beschriebene Weg aus Formylierung und Dakin-Reaktion keine Verwendung finden konnte. Dies unterstreicht nochmals die Wichtigkeit geeigneter Synthesewege, die auch bzw. vor allem bei der Einbettung von Diamantoiden in bestehende Strukturen funktionieren.

Die Skalierungsmöglichkeit des neuen Synthesewegs wurde genutzt, um das erste Mal chirale BINOL-basierte Phosporsäurekatalysatoren mit all-*meta* Adamantyl- bzw. Diamantyl-Substitutionsmuster darzustellen. In einer Vergleichsstudie wurde dieser sterisch besonders anspruchsvolle Katalysator bei einer reduktiven Aminierung von Acetophenon eingesetzt und zeigte vergleichbare Enantiomerenüberschüsse zum bisher besten bekannten Katalysator von bis zu 84% in dieser Reaktion.

Contents

1. Introduction

1.1 Diamondoids

Since their first description[1] and isolation[2] of the smallest representative adamantane (**1**) from crude oil, diamondoids have made their way to a broad application range in all kinds of chemistry for almost a century now. Bearing exceptional properties, i.e., lipophilicity and chemical inertness under physiological conditions,[3, 4] high rigidity,[5] and negative electron affinity,[6] the diamond like structures are found in small molecule drugs,[7] gas sensors[8] or as dispersion energy donors (DEDs).[9, 10] When Stetter published his review about the chemistry of **1** and its structural analogs in 1954,[11] the first artificial synthesis of small amounts was already published 13 years before by Prelog and Seiwerth.[12] However, he stated an exceptional status of adamantane chemistry within the field of organic chemistry and forecasted interesting results in this area if new synthetic routes would allow the isolation of larger quantities and the introduction of functional groups.[11] Hardly surprising, it was Stetter himself who picked up this problem and improved the synthesis of **1** as did von Ragué Schleyer shortly afterwards.[13, 14] Although the introduction and improvements of new synthetic pathways lead to a reliable source of lower diamondoids diamantane (**2**),[15-17] triamantane (**3**),[18, 19] and tetramantane (**4**),[20] selective functionalization for the intended use is still a problem to date.

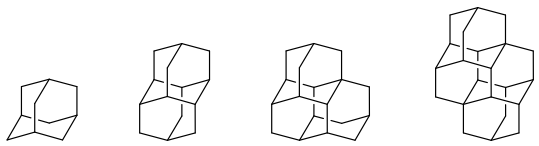


Figure 1: *Lower diamondoids adamantane, diamantane, tetramantane, and [121] tetramantane.*

Diamondoid **1** only bears two different types of C−H bonds, making its functionalization easier in comparison to its higher analogs that contain different tertiary carbon bridgeheads. Selective mono-, di-, tri- and tetrafunctionalizations, especially halogenations, have been described early in literature.[21-23] Brominated or hydroxylated diamondoids were often used as starting materials for further transformations, e.g., amination *via* Ritter reaction,[21, 24] carboxylations *via* Koch-Haaf reaction,[21, 25] or thiolations using thiourea as sulfur source.[26] All these transformations benefit from the exceptional stability of nanodiamonds as they use strongly acidic media, often incompatible with further functional groups. When it comes to higher diamondoids, side reactions like intermolecular hydride shifts and therefore isomerizations may occur.[27] Non-acidic transformations often involve radical mechanisms using hydrogen atom transfer reagents to generate diamondoidyl radicals that react with a trapping agent to introduce further functionalities or perform C−C coupling reactions. Many different systems have been presented, especially in the last years in which photoredox catalysis became more and more popular, and a variety of functional groups, i.e., azides,[28] cyanides,[29] olefins,[30] and imines[31]

were attached to a nanodiamond core. Although a radical pathway may be advantageous in terms of functional group tolerance, it introduces several problems in case of regioselectivity and reactivity. As the difference in the bond-dissociation energy for secondary and tertiary C−H bonds in adamantane is fairly close,[32] and even closer for different tertiary radicals in higher diamondoids,[33] distinguishability between these sites is challenging and a necessary requirement for the system. In addition, monofunctionalizations are hard to achieve and overreactions may occur. Therefore, the diamondoid is often used in excess which attenuates this problem but lowers practical applicability.[34, 35]

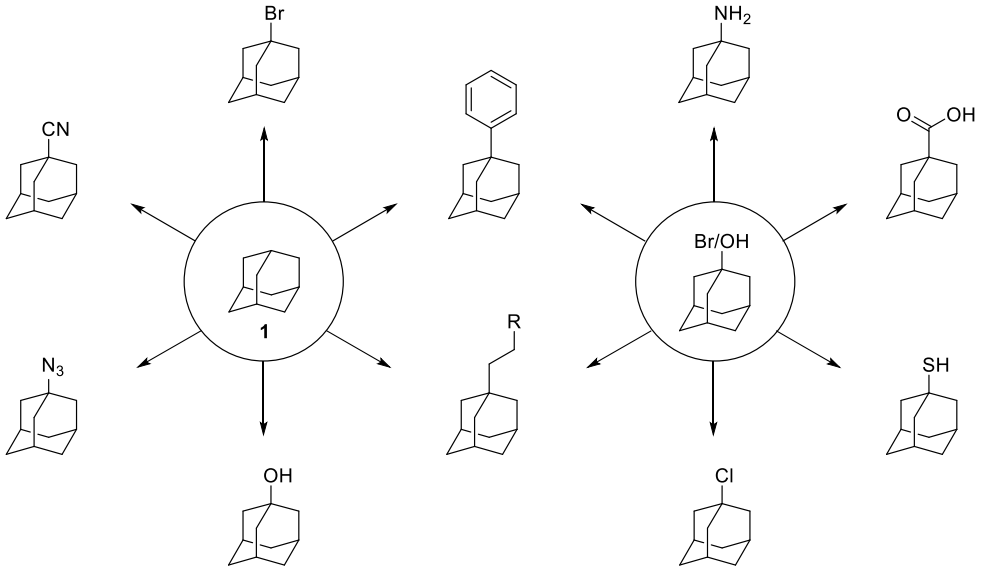


Figure 2: *Functionalization of lower diamondoids via radical or carbocationic intermediates.*

The functionalization of diamondoids is essential for their further application in life and material sciences. By far, the pharmaceutical industry already recognized the potential of diamondoid incorporation for biomedical applications. For instance, the adamantane derivatives vildagliptin (**5**) and saxaglitpin (**6**) are approved active ingredients of commercial drugs against type 2 diabetes. Amantadine and memantine (**7**) are widely used in the treatment of influenza, parkinsonism and Alzheimer's disease and some more adamantane containing drugs like adapalene (**8**), adapromine, bromantane, rimantadine or tromantadine are or have been on the market.[4, 36]

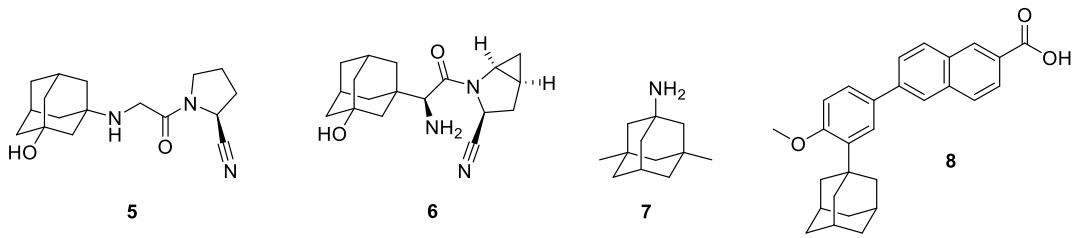
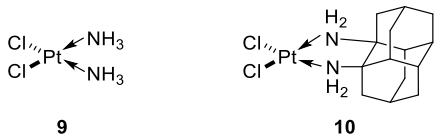


Figure 3: *Commercially available APIs containing **1** vildagliptin, saxagliptin, memantine, and adapalene.*

This success has led to broad research activities for biomedical applications. For instance, Crumpton and Santos incorporated diamondoids into the phosphate backbone of DNA *via* click chemistry of the corresponding diamondoid azides.[37] The diamondoid "doped" DNA showed higher duplex structure stability as well as thermal stability with increasing diamondoid size compared to the unmodified DNA. Bakhonsky *et al.* modified the well-known anti-cancer drug cisplatin (**9**)[38] by exchanging the two ammonia ligands for chiral 1,2-diaminodiamantane.[7] As expected, the diamantane ligand led to a significantly higher lipophilicity compared to plain cisplatin. Cytotoxic assays proved a higher potency of the (*R,R*)-1,2-diaminodiamantane modified complex **10**. Furthermore current hot topics like SARS-CoV-2 treatment are tackled by potential diamondoid containing derivatives, potentially using their anti-viral acitivity.[39]



9 **10**

Figure 4: *Anti-cancer drug cisplatin (left) and diamonodid doped cisplatin (right).*

With an increasing number of chemical transformations, functionalized diamondoids have been used in interdisciplinary fields of chemistry, physics and engineering. Diamondoid thiols, for example, form self-assembled monolayers (SAM) on gold surfaces that exhibit monochromatic electron photoemission and therefore being potential materials for photocathodes.[6, 40, 41] By coating these monolayers with graphene, the stability of the SAMs under photo irradiation was further increased, showing the versatility of different carbon modifications.[42] Hierso and colleagues used the self-assembling properties and the high volatility of **1** and **2** for the formation of diamondoid based organohybrids. Mild vapor deposition techniques allowed them to form well-defined crystals of functionalized diamondoids.[43] Previous phosphorylation of the hydroxylated diamantane starting material made it possible to layer thin palladium films onto the surface of the self-assembled organic crystals.[44] The resulting diamondoid-palladium nanocomposite is capable to detect various gases like NO_2 or NH_3 and opens up a potential application in the field of sp^3-carbon based gas sensors.[8]

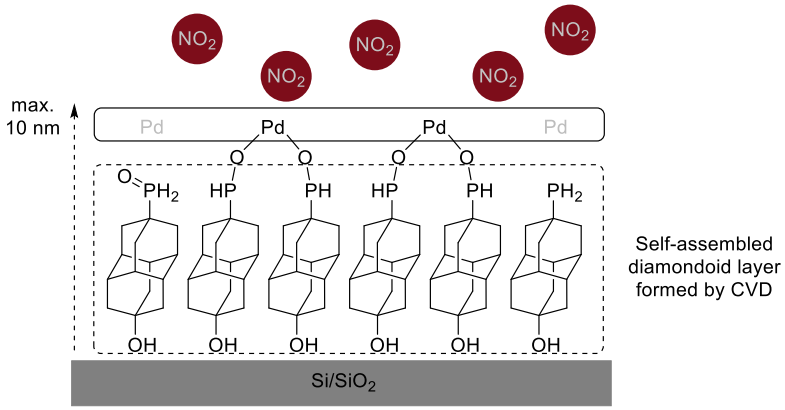


Figure 5: *Schematic representation of an sp^3-carbon gas sensor.*

Due to the renewable energy transition ("Energiewende") and the increasing demand for (portable) energy storage possibilities, diamondoid based materials were even tested as additives in classic alkali metal based batteries. Previous research had already shown a beneficial effect of diamond-like materials, e.g., in metal-organic frameworks,[45, 46] but Kreissl *et al.* showed initially that the supplement of pure diamantane amides in the electrolyte of sodium metal anodes is capable to reduce dendrite growth.[47]

1.2 Redox Condensation Reactions

As early as 1967, Mitsunobu and Yamada first described the esterification of carboxylic acids through alcohol activation by trivalent organic phosphorous compounds, mainly triphenylphosphine (**11**), and diethylazodicarboxylate (**12**, DEAD), today known as Mitsunobu reaction.[48] Releasing an oxidized phosphorous species (**13**) and a reduced hydrazine type leaving group (**14**), this was the birth of the so-called oxidation-reduction or redox condensation reactions in organic synthesis. Mitsunobu postulated a reaction mechanism *via* imidoyl phosphonium salt **15** and the corresponding phosphonium carboxylate salt **16**. However, Morrison as well as Brunn and Huisgen proposed the formation of a betaine structure. The phosphorous lone pair attacks the electrophilic nitrogen forming a P−N bond in a zwitterionic intermediate.[49, 50] Later, Guthrie and Jenkins confirmed this now called Morrison-Brunn-Huisgen intermediate **17** by ^{31}P-NMR studies.[51]

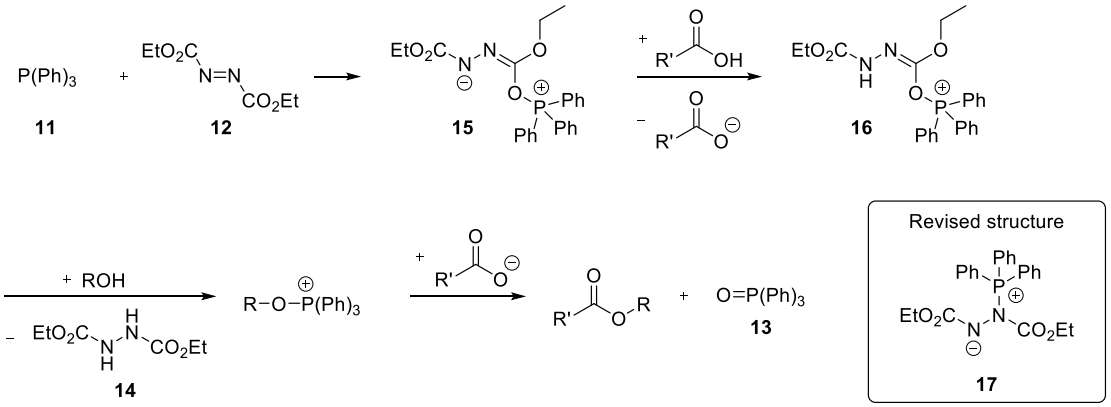


Figure 6: *Initially proposed mechanism of the first redox condensation reaction by Mitsunobu.*

Even though Mitsunobu himself extended the scope of the reaction to the preparation of amines by incorporating parts of the Gabriel synthesis,[52, 53] it took a few years until this powerful tool of alcohol conversion gained further attention in the organic chemistry community. M. J. Miller *et al.* used **11** and **12** in the synthesis of *β*-lactam **18** by an intramolecular cyclization of *β*-hydroxyhydroxamate **19**.[54] Wipf and C. P. Miller expanded the scope to even more strained aziridines implemented in a peptide backbone.[55] Through the feature of inversion of configuration at the alcohol carbon and the mild conditions, the Mitsunobu reaction also found its way into total synthesis of natural products or prodrugs.[56-58] These complex, multi-step transformations often require a non-acidic alcohol conversion due to the use of acid-labile protecting groups, such as silyl ethers. In 2001, Miyaoka *et al.* used a Mitsunobu reaction as the key step in their total synthesis of dysidiolide (**20**). The stereogenic center of free allylic

alcohol **21** was inverted by simultaneous esterification with propiolic acid to give compound **22**. Subsequent Diels-Alder reaction enabled the construction of the decaline core with correct absolute configuration of the stereogenic centers. In the same year Stork and coworkers used the Mitsunobu reaction for the first stereoselective total synthesis of quinine (**23**). They introduced an azide group on primary alcohol **24** to get enol ether **25**. Later, the group used this azide to build up the aza-bicyclo[2.2.2]octane moiety *via* Staudinger reaction[59] and substitution reaction.

