Iodine-Catalyzed Diels-Alder Reactions
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The Diels-Alder cycloaddition is the most popular pericyclic reaction with numerous applications in synthesis and catalysis. We now demonstrate that we can perform this reaction under mild and metal-free conditions relying on molecular iodine as the catalyst. Cycloadditions with cyclohexadiene, cyclopenta diene, or isoprene with various dienophiles can be performed typically within minutes in moderate to good yields and high endo selectivity. The mechanistic studies including kinetic and DFT investigations clearly indicate a halogen-bond activation and rule out other modes of activation. Furthermore, iodine performs equally well as typical metallic Lewis acids like AlCl₃, SnCl₄, or TiCl₄.

Introduction

Over the last years, halogen bonding has grown to become an important concept in various areas of chemistry and particularly in organocatalysis.[1,2] Halogen bonding is defined as the attractive interaction of the Lewis-acidic region of a halogen atom with the lone pair of a Lewis base.[3] The Lewis acidic region of a halogen atom is located in elongation of the R–X bond and the interaction increases from F < Cl < Br < I.[4] One of the first halogen-bond catalyzed reactions, the reduction of quinolines, was published in 2008 by Bolm and colleagues.[5] In the following years, systematic investigations by Huber and others broadened our understanding of halogen-bond catalysis.[6] Within the last years, halogen-bond catalysts were employed amongst others in Michael additions,[7] (hetero)-Diels-Alder reactions,[8] Nazarov cyclizations,[9] or in cross-enolate coupling reactions.[10] Halogen-bond donors can also be used in stereoselective transformations in combination with other modes of activation.[11] In 2020, Huber and colleagues eventually reported on the application on the first pure chiral halogen-bond donor in a Mukaiyama aldol reaction.[12]

Within the concept of halogen-bond catalysis, molecular iodine reemerged into the focus of organocatalysis. Iodine is inexpensive, benign, and well soluble in organic solvents and reactions can typically be performed under mild conditions.[13] For a long time, the origin of the catalytic activity was unknown and different explanations (Brønsted-acid, Lewis-acid, or iodonium-ion catalysis) have been proposed in the literature.[14] We were recently able to show that a halogen-bond activation is the most likely explanation for iodine-catalyzed Michael additions[15] and Nazarov cyclizations (Scheme 1).[16] In contrast, a iodonium-activation seems to be the origin for carbonyl-olefin metathesis reactions.[17] As iodine is frequently comparable or even superior in activity compared to traditional metal catalysts like AlCl₃, FeCl₃, or TiCl₄,[11,12] we wondered whether this simple catalyst can also be employed in other transformations and affords the desired products under mild conditions.

As iodine is particularly effective for the activation of carbonyl groups, we investigated if we could extend the concept of iodine catalysis towards the synthetically important Diels-Alder reaction.[18] Typically, an electron-rich diene reacts with an electron-deficient dienophile in a concerted [4 + 2] cycloaddition. While this reaction can occur thermally (frequently at elevated temperatures), catalytic variants are known for a long time. In 1960, Yates and Eaton reported on the strong accelerating effect of AlCl₃ observed for the reaction between anthracene and dimethyl fumarate.[19] Today, numerous Lewis acids are known to catalyze this transformation (Scheme 2)[19,20] including carbenium[20] and silylum ions,[19] but also organocatalysts with many different catalyst scaffolds.[21]

The Diels-Alder reaction was also already investigated in the context of halogen-bonding. Huber and colleagues relied on

Scheme 1. Selected examples for iodine catalysis.[11–13]
different halogen-bond donors for the model reaction between cyclopentadiene (1b) and methyl vinyl ketone (2a, Scheme 3). In 2021, they also reported on the use of a bidentate iodine(III) system that can also be used to catalyze a cycloaddition involving cyclohexadiene (1a). Similarly,aza-Diels-Alder reactions can also be catalyzed by related azolium-based catalysts. While these examples proposed the formation of a halogen bond to the heteroatom of the dienophile, Arai and colleagues reported on a [4+2] cycloaddition between 2-alkenylnoloids relying on a C—I⋯π halogen bond instead.

Several years before, molecular iodine was already employed as a catalyst in related Povarov reactions, but no mechanistic investigations have been performed so far.

We now report on our computational and experimental studies on iodine-catalyzed Diels-Alder reactions and their mechanistic investigation.

Results and Discussion

Computational investigations

We initially investigated the feasibility of an iodine-catalyzed Diels-Alder reaction by DFT calculations. The effect of iodine on different Diels-Alder reactions was already studied in 2011 by Deuri and Phukan at the B3LYP/6-31G(d) (3-21G(d) for iodine) level of theory and recently by Fernández, Bickelhaupt, and colleagues amongst others at the DLPNO-CCSD(T)/CBS(3,4//def2)//ZORA-BP86/TZ2P level.

Both studies suggest that iodine can coordinate to the carbonyl group of the dienophiles replacing traditional Lewis acids, which results in a reduced activation energy. However, both studies did not consider entropic factors and only referred to (zero point-corrected) electronic energies. Therefore, it is not clear whether the attractive halogen-bond interaction can compensate for the unfavorable entropic contribution. Consequently, we investigated the influence of iodine on several Diels-Alder reactions at the B2PLYP-D3BJ/aug-cc-pVTZ/SMD//M06-2X/6-311+G(d,p)/SMD level of theory. This method turned out to provide very reliable results for iodine-catalyzed Michael additions and Nazarov cyclizations.

In line with the established mechanism for the Diels-Alder reaction, all reactions proceed under kinetic control and the endo transition states are kinetically preferred. As exemplary shown in Figure 1, all transition states are slightly asynchronous and both C—C bonds vary significantly in line with the polarized nature of the dienophile. Iodine coordinates to the carbonyl oxygen atom, and the resulting dienophile-iodine complexes 2-I2 are almost isoenergetic to the separated reactants (∆ΔG° = 23 kJ mol⁻¹). In all cases, the C—O⋯I distances are significantly smaller than the sum of the van der Waals radii.

Figure 1. Calculated endo-transition states with selected bond lengths (in Å) for the uncatalyzed and the iodine-catalyzed Diels-Alder reaction between cyclohexadiene (1a) and methyl vinyl ketone (2a).
(3.54 Å) and, thus, indicating an attractive interaction between these atoms. A closer analysis of the Wiberg bond order for the O···I interaction reveal that the reactant and product complexes are very similar (e.g., 2a-I₂: 0.064, 3aa-I₂: 0.072), while a larger value of 0.172 was calculated for the corresponding transition state. These values are substantially smaller than those for the triiodide anion (I₃⁻: 0.534) and indicate a noncovalent interaction of molecular iodine during the Diels-Alder cycloaddition.

Table 1 collects the calculated activation free energies for the endo transition states for the Diels-Alder reactions of different dienes 1 and dienophiles 2 in the absence and the presence of iodine. More details (e.g., on the exo pathways are summarized in the Supporting Information). The computed reactivity trends are generally in line with previous investigations. 

Similarly, the reactivities of the dienophiles qualitatively agree with experimental rate constants for cycloadditions to 9,10-dimethylanthracene.

For most combinations, the computational investigations predict a significant rate acceleration by iodine. However, in some cases (e.g., 2c, 2d, 2i), similar barriers were calculated which indicates that iodine should not display a strong catalytic effect. Previous investigations of the cycloaddition between 1c and 2d at the DLPNO-CCSD(T)/CBS(3a/def2)/ZORA-ESP/BP86/TZVP level in the gas phase resulted in a transition-state lowering of 5 \(kJ\) mol\(^{-1}\) in electronic barrier (\(\Delta E\)) which nicely agrees with our findings (\(\Delta H^\ddagger = -7 \, kJ\) mol\(^{-1}\)). The favorable enthalpic interaction to iodine cannot compensate for the unfavorable entropic contribution and renders the overall barrier in free energy to be comparable to the uncatalyzed process. For maleic anhydride (2h), a very reactive dienophile, our calculations predict an even higher activation energy in the presence of iodine (see also below).