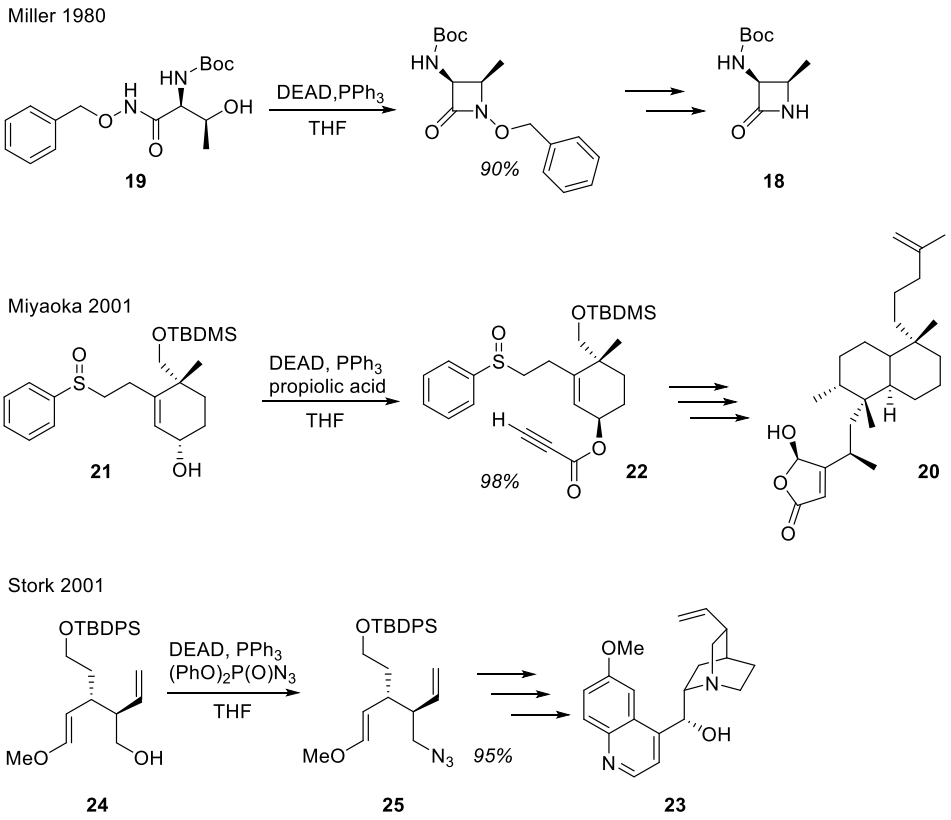


Figure 7: *Selected examples of the Mitsunobu reaction in total synthesis.*

For almost 40 years, the Mitsunobu reaction was limited to primary and secondary alcohols and only very few examples on tertiary alcohols were reported in literature, often suffering from low yields due to dehydration reactions.[60, 61] Notably, Shi *et al.* were able to extend the scope of the stereospecific Mitsunobu reaction to tertiary alcohols in the synthesis of chiral alkyl-aryl ethers at elevated temperatures in the early 2000s.[62] At the same time, the use of tertiary alcohols in redox condensation reactions became more frequent by some slight modifications by Mukaiyama and coworkers. They converted the hydroxyl group of a tertiary alcohol (**26**) to the labile trivalent phosphinite structure **27** that reacted with an electron deficient quinone (**28**, DMBQ) instead of an azo compound in the next step. The intermediate betaine structure, pre-built by oxidant and reductant,[50] now already contained the electrophilic center in form of phosphonium salt **29**. The nucleophile, a deprotonated benzoic acid derivative, releases the oxidated pentavalent diphenylphosphinate **30** as leaving group *via* backside attack, to furnish

the desired stereoinverted alkyl-aryl ester **31**.[63] Inversion rates were good even for sterically hindered menthol derivatives, but the preparation of phosphinite **27** with *n*-butyllithium as base required a solvent exchange from tetrahydrofuran to dichloromethane in the actual redox condensation reaction.

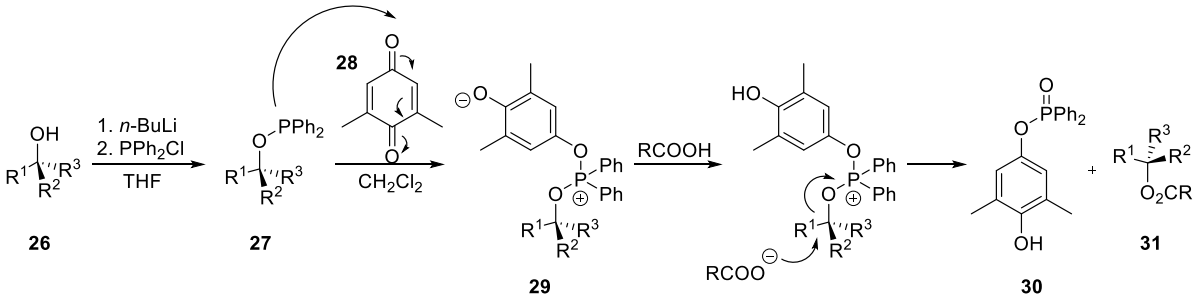


Figure 8: *Mechanistic proposal of the redox condensation reaction for tertiary alcohols with quinone oxidants.*

Further modifications of the employed oxidant lead to a variety of nucleophilic substrates as broad as in the classical Mitsunobu reaction itself. Nonetheless, screening of each nucleophile oxidant combination was necessary since undesired cross reactions like addition reactions between nucleophile and oxidant may occur, especially if basic nucleophiles are employed. Huang and Kang partially overcame this problem at least for benzylic alcohols by modifying the trivalent phosphorous species from a diarylphosphinite to diazaphosphite **32**.[64] By further altering the substituents on the phosphorous center and switching to a different oxidant, they went back to a non-preactivated system, but were still able to use basic amines as pronucleophiles.[65] Control experiments also confirmed the stereospecifity of this Mitsunobu reaction modification, underlining that this type of reaction almost exclusively proceeds *via* an S_N2-type reaction. The synthesis of the antiparkinsonian agent Piribedil (**33**) in one step in 83% yield demonstrated the power of their modification.

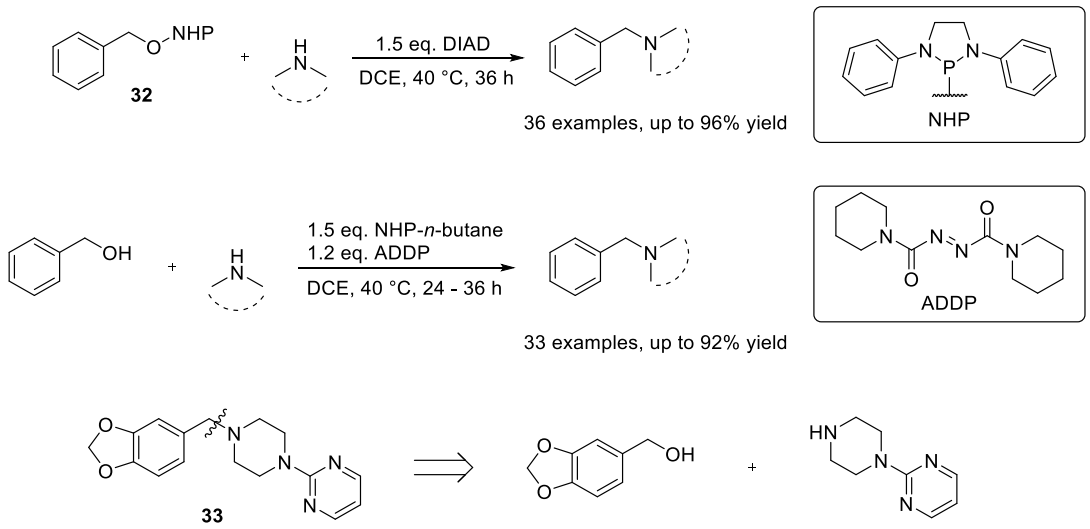


Figure 9: *Modified Mitsunobu-type reaction allowing basic pronucleophiles.*

In this work, we introduce an oxidation-reduction condensation reaction that exclusively proceeds *via* a carbocation intermediate. The S_N1-exclusivity is supported by rearrangement reactions and substitution reactions on diamondoid substrates up to triamantane. Various nucleophiles were introduced and a variety of substrates that stabilize an intermediate cation demonstrate generality.[66]

2. Diamondoids in Catalysis and as Dispersion Energy Donors

2.1 Catalysts and Ligands

Functionalized diamondoids have been implement in ligands for homogeneous and heterogeneous catalysts for more than two decades. Especially electron-rich trivalent diadamantyl phosphine ligands have become widely used in homogeneous transition metal catalysis.[67] Firstly introduced by Buchwald and coworkers in 1999 in the palladium catalyzed preparation of diaryl ethers,[68] the group of Beller picked up the incorporation of bulky and highly electron donating adamantyl groups into their phosphine ligands a year later. By attachment of one *n*-butyl and two adamantyl groups to a phosphorous core, the authors were able to increase their turnover number (TON) of 50 from the reference system (PPh_3) to 17400 (**34**, $BuPAd_2$) in the coupling of 4-chlorotoluene and phenylboronic acid.[69] These impressive initial results on the coupling of non-activated aryl halides led to the synthesis of many adamantyl based phosphorous ligands like **35** and **36**,[70-72] recently even extended to air and moisture stable diamantyl phosphine and phosphine oxide ligands, i.e. **37**.[73, 74]

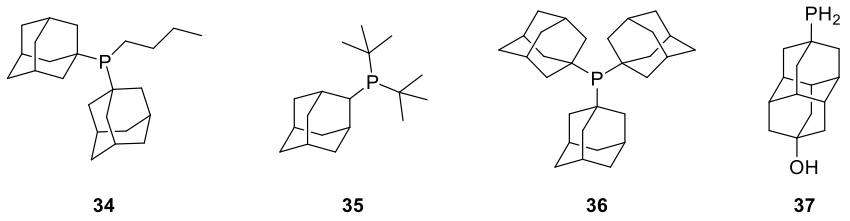


Figure 10: *Selected examples of diamondoid containing primary and tertiary phosphine ligands.*

Contrary to a palladium metal center, rhodium-(II) catalysts often consist of bidentate carboxylate ligands leading to the general formula $Rh_2(A)_4$. Charette and coworkers demonstrated that catalysts of this type are excellent in the cyclopropanation of alkenes, alkynes, and allenes and $Rh_2(Adc)_4$[75] (**38**) was usually outperforming other carboxylate ligands.[76] Despite its high activity, **38** has the drawback of a lacking stereogenic center making it unusable in often desired enantioselective reactions. Reddy and Davies solved this by using tetracarboxylates derived from chiral amino acids, i.e., adamantyl glycine, achieving good enantioselectivities in intra- and intermolecular C−H amination reactions with Rh_2(*S*-TCPTAD) (**39**).[77] Berndt *et al.* used a post-functionalization strategy, enabled by the adamantane ligand backbone, to introduce an additional urea moiety leading to bifunctional rhodium(II) complex **40**. This catalyst allows regioselective nitrenoid insertions on farnesol carbamate **41** *via*

hydrogen bonding control.[78] In this case, adamantane does not solely act as bulky or electron property influencing ligand, but also as a well-defined spacer providing the optimal distance for the second functionality within the catalyst. They were able to invert the intrinsic reactivity of common rhodium catalysts like $Rh_2(esp)_2$ or **38**, which prefer aziridination at site A over B of **41** (1.1 : 1.0 for $Rh_2(esp)_2$ and 1.4 : 1:0 for **38**), to a B site selectivity of 1.0 : 5.0 with catalyst **40**. They attributed this selectivity inversion to remote hydrogen bonding between the urea moiety and carbamate functionality of **41**.

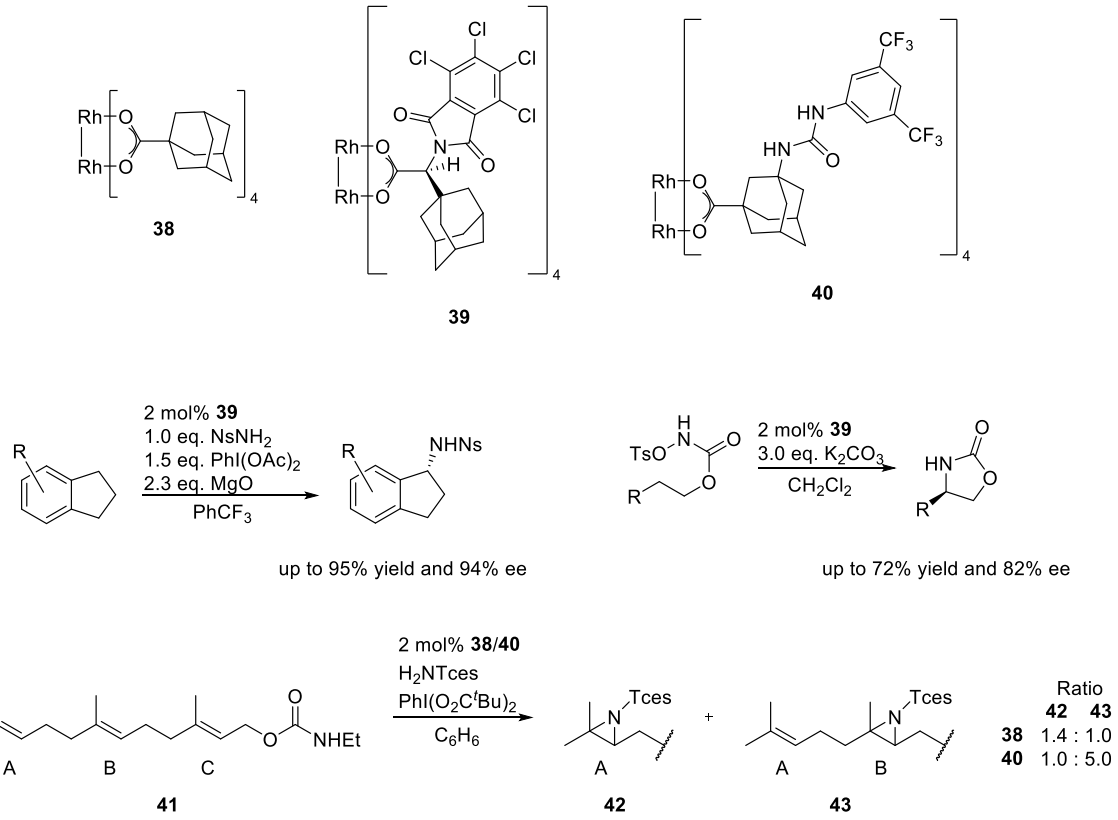


Figure 11: *Adamantane based ligands and their application in rhodium catalysis.*

Diamondoids also found their way into *N*-heterocyclic carbenes (NHCs). Wanzlick predicted this class of reactive intermediates already in 1960,[79] but only when Arduengo attached adamantane moieties directly to the nitrogen atoms, he was able to crystallize a stable NHC in 1991.[80] Mol and coworkers used this so called Arduengo carbene **44** for a modification of the Grubbs type II metathesis catalyst (**45**),[81] but unfortunately the higher thermodynamic and kinetic stability of the diamondoid NHC led to a less active catalyst which was attributed to steric shielding.[82] The group of Grubbs proved them wrong and demonstrated that slight modifications on the ruthenium catalyst lead to an excellent *Z*-selective metathesis catalyst (**46**) with up to 1000 turnovers per catalyst molecule.[83] Glorius and Schreiner instead applied a set of different diamondoid NHCs in the palladium catalyzed Sonogashira coupling.[84] Newly synthesized, more crowded diamantane NHCs performed even better as ligands in this reaction than the well-known adamantane Arduengo carbene.[85]

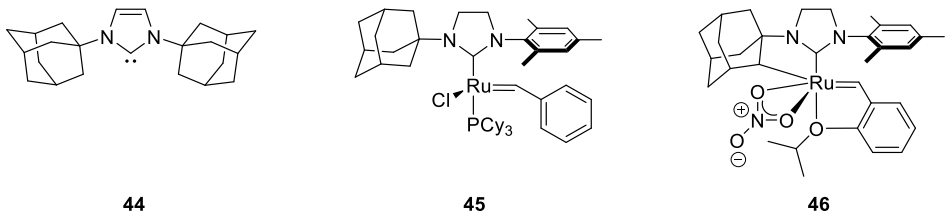


Figure 12: *Arduengo carbene and adamantane containing metathesis catalysts used by Mol and Grubbs.*

Contrary to transition metal catalysis, organocatalysis enables the possibility to include the diamondoid structure directly within the catalyst without adding it as external ligand. NHCs are already known for decades as versatile organocatalysts,[86] in particular for umpolung reactions.[87, 88] Song *et al.* demonstrated that **44** is a highly potent organocatalyst in silyl transfer reactions.[89] Schreiner and coworkers used chiral tetrapeptide **47** with an unnatural amino acid derived from adamantane[90] in the enantioselective kinetic resolution of 1,2-diols **48**.[91] The rigid adamantane backbone tends to be crucial for the high selectivity of the catalyst.[92] The group even refined the tetrapeptide for an application in multicatalytic concepts. The peptide backbone act as structural encoder for an additional catalytic motif that allows tandem reactions, e.g. oxidations, before[93] or after[94] kinetic resolution.

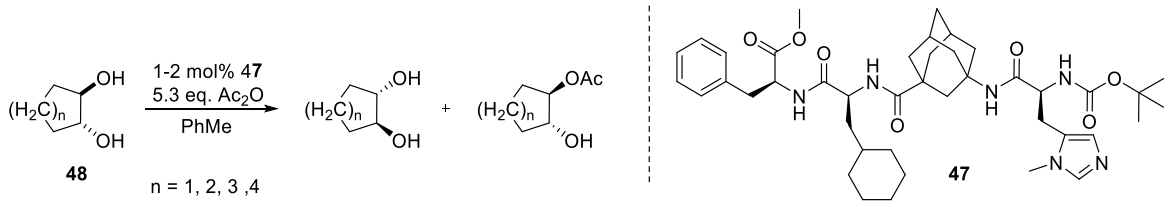


Figure 13: *Kinetic resolution of 1,2-diols catalyzed by an tetrapeptide with an adamantane backbone.*

2.2 *Meta*-Substitution and Diamondoids – a Perfect Match for London Dispersion?

London dispersion represents the attractive part of the van der Waals potential. These forces arise from spontaneously induced dipoles in non or weakly polar atoms or molecules.[95, 96] Additionally to electron richness and rigidity, the influence of London dispersion interactions on equilibria and the selectivity of chemical transformations lately became a hot topic in the community of physical organic chemists.[97] Triggered by some exceptional and unpredictable results in the outcome of chemical reactions,[98] or on the stability of organic molecules,[99-103] dispersion energy donors (DEDs)[10] were more and more implemented into catalysts or ligands to alter selectivity or, even more counter-intuitive, to increase their activity. In 2017, Lu *et al.* published a study about well-known SEGPHOS (**49**) ligands modified with DEDs mainly in the *meta*-positions of the coordination site, i.e., DTBM-SEGPHOS (**50**). They ascertained a much higher activity of catalysts with bulky ligands in the copper-catalyzed hydroamination of unactivated olefins compared to those with decreased steric bulk.[104]

These results were controversial since increased steric bulk should lead to increased steric repulsion which reduces catalytic activity. DFT computations rationalized these findings indicating that attractive through-space dispersion interactions between substrate and ligand lower the transition state energy of the rate-determining hydrocupration step more than repulsive interactions are increasing it. The authors extensively studied further common bidentate phosphorous ligands coming to the result that all investigated ligand families, i.e., MeO-BIPHEP, BINAP, and DPPBz, profit from 3,5-disubstitution and therefore from attractive through-space dispersion interactions between ligand and substrate. Especially additional *tert*-butyl groups led to a significant rate increase in all cases with a very good agreement between predicted and experimentally observed relative reaction rates.

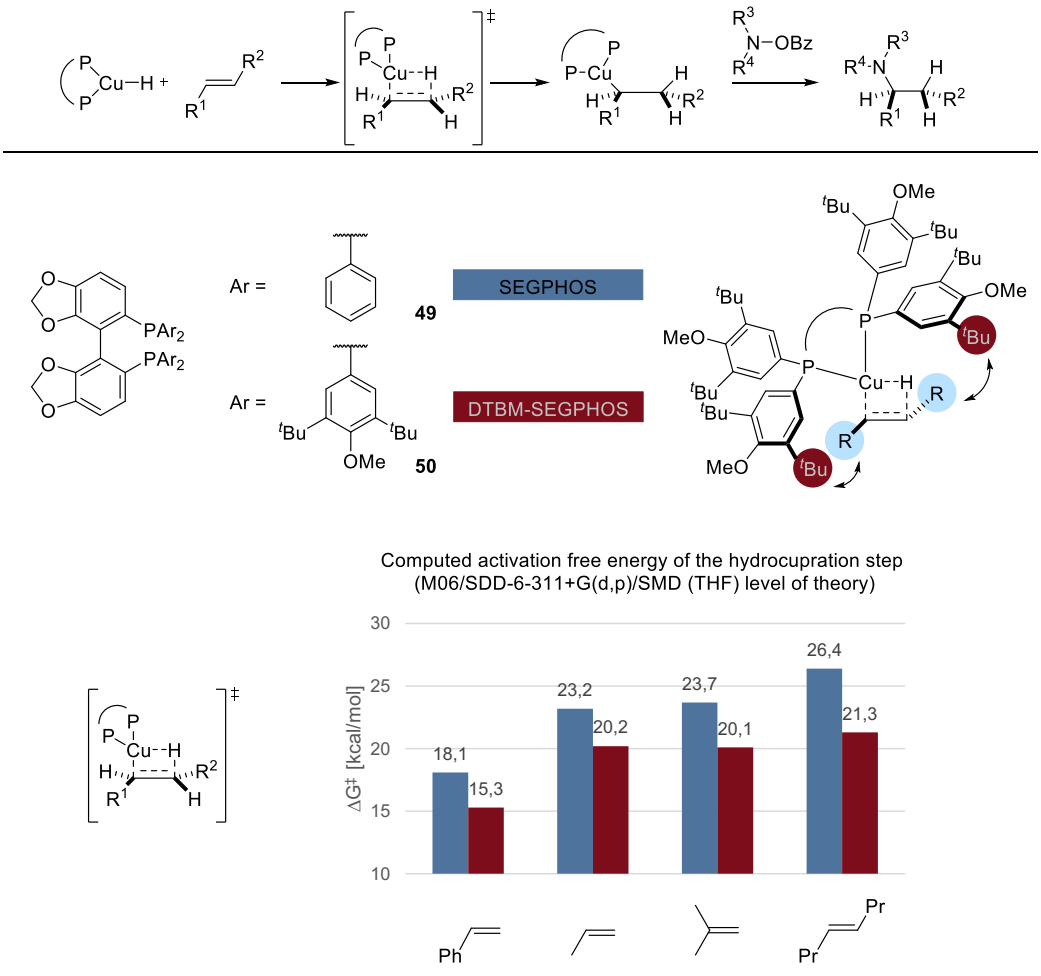


Figure 14: *Dispersion interactions in the copper-catalyzed hydroamination reaction of unactivated olefins.*

The Hartwig group broadened this concept by increasing dispersion interactions in bidentate phosphine ligands to favor enantioselective transformations. By exchanging the *tert*-butyl groups with trimethylsilyl and trimethylgermanyl groups in the *meta* positions of a very similar ligand system, they were not only able to increase the reactivity of the catalytic system, but even to distinguish between different alkyl chains in the copper-catalyzed hydroboration of 1,1'-disubstituted alkenes.[105]

Eschmann *et al.* published a detailed investigation on the effect of DEDs in the 3,5-positions of catalytically active systems shortly afterwards. They picked the Corey-Bakshi-Shibata (CBS)[106] reduction as a model system and increased steric bulk in the *meta* positions of Corey's standard oxazaborolidine (OXB) catalyst. Based on Corey's rationalization of its selectivity based on steric repulsion, the activity should have dropped significantly by increasing steric bulk on the aryl groups of the OXB. Surprisingly, the enantiomeric excess, i.e., in the CBS reduction of 2-butanone or 2-pentanone, increased by bulkier substituents on the aryl substituents of the catalyst without a negative effect on the reaction rates.[107] The influence of London dispersion interactions was additionally proven by attachment of trifluoromethyl groups instead of alkyl groups in the carbinol substituents of the oxazaborolidine. Attractive σ-π interactions were reduced by strongly electron withdrawing fluorine substituents leading to a massive drop in enantioselectivity during reduction.

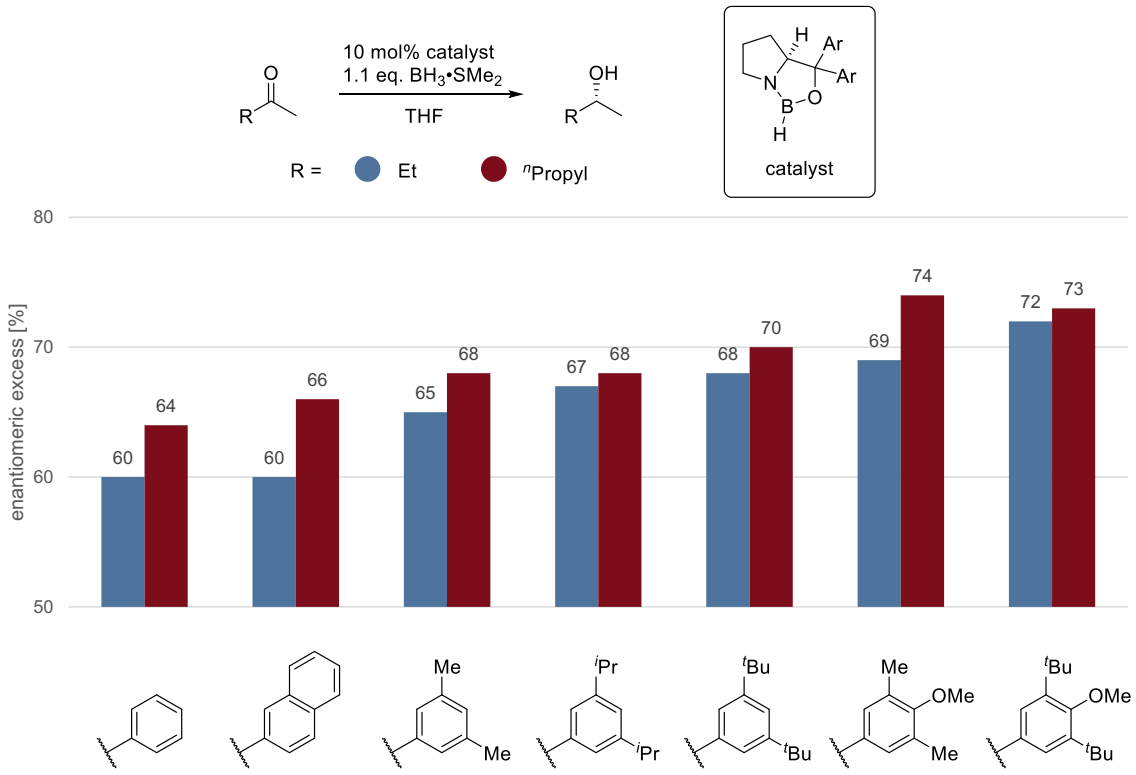


Figure 15: *Dispersion interactions as decisive factor in the CBS-reduction of ketones with similar alkyl chains.*

The examination of molecular balances allow a deeper understanding of these described effects. Molecular balances are microscopic structures, often single molecules with limited conformational flexibility, that allow the quantification of non-covalent interactions by the free energy differences of their different conformers.[108, 109] Schweighauser *et al.* investigated the *E/Z* equilibrium of azobenzene switches depending on the attached DEDs in the *meta* positions. The half-lives of the *Z*-isomer of the considered azobenzenes increased with more crowded and more polarizable substituents in the 3,5-positions, leading to a rate decrease of the *Z* to *E* isomerization. The experimentally measured free energies were in good alignment with computations at a dispersion corrected B3LYP-D3 level of theory, whereas applying uncorrected B3LYP lead to misleading, thus, wrong results.[110] This system shows that the

change from *tert*-butyl to more polarizable adamantyl groups can have a significant effect. The measured *Z*-isomer half-life of the all-*meta* adamantyl substituted azobenzene almost doubled in *n*-octane compared to its *tert*-butyl analogue. This promising result emphasizes that *tert*-butyl substituents are not the end of the road when it comes to stabilizing dispersion interactions from *meta*-substituted arenes.