Table 1. Calculated Activation Free Energies \(\Delta G^\ddagger\) (in kJ mol\(^{-1}\)) for the Uncatalyzed and Iodine-Catalyzed Diels-Alder Reactions of Cyclohexadiene (1a), Cyclopentadiene (1b), and Isoprene (1c) with Different Dienophiles \(^{26}\)

| Transition State | \(\Delta G^\ddagger\) (kJ mol\(^{-1}\)) |
|------------------|-------------------------------|
| 1a               |                               |
| 2a               | + 114 (no I\(_2\)) + 91 (with I\(_2\)) |
| 1b               |                               |
| 2b               | + 111 (no I\(_2\)) + 89 (with I\(_2\)) |
| 1c               |                               |
| 2c               | + 111 (no I\(_2\)) + 109 (with I\(_2\)) |
| 2d               | + 122 (no I\(_2\)) + 113 (with I\(_2\)) |
| 2e               | + 124 (no I\(_2\)) + 105 (with I\(_2\)) |
| 2f               | + 132 (no I\(_2\)) + 113 (with I\(_2\)) |
| 2g               | + 83 (no I\(_2\)) + 89 (with I\(_2\)) |
| 2h               | + 91 (no I\(_2\)) + 87 (with I\(_2\)) |
| 2i               | + 115 (no I\(_2\)) + 97 (with I\(_2\)) |

(a) B2PLYP-D3BJ/aug-cc-pVTZ/SMD(CH\(_3\)CN)//M06-2X/6-31+G(d,p)/SMD (CH\(_3\)CN).

To better understand the role of iodine in these reactions, we performed additional calculations. An NCIPL0T analysis (see the Supporting Information) indicates medium to strong attractive interactions between the dienophile part and the catalyst. A closer investigation with natural population analyses of iodine complexes confirmed a significant interaction between the oxygen lone pairs and the anti-bonding \(\sigma^*\)-orbital of the I–I bond (e.g., for 2a-I\(_2\): 56, TS-I\(_2\): 168, and 3aa-I\(_2\): 61 kJ mol\(^{-1}\)). While the interactions in the reactant and complexes are typically similar, much larger values were calculated for the transition states. This again indicates that the transition states are rather asynchronous resulting in a substantial charge transfer between diene and dienophile. To obtain a more quantitative picture into the interaction between the organic fragments and iodine, we additionally relied on symmetry-adapted perturbation theory (SAPT). Figure 2 summarizes the results of the SAPT2 + 3(2CCD) analysis for the reaction between cyclohexadiene (1a) and methyl vinyl ketone (2a), while the results of the corresponding SAPT0 analysis are shown in the Supporting Information.

As already observed in the DFT calculations described above, the SAPT interaction energies (red bars in Figure 2) in the reactant and product complexes (2a-I\(_2\) and 3aa-I\(_2\)) are very similar (−22 and −26 kJ mol\(^{-1}\)) and a stronger interaction is observed in the transition state (−46 kJ mol\(^{-1}\)). In line with this,
almost identical energy decompositions were calculated for 2a-I$_2$ and 3aa-I$_2$, while significant differences can be observed for the corresponding transition state TS-I$_2$. The exchange contribution (black bars) significantly increases which indicates that there is a substantial Pauli repulsion between the lone pairs on the oxygen and iodine atoms. This unfavorable interaction is compensated by a substantial increase in the electrostatic and induction (green and orange bars) contributions and by a moderate increase in dispersive interactions (blue bars). These results lead to the conclusion that there is a substantial charge transfer from the dienophile onto the catalyst, which is in line with the typical picture of a Lewis-acid or halogen-bond catalysis. While these results focus on the nature of the O-I interaction, different results can be expected for the diene-dienophile interaction. The latter was recently studied by Hamlin, Fernández, Bickelhaupt, and colleagues and highlighted in line with the low reactivity of 1a, no cycloaddition was observed in the absence of iodine in any solvent. In contrast, background reactions could be detected as expected in all solvents for the reaction of the more reactive diene 1b (see the Supporting Information for details). Nonetheless, a significant acceleration was observed in acetonitrile for both dienes and the cycloadducts were formed in fast reactions (73 and 94%, Table 2). Isolated product yields were almost identical to those determined by GC. In line with the expectations from our computational investigations and from previous experimental studies,[14] the endo-cycloadduct 3aa could be observed as the only product (endo : exo > 50:1) for the combination of 1a and 2a. A slightly smaller selectivity (ca 9:1) was determined for the cycloadditions involving cyclopentadiene (1b) and the combined yield of both cycloadducts is given in Table 2 for this system (see the Supporting Information for more details).