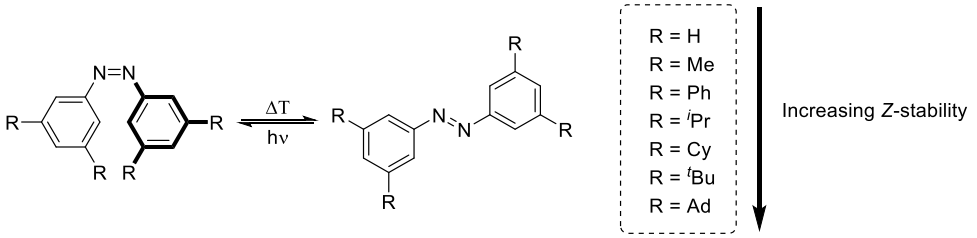


Figure 16: *Molecular azobenzene balance substituted with DEDs in meta-positions.*

Furthermore, these findings were contrary to the popular opinion that London dispersion vanishes in systems where solvent interactions come into play.[111] Schreiner and coworkers demonstrated later that intramolecular London dispersion interactions do not cancel in solution.[112] Rummel *et al.* transferred this concept to the conformational analysis of thiourea derivatives. By attaching DEDs again to the *meta* positions of bisaryl thioureas, it was possible to lower the energies of the *syn-syn* conformers and therefore shift the equilibrium towards the sterically more hindered isomers of the molecule.[113] DFT computations at the B3LYP-D3(BJ)/def2-TZVPP level of theory showed a decrease in distance of the shortest σ-σ contacts in the lowest energy conformers, indicating that the *syn-anti* and *syn-syn* conformer of **51** might benefit from London dispersion interactions. Cryogenic ^{1}H-NMR measurements proved a higher population of the *syn-syn* conformer within their investigated homologous series of dispersion energy donor substituted thioureas (H, Me, Et, ^{i}Pr, ^{t}Bu). This supports the hypothesis that bulky substituents will shift the equilibrium to the more crowded conformer due to their ability to contribute as attractive forces.

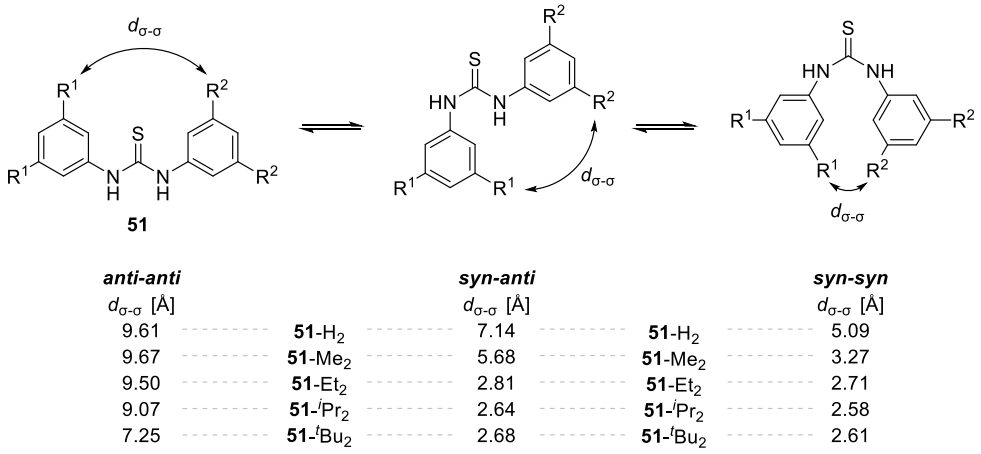


Figure 17: *Anti-anti, syn-anti, and syn-syn conformers of **51** with their shortest σ-σ distances.*

The Gschwind group expanded this concept to an organocatalytic system. Goodman and Gschwind showed in previous work that the reaction rate and the enantioselectivity of chiral BINOL-phosphoric acid catalyzed Hantzsch ester hydrogenation of imines is highly dependent on the energy levels of four types of competing transition states which they called type E_I, E_{II}, Z_I, and Z_{II}. While type E_I and Z_{II} lead to an *S*-configuration of the final amine, Z_I and E_{II} will lead to an *R*-configuration in the product. Influencing the energy levels will impact the reaction rate as well as the enantioselective outcome of the reaction which was already demonstrated by Gschwind through irradiation of the reaction mixture by UV-light (λ = 365 nm) to populate the *Z*-ketimine structure.[114, 115] A similar influence was possible by attachment of bulky *tert*-butyl groups as DEDs and therefore stabilization of the *Z*-imine in the ground state. In this case, E_I and Z_I type are predominantly in operation having a direct influence on the stereochemical outcome of the reaction. A higher population of the *Z*-imine results in a Z_I pathway whereas the *E*-imine favors type E_I. Strong dispersion energy donors made it possible to shift the equilibrium of the CPA-imine complex in favor of the *Z*-isomer and reach excellent enantioselectivities up to 99%. Again, the all-*meta* substitution pattern was the most effective in maximizing stabilizing interactions.[116]

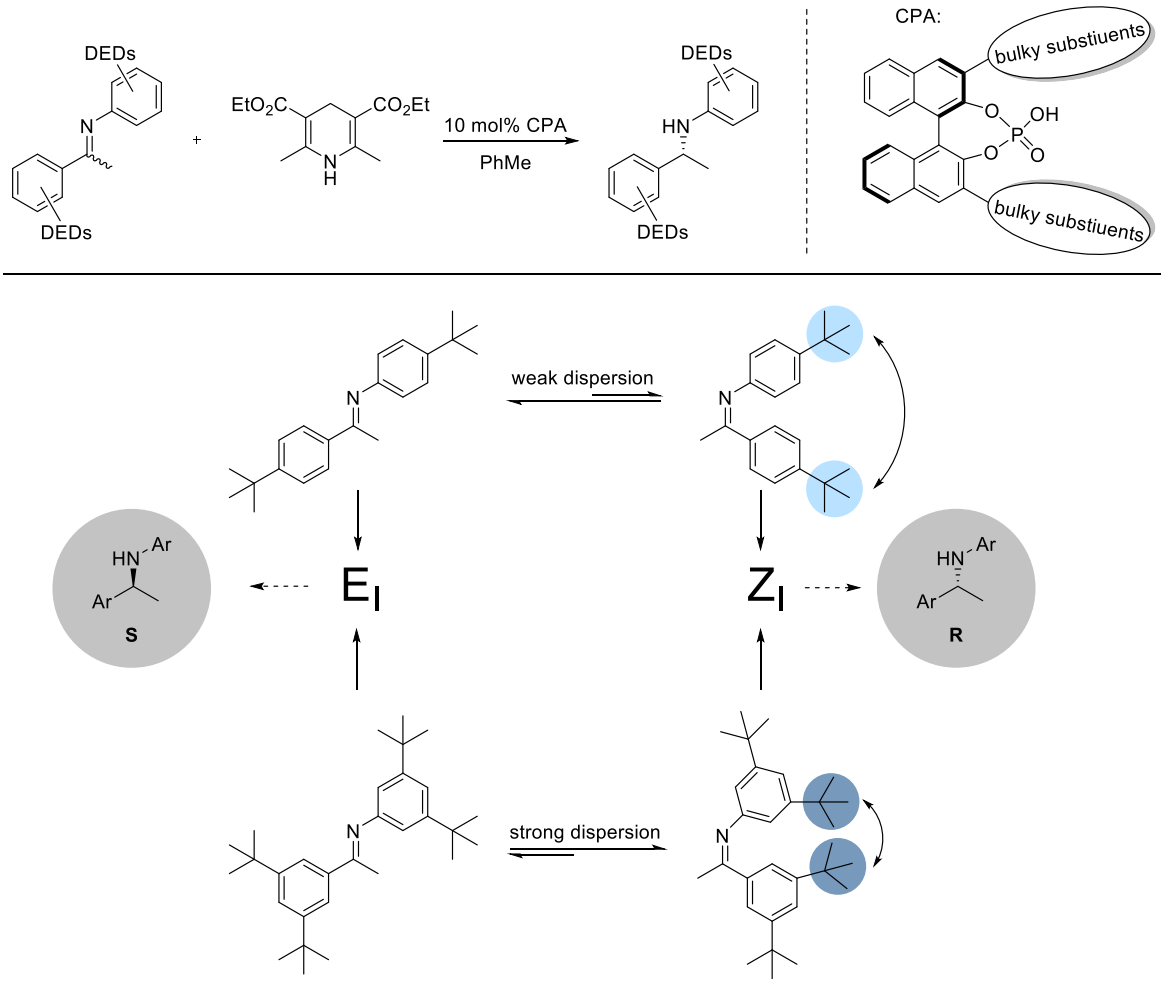


Figure 18: *Dispersion interactions as key factor in enantioselective organocatalyzed hydroaminations.*

Rösel *et al.* used DEDs to stabilize the labile molecule hexaphenylethane,[117] which was mistakenly introduced by Gomberg in 1900.[118] Already predicted by Schreiner and Grimme, this molecular system is counterintuitively stabilized by increased steric bulk.[100] The London dispersion forces by additional substituents in the *meta*-positions of the molecule's arenes add up to overcompensate repulsive interactions, making the molecule more stable and even observable in solution, which was demonstrated for the *tert*-butyl and the adamantyl derivative (**52**). While investigating several groups for their ability to act as DED including Me, ^{i}Pr, ^{t}Bu, Ad, Cy, and Ph, it manifested that spherical rather than flat substituents contributed with stronger interactions, making them a better choice in most cases when it comes to stabilization *via* London dispersion interactions.

This does not only apply intramolecularly, but also intermolecularly, which was demonstrated at the "monomeric" triphenylmethane system enabling the shortest intermolecular hydrocarbon H−H contact of 1.566 Å in 2017.[119] Normally, such short H−H contacts predominantly occur intramolecularly where the configuration of the molecule make these "collisions" unavoidable.[120] In this special case, stabilizing non-covalent interactions between the *tert*-butyl groups of triphenylmethane derivative **53** lead to a spontaneous close head-to-head contact of the two terminal hydrogen atoms. This is not only applicable to pure hydrocarbon systems. Holtrop *et al.* showed that frustrated Lewis pairs[121] of triarylamine and triarylborane are stabilized in the same manner like their triphenylmethane counterpart.[122]

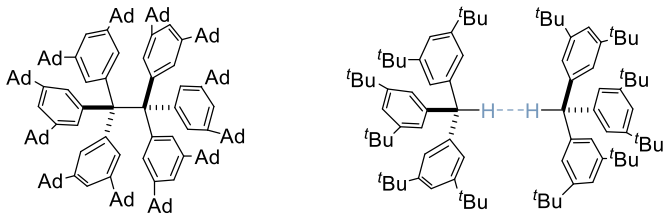
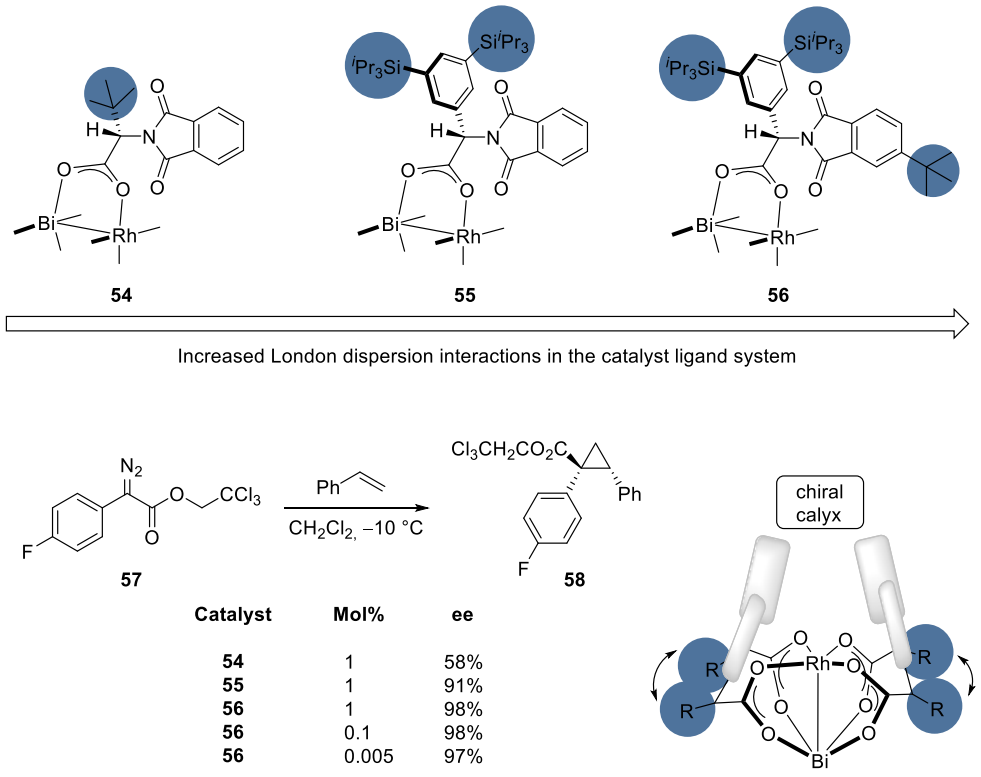