Table 2. Solvent Influence on the Iodine-Catalyzed Diels-Alder Reaction of Cyclohexadiene (1a) and Cyclopentadiene (1b) with Methyl Vinyl Ketone (2a).[16]

| Solvent     | 3aa [%] | 3ba [%] | Solvent     | 3aa [%] | 3ba [%] |
|-------------|---------|---------|-------------|---------|---------|
| CH$_2$CN    | 73      | 94 [13][n] | THF         | <1      | 98 [28][n] |
| C$_3$H$_7$Cl | 39      | 99 [23][n] | MTBE        | <1      | 98 [38][n] |
| CH$_3$Cl    | 38      | 93 [10][n] | benzene     | <1      | 87 [16][n] |
| PHNO$_2$    | 79      | 98 [8][n]  | toluene     | <1      | 87 [10][n] |
| H$_2$CNO$_2$ | 67      | 86 [18][n] | p-xylene    | <1      | 80 [18][n] |
| PKCN        | 33      | 98 [8][n]  | pentane     | <1      | 83 [21][n] |
| acetone     | 11      | 90 [18][n] | DMF         | <1      | 41 [57][n] |
| CHCl$_3$[x] | <1      | 73 [28][n] | DMCO        | <1      | 79 [56][n] |
| CCl$_4$     | <1      | 98 [59][n] | HFIP        | <1      | 61 [8][n]  |
| EtoAc       | <1      | 94 [14][n] | MeOH        | <1      | 55 [21][n] |
| E$_2$O$_5$  | <1      | 97 [26][n] |             |         |         |

[a] Conditions: [1a] = [2a] = 0.5 M, [1b] = 0.6 M, [I$_2$] = 7.5 mM, 25 °C, 30 min, GC yields, Ph$_3$PO as internal standard. [b] background reaction in the absence of I$_2$. [c] not determined due to comparable retention times. [d] only 5 mol% I$_2$ were used. [e] Stirred over Na$_2$CO$_3$ prior to use to remove traces of acid.

Figure 2. Analysis of the interaction energies by symmetry-adapted perturbation theory (SAPT2 + 3(CCD)/def2-TZVPP, in kJ mol$^{-1}$).
While iodine-catalyzed Nazarov cyclizations\(^{[12]}\) and Michael additions\(^{[11b,13]}\) tolerated many different solvents, iodine-catalyzed Diels-Alder reactions seem to be more solvent-dependent. While cycloadditions with the highly reactive cyclopentadiene (1b) again proceed in almost all solvents (also in the absence of iodine), reactions of cyclohexadiene (1a) only take place in polar solvents. For the latter, nitromethane (67\%) and nitrobenzene (79\%) resulted in comparable GC yields than acetonitrile (73\%). Remarkably, only 5 mol\% iodine could be used in nitromethane, indicating that lower catalyst loadings should also be feasible in some solvents. A moderate yield (38\%) was also observed for dichloromethane in contrast to previous reports in the literature\(^{[21]}\). While very Lewis-basic solvents like DMF or DMSO are known to interact with iodine and deactivate it for further reactions,\(^{[23]}\) apolar solvents like toluene or pentane are also unsuitable for the iodine-catalyzed Diels-Alder reaction of 1a. Interestingly, with the exception of DMSO and DMF, cycloadditions with 1b proceed in almost all solvents and high yields were typically observed after 30 min. Although there is no general correlation with e.g., Reichardt’s \(E_s\) parameter,\(^{[26]}\) a certain solvent polarity (approx. 0.3) seems to be required for a successful reaction of cyclohexadiene (1a). A similar observation has also been reported for iodine-catalyzed Povarov reactions\(^{[23a,24]}\) and was also observed in other Diels-Alder reactions.\(^{[40]}\)