Figure 19: *London dispersion enabling short intermolecular H-H contact as well as hexaphenylethane evidence.*

The group of Fürstner introduced stabilizing dispersion energy donors into their bismuth-rhodium paddlewheel catalysts. One key factor for these types of catalysts is a well-defined chiral calyx, formed by the *N*-phthalimido part of the ligand system. Several groups made improvements towards a more confined binding-site by replacing one rhodium atom of the former dirhodium complexes by bismuth, giving highly active and enantioselective heterobimetallic catalysts like **54**.[123, 124] Changes on the ligand system are often made with the objective to increase enantioselectivity by increased steric bulk, negatively affecting the activity of the catalyst. To circumvent this problem, the Fürstner group envisioned an improved ligand design based on attractive London dispersion interactions. Replacement of the *tert*-butyl group of **54** by an all-*meta* tri-*iso*-propyl-silyl (TIPS) substituted phenyl ring brings multiple non-covalent attractive interactions in the ligand backbone, leading to a catalyst with a more confined chiral calyx (**55**). Addition of an extra *tert*-butyl group at the *N*-phthalimido residue

further increases possible non-covalent interactions. Indeed, Fürstner and coworkers were able to demonstrate an increase in enantioselectivity in the [2+1] cycloaddition reaction between carbene precursor **57** and styrene. Whereas **54** gives an enantiomeric excess (*ee*) of only 58%, "dispersion improved" catalyst **55** yield the desired product **58** with an *ee* of 91%. Superior catalyst **56** added additional 7% *ee*, demonstrating that London dispersion is a powerful tool in catalyst/ligand design. DFT computations (def2-SVP level of theory) validated that the TIPS groups are accountable for 32% of total dispersion energy in the molecule while the *tert*-butyl groups add not negligible 12%. Most importantly, the high activity of the cyclopropanation catalysts did not suffer from the modifications made on the ligand, which they demonstrated by low catalyst loadings down to 0.005 mol% while maintaining full conversion of the substrate under reference conditions. Further 32 examples in [2+1] cycloaddition reactions always showed an outperformance of **56** over **54** with former inaccessible high enantiomeric excesses of up to 99%.[125]



Catalyst	Mol%	ee
54	1	58%
55	1	91%
56	1	98%
56	0.1	98%
56	0.005	97%

Figure 20: *DED-doped bismuth-rhodium complex for increased enantioselectivity in cyclopropanations.*

Schoenebeck and coworkers chose a different route for the investigation of London dispersion in transition metal catalysis. Their selective *ortho*-functionalization of adamantyl arenes enables direct implementation of lipophilic tails into medically relevant compounds *via* cross-coupling reaction. They introduced an adamantane moiety at the positon *ortho* to a bromide residue of their starting material. The latter performed Negishi type coupling reaction only addressed the sterically hindered site of the molecules and left other less sterically hampered reactive sites like triflates or chlorides untouched. This can be explained by an stabilization of

the transition state for the oxidative addition by London dispersion interactions between the *tert*-butyl groups of the palladium catalyst's ligand and the adamantane framework in *ortho*-position of the substrate.[9] This example proves that the effect of London dispersion interactions is not necessarily connected to *meta*-substituents, even though an empirical accumulation is observed in certain systems.

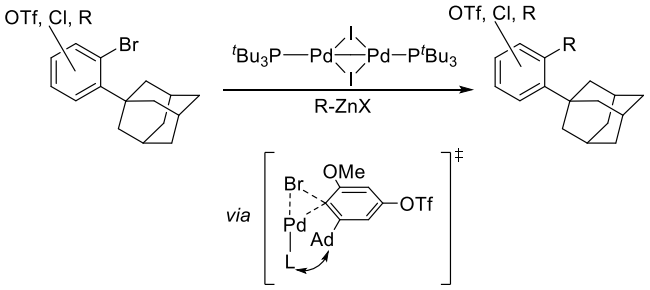


Figure 21: *Selective ortho-functionalization by cross-coupling facilitated by London dispersion interactions.*

Nonetheless, the decisive influence of non-covalent interactions can be found in many other instances, even in cases that were believed as being well understood, for example, the A-values for cyclohexyl derivatives.[126, 127] Wilming *et al.* shifted the equilibrium of a 2,2'-disubstitued 9,9'-bifluorenylidenes system (**59**) with the attachment of various DEDs. Even though the authors showed with symmetry-adapted perturbation theory that the dispersion energy theoretically increases by implementation of very bulky adamantane and diamantane residues in 2 and 2' positions, the spatial proximity of the substituents in the folded state of this molecule led also to a distinct increase of repulsive interactions that cannot always be compensated by London dispersion. However, in this case the cyclohexyl moiety seemed to perfectly fit the requirements of this molecular balance system outperforming all other DEDs when it comes to *Z*/*E* ratio. [128]

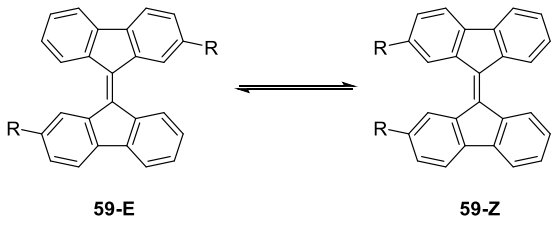


Figure 22: *Equilibrium of a bifluorenylidene balance influenced by DEDs in 2,2'-positions.*

König *et al.* and Schümann *et al.* gained further insights by investigation of a disubstituted cyclooctratetraene balance system.[129, 130] Firstly introduced by Streitwieser and coworkers in 1981, the unusual equilibrium between the 1,4 (or unfolded) and 1,6 (or folded) conformer was a topic of interest. Unexpectedly, the folded conformer was favored over the unfolded one, as observed during ^{1}H-NMR experiments. Streitwieser and Paquette rationalized that the *tert*-butyl group had to be positioned at the edge of steric repulsion so that the more congested isomer is

still in favor. Additionally they already speculated about attractive intramolecular van der Waals forces shifting the equilibrium towards the crowded 1,6-conformer.[131-133] König and Schümann connected the equilibrium between the unfolded 1,4- and the folded 1,6-isomer to the dispersion energy contribution of the substituents showing that bulky silyl groups or diamondoids as DEDs are important contributors in the shift of the equilibrium to the folded state.

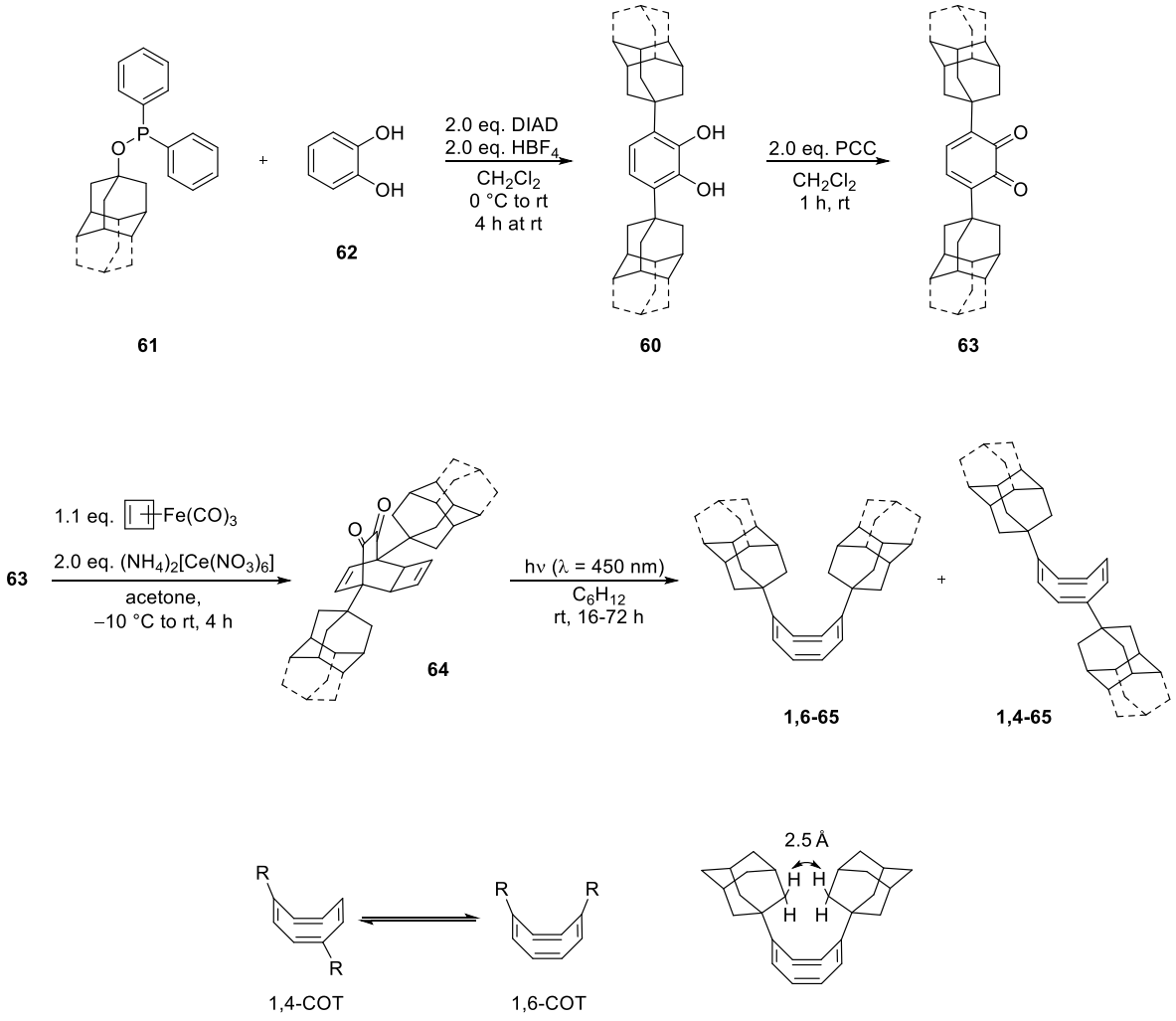
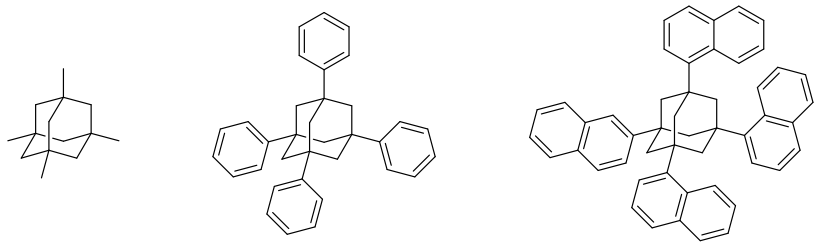


Figure 23: *COT-balance containing lower diamondoids for increased London dispersion interactions.*

For this study, especially the incorporation of lower diamondoids **1** and **2** was a significant obstacle since appropriate precursors comparable to the *tert*-butyl system were not available to date. By implementation of our recently published method for the generation of carbocations, which works particularly well for diamondoids, the generation of the desired 3,6-diamondoid substituted *ortho*-hydroquinones **60** was facile and reproducible. Starting from adamantyl diphenylphosphinite **61**, direct alkylation of readily available 1,2-dihydroxybenzene **62** was achieved. Although the 3,5-alkylated isomer was the main product, sufficient amounts of **60** were accessible and separable even on gram-scale. After oxidation, the corresponding *ortho*-

quinone **63** reacted in a [4+2] cycloaddition with cyclobutadiene to cyclic structure **64** that, upon irradiation with blue light (λ = 450 nm), decarbonylates and undergoes electrocyclic ring opening to yield a mixture of the desired COT isomers (**65**). The van der Waals contact between hydrogen atoms within the substituents of disubstituted COT **65** is around 2.5 Å and therefore in the ideal range of the delicate equilibrium between steric repulsion and dispersive attractive interactions.[134]

Mollenhauer and colleagues demonstrated that stabilization of molecules by London dispersion interactions is not only applicable if bulky substituents like diamondoids are attached in the periphery of various molecules, but also if materials have an adamantane-like core structure,[135] which might be interesting for tuning the physical properties of such compounds.[136] Within their theoretical study, they systematically investigated the contribution of medium- and long-range dispersion interactions to the binding energy of inorganic and organic cluster dimers, e.g., $AdMe_4$ (**66**), $AdPh_4$ (**67**), and $AdNP_4$ (**68**). They demonstrated that dispersion energy contributions increase with increasing substituent size, which can mainly be attributed to increasing core-substituent and substituent-substituent interactions.



66 **67** **68**

Figure 24: *Organic molecular cluster materials with general structure AdR_4.*

In this work we present a general method for the funtionalization of lower diamondoids with various nucleophiles. This strategy allows the incorporation of diamondoid structures into natural as well as artificial systems, e.g., giving access to important precursors for the synthesis of double *meta*-substituted iodobenzenes and anilines. These structures are important building blocks for the construction of systems or catalysts that benefit from London dispersion interactions. So far, the attached DEDs were often limited to *tert*-butyl or bulky silyl groups. Our work expands the limits of highly available DEDs by a general method for diamondoid substituted all-*meta* arenes to push boundaries in catalyst design and molecular balances.[137]

3. Perspective

The mild functionalization of diamondoids *via* redox condensation may provide facile access to different structures in the field of material science. For instance, Langhals and coworkers connected the two chromophores benzoperylenetriscarboximide and perylenecarboximide by a rigid diamantane core to investigate the Förster resonance energy transfer (FRET)[138] in such dyads.[139] They used the corresponding anhydrides **69** and **70** as well as 4,9-diaminodiamantane **71** in a condensation reaction to prepare their desired donor acceptor substituted diamantane linked dyad **72**. In comparison to, e.g., a bicyclo[2.2.2]octane linker, they had to run the reaction at 230 °C for 3 h to get reasonable amounts of **72**, but still the yield of the reaction was very low only achieving 3% of the target compound. Furthermore, the reaction temperature had to be increased beyond 150 °C, which is on the edge of stability for many organic compounds.

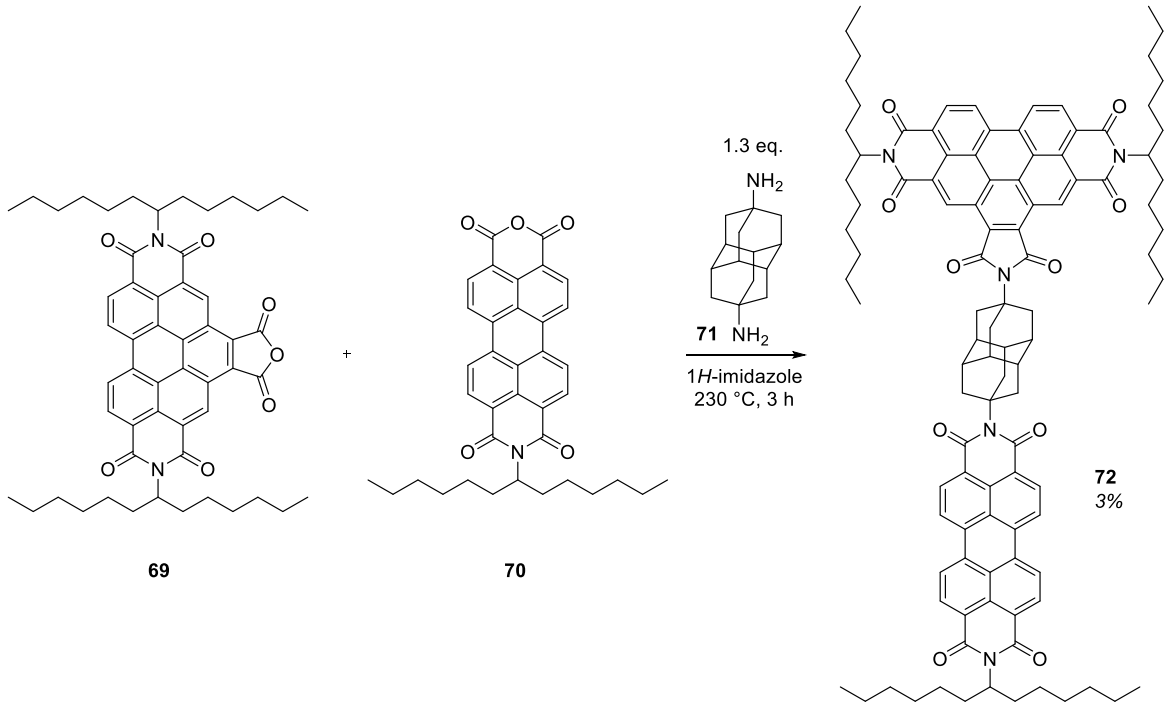


Figure 25: *Synthesis of a dye with a stiff diamantane linker between the chromophores.*

Since our newly developed method allows the functionalization of diamondoids in high yields already at room temperature in neutral media, previously excluded labile structural motifs can now be connected to diamondoids, making use of their exceptional properties in the future. Diamondoid containing bioactive molecules do not longer have to be built by a bottom-up principle, but direct alkylation at suitable nucleophilic positions is possible. This might even effect retrosynthetic planning in total synthesis, a field in which late stage functionalization of complex molecules is highly appreciated.

In addition, the high-volume access to diamondoid containing and therefore rigid, polarizable and bulky end-groups opens up further improvements in reactions in which London dispersion represents the decisive factor in controlling selectivity and/or reactivity. To date, limited synthetic access to these building blocks only allowed theoretical or conceptual studies and, e.g., catalyst improvement could not be tackled. We hope that our promising initial results act as a starting point in this research field and further theoretical understanding will be supported by experimental evidence.

Research topics not attributed to London dispersion or catalysis might also directly profit from the incorporation of all-*meta* diamondoid substituted arenes. Until 1985, only two allotropes of carbon were known, namely diamond and graphite.[140] Discovery of C_{60}-buckminsterfullerene led to intense studies on further carbon allotropes, including, e.g., graphene[141] and carbyne, a linear chain consisting of sp-hybridized carbons. The latter is often modelled by oligoynes capped by bulky endgroups,[142, 143] stabilizing this labile molecule.[144] The loss of the endgroup effect by increased alkyne chain length emphasizes the necessity of new capping groups providing additional stability to monodisperse polyynes.[145] Here, all-*meta* diamondoid substituted arene substituents might be a rational way to increase the possible chain length of oligoyne structures.

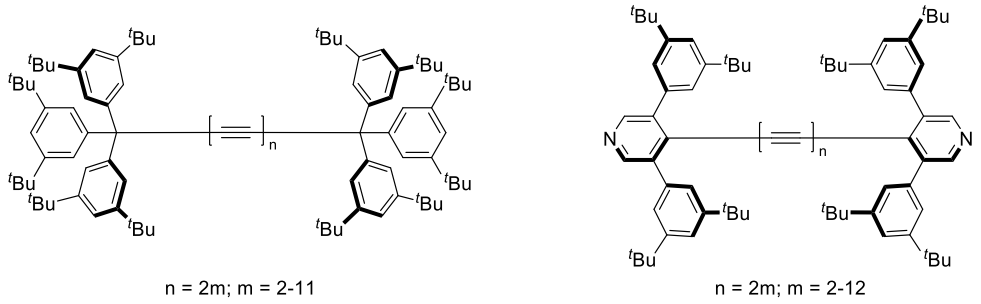


Figure 26: *Air and moisture stable oligoynes as models on the way to the elusive carbon allotrope carbyne.*

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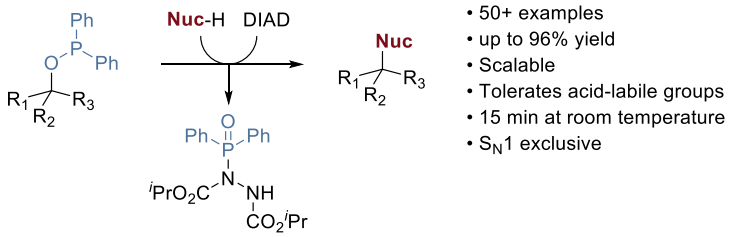
5. Publications

5.1 Functionalization of Diamondoids *via* a New S_N1 Redox Condensation



"We present a new acid free method for the generation of carbocations based on a redox condensation reaction that enables S_N1 reactions with a variety of nucleophiles. We utilize readily synthesized phosphinites that are activated by diisopropyl azodicarboxylate to form betaine structures that collapse upon adding a pronucleophile, thereby yielding reactive carbocation intermediates. We also employ this approach for the alkylation of some bioactive molecules."

Reference

L. Ochmann, M. L. Kessler, P. R. Schreiner, *Org. Lett.* **2022**, *24*, 1460-1464.

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Alkylphosphinites as Synthons for Stabilized Carbocations

Lukas Ochmann, Mika L. Kessler, and Peter R. Schreiner*

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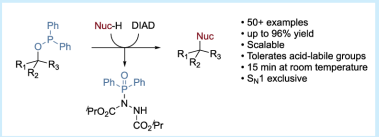
ABSTRACT: We present a new acid-free method for the generation of carbocations based on a redox condensation reaction that enables S_N1 reactions with a variety of nucleophiles. We utilize readily synthesized phosphinites that are activated by diisopropyl azodicarboxylate to form betaine structures that collapse upon adding a pronucleophile, thereby yielding reactive carbocation intermediates. We also employ this approach for the alkylation of some bioactive molecules.



Since their discovery by Mukaiyama,[1] oxidation−reduction condensation reactions have been widely used as tools for the interconversion of alcohols to many different functional groups. Best known is the Mitsunobu reaction that has been key for the construction of complex molecules for over 50 years.[2] Although the substrate scope was expanded by improvement of the reaction conditions, oxidation−reduction condensation reactions are mainly limited to structures that allow an S_N2 reaction pathway.[3] The necessity of a backside attack of the nucleophile toward the corresponding phosphonium salt excludes substrates that do not allow these trajectories, such as cage compounds, e.g., diamondoids.[4] This compound class with adamantane as its parent structure combines many different properties such as high rigidity,[5] negative electron affinity,[6] lipophilicity,[7] and chemical inertness under physiological conditions,[8] therefore leading to many applications in various fields. Derivatives of the smallest diamondoids, adamantane and diamantane, have been used as catalyst backbones,[9] linear spacers,[10] dispersion energy donors,[11] gas sensors,[12] or highly potent drugs.[13] The selective functionalization of such diamond-like structures is important for the further utilization and incorporation in multifunctional complex structures. Nonetheless, this functionalization remains challenging due to the high stability of diamondoids, and many different methods have been presented over the years, often requiring harsh reactions conditions like overstoichiometric addition of Brønsted/Lewis acids and nucleophiles,[14] high reaction temperatures and long reaction times,[15] or the necessity of special electrochemical[16] or photochemical equipment.[17] This often leads to a lack of generality for varying functional groups and low yields. We envisioned the development of a redox condensation for the generation of stabilized carbocations that then can be trapped by any given nucleophile. As a starting point, we chose the latest developed method for the nucleophilic substitutions of tertiary alcohols via this reaction type by Mukaiyama and co-workers using various trivalent phosphorus species as the reductant and substituted *p*-benzoquinones as the oxidant. As already shown in a few examples by Mukaiyama et al., the combination of $PhOPPh_2$ and 2,6-di-*tert*-butyl-benzoquinone (DBBQ) performed best in the substitution for 1-adamantanol, i.e., giving adamant-1-yl-4-chlorobenzoate in up to 83% yield after 24 h reflux in DCM.[3b] This route was only applicable to carboxylic acids and not to generic nucleophiles since most of them also react with the deployed oxidant/reductant or lack of sufficient acidity for the protonation of the intermediate betaine structure. Preformation of the O−P bond via synthesis of the corresponding phosphinites or diazaphosphites overcame this problem and extended the scope to a larger variety than just carboxylic acids, but isolation of these trivalent phosphorus intermediates is often tedious.[18] This limits upscaling processes and decreases practical applicability. Also every change in reactants must typically be accompanied by a new screening for suitable oxidants.[19]

Mixing readily available diamondoid alcohols[20] (**1a−1c**) with cheap commercially available chlorodiphenylphosphine and a slight excess of pyridine in DCM resulted in quick formation of the diamondoid diphenylphosphinites (**2a−2c**), which are simply isolated by filtration over a pad of neutral alumina oxide, in excellent yields of 90−96% in quantities up to 100 mmol (Scheme 1). The use of mild amine bases instead of strong alkoxides or lithium bases is rather unusual, as is the stability of the isolated diamondoid phosphinites against air and moisture.[18,21] No degradation was observed by GC-MS or ^{31}P NMR spectroscopy even after 12 months of storage.

Activation of the phosphinite with quinones is proposed to form a betaine structure that deprotonates an acidic pronucleophile. The intermediate phosphonium salt then collapses upon attack of the anionic nucleophile to a

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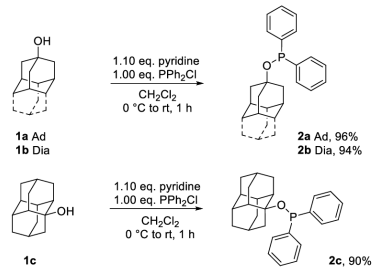
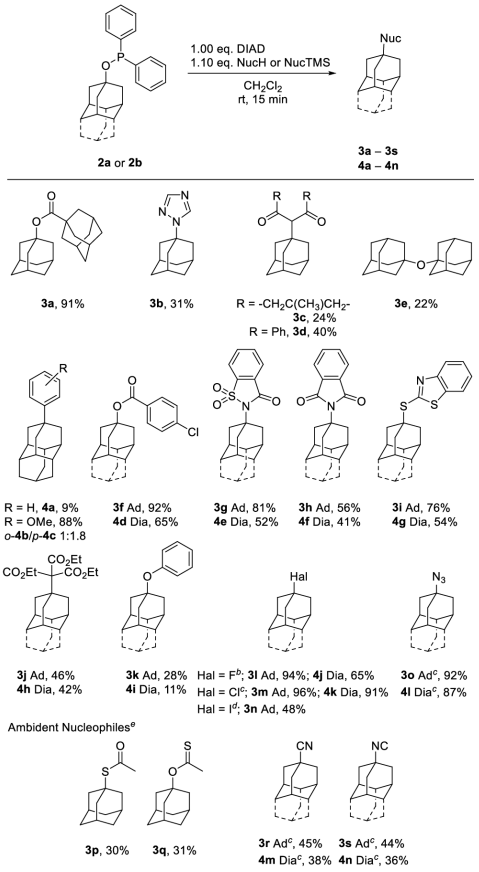
Scheme 1. Synthesis of Diamondoid Phosphinites

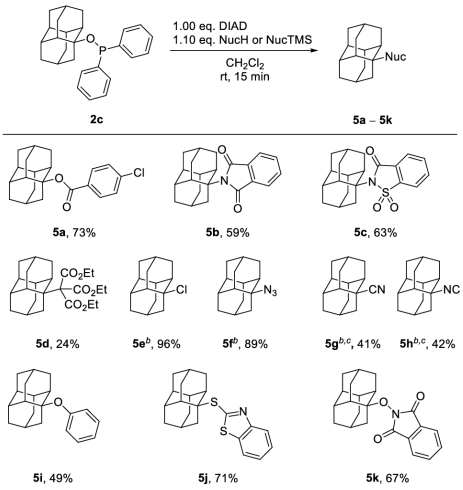


Scheme 2. Scope for 1-Adamantanol/4-Diamantanol-Derived Phosphinites[a]



[a]Yields of pure, isolated products are given on a 1 mmol scale. [b]HBF_4 as the nucleophile. [c]TMS derivative as the nucleophile. [d]NH_4I as the nucleophile. [e]In each case both products were isolated from the same reaction mixture.

Scheme 3. Scope for 1-Diamantanol-Derived Phosphinites[a]



[a]Yields of pure, isolated products are given on a 1 mmol scale. [b]TMS derivative as the nucleophile. [c]Nitrile **5g** and isonitrile **5h** were isolated from the same reaction mixture.

phosphinate leaving group and the desired substituted alcohol.[3b] Screening of further structures for the oxidative activation of the phosphinite showed that azo compounds are superior in this former rate-determing step, and they react quickly with the trivalent phosphorus already at room temperature. Subsequent addition of an acidic pronucleophile leaves indeed the desired substitution product as well as a phosphonohydrazine as the leaving group.[22] Screening of nucleophiles revealed that this is a general reaction that works with many (mildly) acidic nucleophiles or compounds bearing labile TMS−R bonds. The scope of nucleophiles is at least as broad as in Mitsunobu reactions, allowing the formation of C−C (sp, sp^2, sp^3), C−N, C−S, C−O, and C−Hal bonds on severely sterically hindered substrates in reasonable to excellent yields within very short reactions times at ambient conditions (Schemes 2 and 3). As expected, anisole as activated arene gives a much higher yield of 88% (**4b**/**4c**) in an electrophilic aromatic substitution reaction compared to only 9% for relatively unreactive benzene (**4a**).