**Mode of activation**

Although the computational investigations described above support the picture of a halogen-bond catalysis by molecular iodine, we wanted to elucidate the role of the catalyst in these reactions as well. Besides the activation as a Lewis acid, Brønsted-acid catalysis by HI (generated via decomposition of iodine) and an iodonium-ion activation are frequently proposed as alternate explanations.\(^{[10]}\) For the mechanistic analysis, we again selected the reaction between cyclohexadiene (1a) and methyl vinyl ketone (2a) in acetonitrile (Table 3). As the observed yields were identical under normal lab lighting and in the dark as well as in the presence of a radical scavenger (entries 1–3 in Table 3), radical pathways are unlikely. N-Iodosuccinimide, a typical source for iodonium ions, was completely inactive under the reaction conditions and the starting materials remained unchanged as indicated by GC analysis. Similarly, Brensted acids (entries 6–9) perform poorly and only afford small quantities of the cycloadduct 3aa. As the low catalytic activity of aqueous HI in acetonitrile can be suppressed by the addition of NaI (entry 8), it is likely that this effect is caused by trace impurities of iodine (obtained through an oxidation of HI). Based on the results of Table 3, both a Brønsted-acid as well as an iodonium activation are unlikely to account for the catalytic effect of iodine.

To further support our hypothesis of a halogen-bond-catalyzed cycloaddition, we also determined the reaction order in iodine kinetically. We measured the initial rates for different iodine concentrations (7–14 mol\%) under otherwise identical conditions by IR spectroscopy. The resulting double-logarithmic plot between the initial rates and the iodine concentrations resulted in a linear correlation with a slope of one (Figure 3), indicating that only one iodine molecule is involved in the rate-determining transition state. This reaction order also renders an activation via the iodonium ion (I\(^{+}\)) very unlikely. Both I\(^{-}\) and I\(^{-}\) readily react with iodine to form higher iodine species which in turn should result in a higher reaction order.\(^{[13]}\)

We additionally aimed to determine the activation parameters for the iodine-catalyzed cycloaddition of 1a and 2a. Therefore, we measured the initial rates for these reactions at different temperatures (15–40 \(^\circ\)C) in CH\(_3\)CN using 8 mol\% iodine (Figure 4). An Eyring analysis revealed a relatively small activation enthalpy (\(\Delta H^*\)) of 31 kJ mol\(^{-1}\) that perfectly agrees with the calculated \(\Delta H^\circ\) of 32 kJ mol\(^{-1}\). The formal termolecular reaction is also reflected in a considerable activation entropy.

| Table 3. Influence of Different Catalysts and Additives on the Diels-Alder Reaction of Cyclohexadiene (1a) and Methyl Vinyl Ketone (2a).\(^{[5]}\) |
|-----------------|-----------------|-----------------|
| no.             | Additive        | GC-Yield [%]    |
| 1               | I\(_2\) (15 mol%, lab lighting) | 73              |
| 2               | I\(_2\) (15 mol%, in the dark)  | 73              |
| 3               | I\(_2\) (15 mol%) + BHT\(^{[30]}\) (15 mol%) | 73              |
| 4               | I\(_2\) (15 mol%) + NaI (15 mol%) | < 1             |
| 5               | NIS\(^{[31]}\) (15 mol%) | < 1             |
| 6               | aq. HI (15 mol%)  | 8               |
| 7               | aq. HI (15 mol%) in MeOH | < 1             |
| 8               | aq. HI (15 mol%) + NaI (15 mol%) | < 1             |
| 9               | CF\(_3\)COJH (15 mol%) | < 1             |

\[a\] Conditions: [1a] = [2a] = 0.5 M, [I\(_2\)] = 7.5 mm, CH\(_3\)CN, 25 °C, 30 min.

\[b\] BHT: dibutylhydroxytoluene. \[c\] NIS: N-iodosuccinimide.

![Figure 3](image-url)
\[ \Delta S^\circ = -181 \text{ J K}^{-1} \text{ mol}^{-1}. \] From these values, the activation free energy at 298 K can be calculated to 85 kJ mol\(^{-1}\). This value is also in excellent agreement with the calculated barrier of 91 kJ mol\(^{-1}\) (Table 1) and further supports a halogen-bond pathway.

**Substrate scope**

After establishing the mode of activation, we next investigated the substrate scope of this reaction (Scheme 4). All reactions were performed in acetonitrile using 15 mol% of the catalyst. These conditions should allow for reasonable reaction rates and the kinetics discussed above indicate that lower catalyst loadings should be feasible for most cases. The reaction mixtures were deactivated when TLC analyses indicated the complete consumption of the dienophile.

With the exception of acrylic (2c) and maleic acid (2k) as well as maleic anhydride (2h), no background reaction was observed without a catalyst. While the carboxylic acids only afforded relatively small amounts of the corresponding cycloadduct, reactions involving maleic anhydride proceeded very quickly in the absence of iodine and were typically completed within minutes. Consequently, no iodine catalysis was attempted for 2h.

As expected from their reactivities,\(^{[32a-e]}\) cyclohexadiene (1a) and isoprene (1c) reacted only with aldehydes and ketones as dienophiles. Cycloadditions occurred more readily with cyclopentadiene (1b) and different functional groups including acids, amides, and nitriles were tolerated in the dienophile. In most cases, cycloadditions were obtained within minutes and with high endo selectivities. For methacrolein (2j), a partial decomposition of the dienophile was observed under the reaction conditions, which is most likely caused by polymerization.

Several dienophiles did not result in the desired products: Cinnamaldehyde (2g), acrylic acid (2c), and several esters (e.g., 2d,m,n) did not afford the corresponding cycloadducts even with the most reactive diene 1b. While the DFT calculations already indicated high barriers for 2g (presumably due to the better conjugation of the \(\pi\)-system), reasonable activation free energies have been calculated for the ester 2d. Although similar observation has also been made for tritylium ions,\(^{[17]}\) no obvious reaction could be identified that accounts for that finding.
Comparison with other catalysts

As our mechanistic analysis clearly suggested the assumption of a halogen-bond activation by iodine, we eventually wanted to compare the catalytic activity of iodine to that of other typical catalysts. We, therefore, performed the reaction between cyclohexadiene (1a) and methyl vinyl ketone (2a) in acetonitrile with different catalysts (10 mol%) that are frequently employed in Diels-Alder reactions (Table 4).[41] It should be noted that the optimal reaction conditions vary from catalyst to catalyst, but for the sake of simplicity, we selected acetonitrile as the solvent of choice for this comparison. As discussed above, many catalysts are highly active in this cycloaddition and BF₃·OEt₂ performs best under the reaction conditions affording almost quantitative conversion after 5 minutes. Remarkably, iodine can compete with strong Lewis acids such as AlCl₃, TiCl₄, SnCl₄ or also tritylium ions. In all cases, an endo-exo equilibration was observed after the cycloaddition was complete, but again, it seems that this isomerization is slower for iodine compared to AlCl₃ or TiCl₄.

Although a direct comparison with other halogen-bond donors used in Diels-Alder reactions is somewhat difficult due to the different reaction conditions,[36,37,28,29] our investigations clearly demonstrate that iodine is superior to most of them and can also compete with bidentate iodine(III) systems. Interestingly, molecular bromine, which can occasionally be used to replace iodine as a catalyst,[41] is inactive under the reaction conditions. On the one hand, bromine is generally a weaker halogen-bond donor compared to iodine.[11] On the other hand, addition reactions of bromine are thermodynamically more favorable and could result in catalyst consumption.[42] Furthermore, typical organocatalysts including Schreiner’s thiourea 4a[18] and secondary amines 4b,c[19b, c-g, i] were found to be completely inactive under these reaction conditions.