There is a noticeable significant difference in yields with silylated nucleophiles as compared to those with the corresponding acids (i.e., **3m**, **3o**, and **3r**/**3s**). This might be a direct cause of the transsilylation/deprotonation step after betaine formation. Upon protonation, oxygen remains reasonably nucleophilic, attacking the positively charged phosphorus forming a five-membered ring[23] with subsequent fragmentation to the diphenylalkylphosphinate (**6**, see SI). Indeed, this structure is observed as the only byproduct if the deployed pronucleophile is not acidic enough to quantitatively protonate the betaine structure.

Further substrate screening was carried out with $TMSN_3$ as the nucleophile. TMSCl was unsuitable in most cases due to the formation of volatile compounds or hydrolytically labile bonds. We were able to functionalize bridgehead diamondoid alcohols bearing additional functional groups to generate

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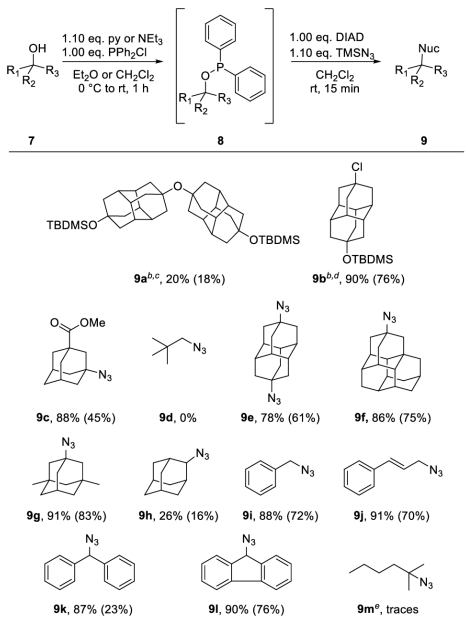
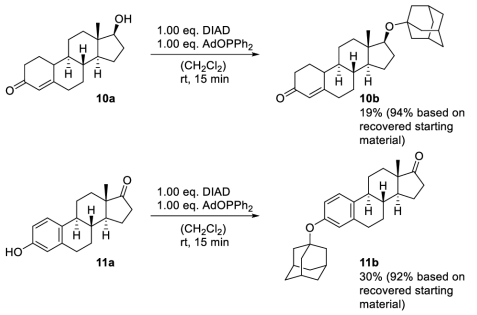
Scheme 4. Scope for Additional Primary, Secondary, and Tertiary Substrates[a]



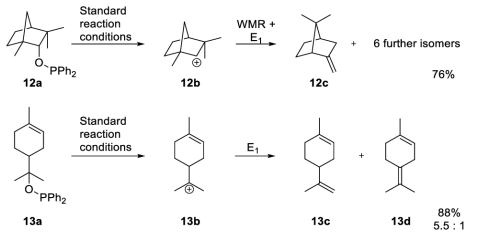
[a]Yield is given based on trivalent phosphorus content (determined by DIAD titration) for comparability; yield of pure, isolated products over two steps is given in parentheses; 1 mmol scale. [b]0.1 mmol scale. [c]9-(*tert*-Butyldimethylsiloxy)diamantan-4-ol as a nucleophile. [d]TMSCl as a nucleophile. [e]*n*-BuLi as a base.

Scheme 5. Phosphinite Activation as an Alkylation Method for Complex Bioactive Molecules



precursors of γ-adamantyl glycine[24] or memantine (cf. Scheme 4, **9c** and **9g**), higher diamondoids like 9-triamantanol (cf. **9f**), and even 2-adamantanol via its secondary carbocation (cf. **9h**). Further, (diamondoid)diols like 4,9-hydroxydiamantane (cf. **9e**) and monoprotected diols (cf. **9a** and **9b**) react in a similar fashion in comparable yields without observable decomposition of the acid-labile protecting group.

Scheme 6. Experiments to Support Carbocation Formation



We also employed stabilized allylic and benzylic carbocations and obtained benzylazide **9i**, cinnamyl azide **9j**, and 9-azidofluorene **9l** in yields above 70% over two steps. The significantly lower yield for diphenylazide **9k** is the result of the decreased air stability of its phosphinite structure (87% isolated product relative to trivalent phosphorus content vs 23% relative to the starting alcohol). For primary alkyl substrates, where the formation of a cation would be highly disfavored, fragmentation of the betaine occurs instead of carbocation formation. A substitution or rearrangement product is not observed (cf. Scheme 4, **9d**). For tertiary alkyl substrates, we just found traces of the desired substitution product (**9m**). Analysis of the reaction mixture via GC-MS indicated significant formation of olefinic products which is a direct consequence of the instability of the carbocationic intermediate that triggers α-proton elimination. The neutral conditions of the reaction prevent further equilibration to the substitution product.

Due to the mild reaction conditions, we envisioned that this redox condensation substitution is also a suitable alkylation method for complex molecules that circumvents potential isomerization or decomposition. Especially the incorporation of adamantane moieties to bioactive molecules is of great value, as it increases their lipophilicity and therefore the ability to pass the blood−brain barrier.[7,25] We chose the steroids testosterone **10a** and estrone **11a** as model substrates. Both are adamantylated at their alcoholic position to the new compounds **10b** and **11b** with just 1 equiv of *in situ* generated alkylation reagent in yields of 19% and 30% within 15 min and almost full recovery of unreacted starting material (Scheme 5).

To provide evidence for the formation of a carbocation intermediate, we applied this reaction to fenchyl alcohol and α-terpineol. The generation of 2-norbornyl cation derivative **12b** should lead to a kinetically favored Wagner−Meerwein rearrangement followed by substitution/elimination.[26] For the terpinyl cation (**13b**), an E_1 elimination to the kinetic product limonene **13c** should be favored, and the neutral conditions of the reaction disable isomerization to the more highly substituted double bond.

Indeed, reaction of phosphinite **12a** gives seven isomers of fenchene **12c** (by GC-MS) in 76% total yield. Phosphinite **13a** leads to limonene **13c** as the major and 1-methyl-4-(1-methylethylidene)cyclohexene **13d** as the minor product in a ratio of approximately 5.5:1 in a combined yield of 88% (Scheme 6). Together with the observation of nearly 1:1 product mixtures in the case of ambident nucleophiles, these findings strongly underline the formation of free carbocations (in the sense of solvent-separated ion pairs) in the case of

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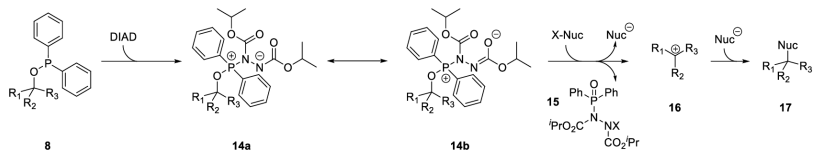

Figure 1. Proposed mechanism for the presented redox condensation S_N1 reaction.

substrates that are able to reasonably stabilize cationic intermediates.

General mechanistic considerations for this new redox condensation S_N1 reaction are shown in Figure 1. DIAD activates phosphinite **8** to form betaine **14a**, which tautomerizes to its more stable form **14b**. In the case of adamantane structure **14** was confirmed by ^{31}P NMR spectroscopy (δ = 43.7 ppm)[27] and ESI-MS ($[M - Ad + Na]^+$, m/z = 427.141) and forms in quantitative fashion at reaction times under 1 min at room temperature. Upon protonation or transsilylation, the betaine collapses immediately to a phosphonohydrazine structure **15**, leaving an isolated carbocation **16** and an anionic nucleophile. Recombination of the two ionic structures results in the desired substitution product **17**.

In conclusion, we have developed a neutral and fast method for the generation of stabilized carbocations from readily available and cheap chemicals. Cations that cannot undergo elimination due to missing α-protons or resulting ring strain can be trapped by nucleophiles in substitution reactions, whereas others undergo kinetically favored intramolecular rearrangements and elimination reactions. This approach might also be useful for the construction of complex molecules which often do not tolerate the harsh (acidic) reaction conditions usually used for the generation of cationic intermediates.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c00042.

Full experimental procedures, compound characterization, and spectra of all compounds (PDF)

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Author Contributions

L.O. designed the study. L.O. and M.L.K. carried out all experiments. L.O. and P.R.S. wrote the manuscript. P.R.S. supervised the work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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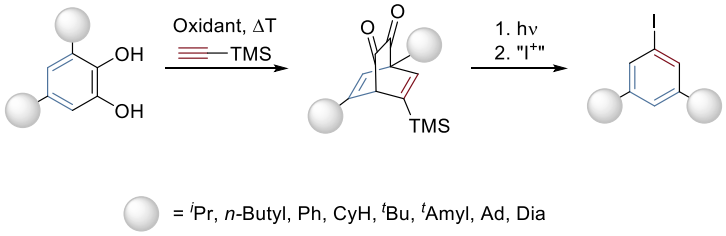
5.2 Synthesis of all-*meta* Substituted Arenes



"We report a general and scalable method for the synthesis of all-*meta*-trisubstituted benzenes from readily available 3,5-disubstituted catechols. Oxidation and [4+2] cycloaddition with an acetylene dienophile generate a bicyclo[2.2.2]octane structure that is doubly decarbonylated by blue light irradiation leading to a *meta,meta*-disubstitution pattern on the re-aromatized system. This enables this substitution pattern even with very bulky alkyl groups (deemed excellent dispersion energy donors) to be incorporated into, for example, chiral phosphoric acid catalysts."

Reference

L. Ochmann, M. Fuhrmann, F. J. Gössl, A. Makaveev, P. R. Schreiner, *Org. Lett.* **2022**, *24*, 6968-6972.

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All That *metas*—Synthesis of Dispersion Energy Donor-Substituted Benzenes

Lukas Ochmann, Michael Fuhrmann, Felix J. Gössl, Alexander Makaveev, and Peter R. Schreiner*

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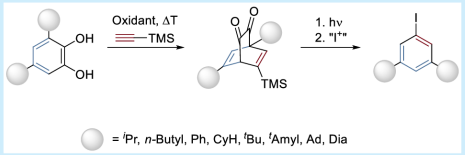
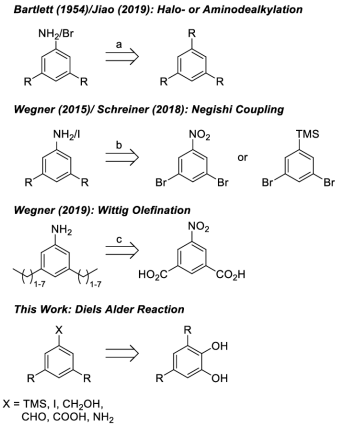
ABSTRACT: We report a general and scalable method for the synthesis of all-*meta*-trisubstituted benzenes from readily available 3,5-disubstituted catechols. Oxidation and [4 + 2] cycloaddition with acetylene dienophiles generate a bicyclo[2.2.2]octane structure that is doubly decarbonylated initiated by blue-light irradiation, leading to a *meta,meta*-disubstitution pattern on the re-aromatized system. This enables this substitution pattern even with very bulky alkyl groups (deemed excellent dispersion energy donors) to be incorporated into, for example, chiral phosphoric acid catalysts.



Even though aromatic compounds have been known for more than 150 years,[1] arene chemistry is still a pillar of organic synthesis for the preparation of natural and non-natural compounds. Many electrophilic substitution methods have been presented, beginning with traditional Friedel−Crafts chemistry[2] and ending with sophisticated transition-metal-catalyzed cross-coupling reactions.[3] The regioselectivity is usually determined by the electronic properties of the substrate[4] or through strategic placement of functional groups, often leading to nearly inseparable mixtures of isomers or excluding certain substitution patterns.[5] Recently, *meta*-substituted arenes have gained momentum, e.g., for the investigation of London dispersion (LD) interactions[6] or the tuning of steric[7] or electronic[8] properties of catalysts and ligands. Especially, bulky alkyl or alkyl silyl substituents in the *meta* positions showed a considerable increase in LD interactions and were, therefore, successfully used as so-called dispersion energy donors (DEDs)[9] in molecular azobenzene switches,[10] for the stabilization of labile molecules, like hexaphenylethane[11] or polyynes,[12] and to increase or rationalize catalyst activity and selectivity.[7d,13]

Nevertheless, the direct synthesis of the needed *meta*-substituted aryl precursors often remains challenging, especially for sterically demanding alkyl groups. Labile reagents have to be prepared;[14] however, the generality of the described methods is low, and every substituent class requires different reaction sequences.[11b,15] In 1954, Bartlett et al. synthesized 1-bromo-3,5-di-*tert*-butylbenzene from 1,3,5-tri-*tert*-butylbenzene by bromination in the presence of iron.[16] Jiao et al. picked up the idea of dealkylation in 2019 by synthesizing 3,5-dicyclohexylaniline from the 1,3,5-trialkyl derivative by a site-directed carbon−carbon amination, although the reaction was only carried out at a small scale (50 mg; Scheme 1a).[17] Wegner and co-workers as well as our group used a Negishi coupling strategy for the preparation of 3,5-dicyclohexyl and 3,5-diadamantyl aniline as well as the corresponding iodides, respectively (Scheme 1b).[10a,11b]

Scheme 1. Retrosynthetic Analysis of *m,m*-Substituted Benzenes



Nonetheless, this requires freshly prepared organozinc reagents, and the yields drop significantly for gram-scale

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reactions, especially for bulky substituents. Furthermore, reactive groups already have to be attached at the right position in the precursor molecules.

In 2019, Wegner et al. expanded the scope to linear 3,5-dialkyl-substituted anilines using a Wittig olefination instead of cross-coupling reactions as the key step (Scheme 1c), but generality is missing when it comes to secondary or even tertiary alkyl substituents.[10b] We sought unifying the synthesis of (bulky) *meta,meta*-substituted benzenes via a straightforward and scalable synthesis starting from 3,5-disubstituted catechols. Their oxidation to the corresponding quinones yields dienes that are set up for subsequent [4 + 2] cycloaddition reactions. The resulting bicyclo[2.2.2]octane derivatives re-aromatize to the corresponding 1,2,4- or 1,3,5-trisubstituted (depending upon the regioselectivity of the cycloaddition) arene by double decarbonylation triggered by blue-light irradiation.[18]

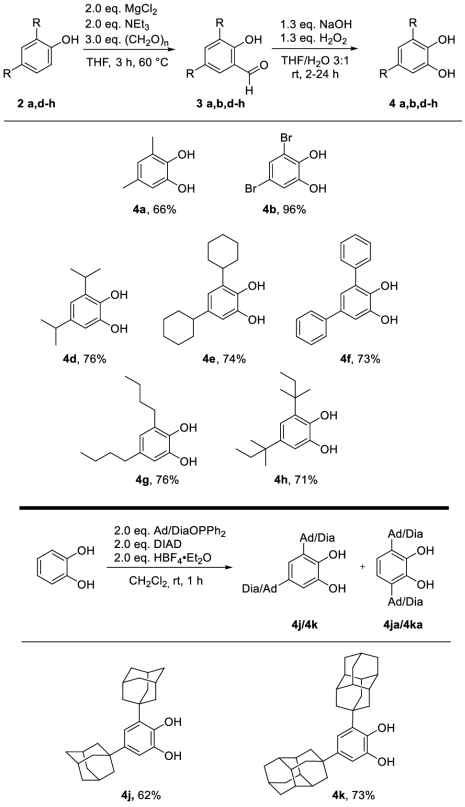
We began our studies with the synthesis of a broad variety of 3,5-disubstituted catechols. These substituted 1,2-dihydroxybenzenes are readily available for a broad variety of substrates through direct alkylations of catechol[19] or salicylic acid derivatives. The latter can be converted to the corresponding catechols via functional group interconversion of the acid to the aldehyde and subsequent Dakin oxidation.[20] Therefore, we *ortho*-formylated a variety of commercially available or easily accessible 2,4-disubstituted phenols.[21] The resulting salicylaldehydes reacted smoothly to the desired catechols using 1.3 equiv of H_2O_2 in alkaline tetrahydrofuran (THF) solution.[22] In the case of compounds **4b** and **4c**, the formylation was skipped because either the salicylaldehyde or *ortho*-methoxy benzaldehyde were commercially available and were easily converted to the dihydroxybenzene by deprotection and/or Dakin reaction.

The phenols for the synthesis of compounds **4d** and **4e** were obtained by decarboxylation of commercial 3,5-diisopropylsalicylic acid and 3,5-dicyclohexylsalicylic acid, which was prepared by a new direct Friedel−Crafts alkylation from cyclohexanol and salicylic acid in neat sulfuric acid. Straightforward reduction of the acid to the alcohol and reoxidation to the aldehyde led to inseparable mixtures of unidentifiable products. The yields are comparable in all cases and vary between 66 and 76% over two steps (Scheme 2). Diamondoid-substituted catechols were obtained via alkylation of 1,2-dihydroxybenzene by activation of diamondoid phosphinites[23] to yield mainly the 3,5-isomers **4j** and **4k**, with small amounts of the 3,6-substituted isomers **4ja** and **4ka** (for detailed procedures, see the Supporting Information).

With the 3,5-disubstituted catechols in hand, we decided to adapt a reaction sequence from the total synthesis of atisane-type diterpenoids presented by Liu et al.[24] Oxidation *in situ* with manganese dioxide led to the corresponding *o*-benzoquinones that were reacted further in a Diels−Alder reaction with trimethylsilylacetylene to a trisubstituted bicyclo[2.2.2]octane framework (step 1 in Scheme 3). Because these labile compounds already partially aromatized upon irradiation with sunlight, we decided to purify all 3,5-disubstituted (trimethylsilyl)arenes after blue light-emitting diode (LED) irradiation (λ = 448 nm; step 2 in Scheme 3). The corresponding iodides were obtained quantitatively in all cases by mixing the trimethylsilyl (TMS) derivative with a slight excess of iodine monochloride in dichloromethane (DCM) (last step in Scheme 3).

In the case of secondary alkyl substituents (**7d** and **7e**), the reaction was performed neat in trimethylsilylacetylene and DCM was not necessary to ensure sufficient solubility of

Scheme 2. Synthesis of 3,5-Disubstituted Catechols, with Yields Given over Two Steps



catechol/*o*-benzoquinone, in contrast to all tertiary-substituted derivatives (**7h**−**7k**). Because the yields for the *in situ* MnO_2 oxidation to the *o*-quinones for secondary and aryl substrates were not quantitative, we decided to oxidize the catechols **4d**−**4f** to the corresponding quinones **5d**−**5f** first (quinones **5a**−**5c** and **5g** were not stable enough to be isolated), before proceeding with the [4 + 2] cycloaddition with substoichiometric amounts MnO_2 to ensure oxidative conditions. All investigated *in situ* oxidants [Ag_2O, ceric ammonium nitrate (CAN), pyridinium chlorochromate (PCC), $NaIO_4$] either did not yield the *o*-quinone (in the case of PCC), reacted with the acetylene moiety (in the case of Ag_2O), or gave undesired side products (i.e., nitration in the case of CAN). To our great delight, all reactions with secondary and tertiary substituents selectively gave the desired 1,3,5 regioisomer [traces of the 1,2,4 isomer were detected by gas chromatography−mass spectrometry (GC−MS) for compounds **7d** and **7e**], indicating high regioselectivity for the cycloaddition. For primary and phenyl substituents (**6f** and **6g**), the regioisomer ratios were 19:1 and 3:1, respectively. Therefore, we employed sterically more hindered triisopropylsilylacetylene as the dienophile to improve the regioselectivity of the cycloaddition step but observed only a slight increase in

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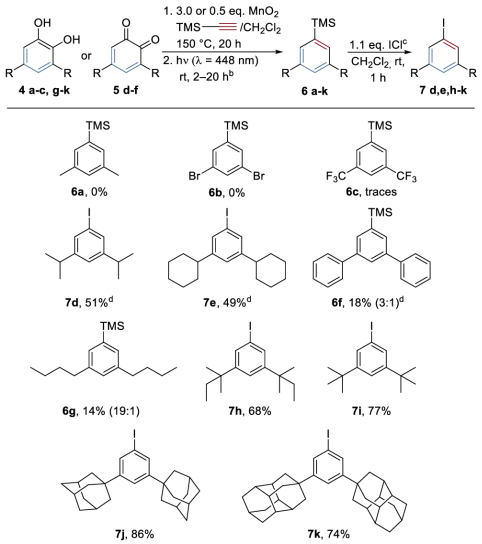
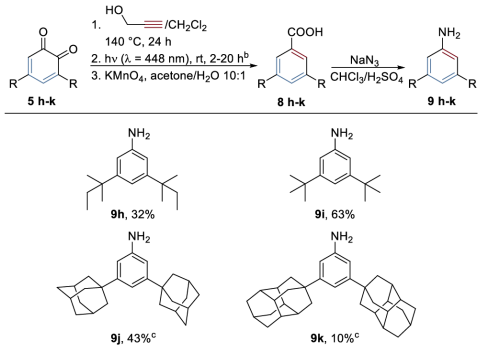
Scheme 3. Synthesis of 3,5-Disubstituted Iodobenzenes,[a] with Yields Given over Three Steps and Regioisomeric Ratios in Parentheses



[a]All reactions were carried out at least on a 2 mmol scale (catechol or quinone). [b]Reaction times depend upon the concentration of the irradiated solution. [c]ICl can be used neat or as 1 M solution in DCM. [d]Synthesized from the corresponding quinone.

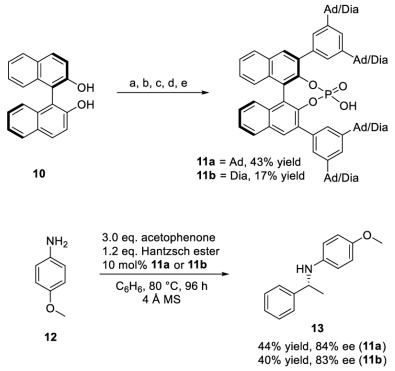
Scheme 4. Synthesis of 3,5-Disubstituted Anilines from Unmasked *o*-Benzoquinones,[a] with Yields Given over Four Steps



[a]All reactions were carried out at least at 1 mmol scale (quinone). [b]Without oxidation, benzylic alcohol can be isolated, and oxidation with PCC gives the corresponding aldehyde. [c]Oxidation was carried out in DCM/H_2O with phase-transfer catalysis (PTC).

selectivity. *In situ* generated quinones bearing methyl (**5a**), bromo (**5b**), or trifluoromethyl (**5c**) substituents did not react in the desired [4 + 2] cycloaddition but yielded a mixture of unidentified and insoluble products, most likely because of side

Scheme 5. Synthesis of New Bulky Chiral Phosphoric Acids (CPAs) and Their Activity in an Organocatalytic Reductive Amination Reaction[a]



[a]Yields of catalyst synthesis are given over five steps: (a) 3.4 equiv of K_2CO_3, 5.0 equiv of MeI, acetone, 40 °C, and 72 h, (b) (1) 3.3 equiv of *n*-BuLi, 3.1 equiv of tetramethylethylenediamine (TMEDA), Et_2O, room temperature, and 3 h, (2) 7.2 equiv of $B(OMe)_3$, from −78 °C to room temperature, and 12 h, and (3) 1 M HCl, room temperature, and 2 h, (c) 3.0 equiv of compound **7j** or **7k**, 3.0 equiv of K_2CO_3, 10 mol % $Pd(PPh_3)_4$, THF/H_2O (1:1), 60 °C, and 16 h, (d) 7.1 equiv of BBr_3, CH_2Cl_2, room temperature, and 16 h, and (e) 2.0 equiv of $POCl_3$, pyridine, 60 °C, and 18 h.

reactions, such as Michael addition or self-polymerization, as a result of reduced steric hindrance or increased electrophilicity. The yields over all three steps are between 14 and 51% for primary (**6g**) and secondary (**7d** and **7e**) alkyl substituents and increase to more than 80% for tertiary (**7h**−**7k**) alkyl substituents (Scheme 3). To demonstrate the scalability of the presented route, we synthesized 15 g of 3,5-diadamantyl-1-iodobenzene (**7j**) in one batch with the same yield as for the 2 mmol scale.

To emphasize the generality for the synthesis of all *meta*-substituted arenes with the method presented here, we also aimed for a convenient synthesis of the corresponding anilines. Although the literature provides simple methods for the amination of iodobenzenes,[25] these transformations were proven to be suitable only for primary and secondary alkyl substituents.[13d] Therefore, we changed the dienophile to propargylic alcohol to form the corresponding benzylic alcohol after light-induced double decarbonylation (steps 1 and 2 in Scheme 4). Usage of propargylic acid, aldehydes, or methyl esters was not possible as a result of insufficient regioselectivity during the cycloaddition step, even for tertiary substrates. Again, the product was isolated after blue-light irradiation or after oxidation to the corresponding aldehyde or benzoic acid, respectively. Schmidt reaction[26] gave the desired anilines (**9h**−**9k**) in yields from 10 up to 63% over four steps (Scheme 4). The reduced yields for compounds **9h** and **9k** can be explained by an additional crystallization step in the purification of compound **8h** and low conversion as a result of the decreased solubility of compound **8k** in chloroform/sulfuric acid in the last step.

To showcase the versatility of the all-*meta* motif in organocatalytic reactions, we incorporated 3,5-disubstituted adamantyl and diamantyl benzenes in 1,1′-bi-2-naphthol

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(BINOL)-derived chiral phosphoric acids **11a** and **11b** and tested the efficacy of compounds **11a** and **11b** in an established reductive amination reaction (Scheme 5).[27] Indeed, compound **11a** gave an enantiomeric excess (ee) of 84% (83% for compound **11b**) for the reductive amination of acetophenone with *p*-methoxyaniline under unoptimized conditions and, therefore, shows comparable selectivity as the best catalyst from MacMillan and co-workers with extremely bulky $SiPh_3$ groups (87%).[27]

In conclusion, we developed a general and metal-free procedure to synthesize challenging *meta*,*meta*-trisubstituted benzenes. The route works well for a variety of bulky alkyl substituents that are highly desirable as dispersion energy donors. Our protocol is readily scalable to the multigram scale and, therefore, highly suitable for the incorporation of all-*meta* arenes into catalysts, as demonstrated for an enantioselective reductive amination using a new sterically bulky chiral phosphoric acid catalyst.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c02780.

Full experimental procedures and compound characterization (PDF)

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Author Contributions

Lukas Ochmann designed the study. Lukas Ochmann, Michael Fuhrmann, Felix J. Gössl, and Alexander Makaveev carried out all experiments. Lukas Ochmann and Peter R. Schreiner wrote the manuscript. Peter R. Schreiner supervised the work.

Notes

The authors declare no competing financial interest.

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6. Appendix

6.1 List of Publications in Peer Reviewed Journals

J. M. Schümann, L. Ochmann, J. Becker, A. Altun, I. Harden, G. Bistoni, P. R. Schreiner, *J. Am. Chem. Soc.* **2023**, *145*, 2093-2097.

L. Ochmann, M. Fuhrmann, F. J. Gössl, A. Makaveev, P. R. Schreiner, *Org. Lett.* **2022**, *24*, 6968-6972.

L. Ochmann, M. L. Kessler, P. R. Schreiner, *Org. Lett.* **2022**, *24*, 1460-1464.

O. Moncea, J. Casanova-Chafer, D. Poinsot, L. Ochmann, C. D. Mboyi, H. O. Nasrallah, E. Llobet, I. Makni, M. El Atrous, S. Brandès, Y. Rousselin, B. Domenichini, N. Nuns, A. A. Fokin, P. R. Schreiner, J.-C. Hierso, *Angew. Chem. Int. Ed.* **2019**, *58*, 9933-9938.

J.-P. Berndt, F. R. Erb, L. Ochmann, J. Beppler, P. R. Schreiner, *Synlett* **2019**, *30*, 493-498.

6.2 Participation in Conferences

ESOC **2019**, Vienna (poster presentation)

19. Leibniz Symposium **2018**, Hannover

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