The different reactivity observed for various Lewis acids in our experimental investigation seems to contradict previous high-level calculations (see above).[26] This prediction predicted an increasing catalytic effect within the series I₂ < SnCl₄ < TiCl₄ < ZnCl₂ < BF₃ < AlCl₃ for the reaction between isoprene (1c) and methyl acrylate (2d).[26] One explanation for this deviation could result from acetonitrile as the solvent chosen for this comparison. Acetonitrile is weakly Lewis basic itself and could, therefore, interact with the stronger Lewis acids and reduce their activities. Furthermore, it should be noted again that we were unable to observe any iodine-catalyzed cycloaddition involving esters that were used for the computational investigation (see above). However, as iodine is usually considered to be environmentally more favorable compared to metallic Lewis acids and furthermore tolerates also weakly Lewis-basic solvents, these findings once again underline the practical importance of iodine catalysis.

Table 4. Comparison of the Catalytic Activity of Different Catalysts in the Diels-Alder Reaction between Cyclohexadiene (1a) and Methyl Vinyl Ketone (2a).[41]

| Catalyst | Yield [%] 5 min (endo:exo) | Yield [%] 15 min (endo:exo) | Yield [%] 30 min (endo:exo) | Yield [%] 3 h (endo:exo) |
|----------|-----------------------------|-------------------------------|-------------------------------|-------------------------|
| I₂       | 79 (97:3)                   | 78 (95:5)                     | 78 (94:6)                     | 77 (96:4)               |
| BF₃·OEt₂ | 93 (97:3)                   | 96 (96:4)                     | 94 (91:7)                     | 86 (86:14)             |
| AlCl₃    | 81 (99:1)                   | 84 (97:3)                     | 83 (97:3)                     | 84 (94:6)               |
| TiCl₄    | 77 (84:16)                  | 77 (79:21)                    | 80 (72:28)                    | 81 (73:27)             |
| Ph₃C·BF₄⁻ | 76 (99:1)                   | 75 (99:1)                     | 77 (97:3)                     | 77 (96:4)              |
| SnCl₄    | 74 (98:2)                   | 82 (98:2)                     | 87 (98:2)                     | 92 (98:2)              |
| Sc(OTf)₃ | 24 (99:1)                   | 47 (99:1)                     | 62 (98:2)                     | 83 (97:3)              |
| FeCl₃    | 1 (n.d.)                    | 2 (n.d.)                      | 4 (n.d.)                      | 10 (n.d.)              |

Unreactive Catalysts[31]

| B₃H₆, SnCl₂[21] | F₃CF₂CF₃, SnCl₂ | ZnCl₂ | CuOTf | CuOTf |
|-----------------|-----------------|-------|-------|-------|
| 4a              | 4b              | 4c    |

[a] Conditions: [1a] = [2a] = 0.5 M, [Catalyst] = 5 mM, CH₂CN, 25 °C. [b] < 5 % yield after 3 h. [c] Solvent: CH₂CN:THF 1:1.

Conclusion

We have developed a new and mild protocol for Diels-Alder reactions relying on molecular iodine as a catalyst. The cycloadditions can be performed under mild and metal-free conditions with a cheap and environmentally benign catalyst. Mechanistic investigations indicate that iodine activates the dienophile via a halogen bond and other pathways like a hidden Brensted-acid catalysis or an iodonium activation seem unlikely.

Experimental Section

Experimental details

General procedure for iodine-catalyzed Diels-Alder reactions. The diene 1 (1.0 eq. for 1a and 1.2 eq. for freshly cracked 1b) and the dienophile 2 (1.0 eq.) were dissolved in CH₂CN (0.5 mL) under argon. The same volume of an iodine solution in CH₂CN was immediately added resulting in a catalyst loading of 15 mol%. The reaction mixture was stirred at 25 °C until TLC analysis indicated full consumption of the dienophile. The reaction mixture was directly subjected to column chromatography on silica gel to give the desired cycloadduct.
Conflict of Interest

The authors declare no conflict of interest.

Keywords: Catalysis · Cycloadditions · DFT Calculations · Halogen Bonding · Reaction Mechanisms
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