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# Reductive Eliminations from $\lambda^3$-Iodanes: Understanding Selectivity and the Crucial Role of the Hypervalent Bond

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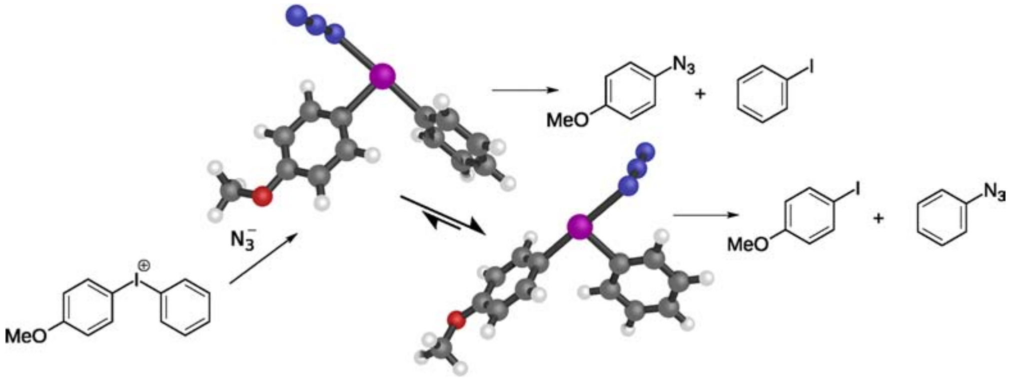
## ABSTRACT



**This computational study investigates the factors governing the selectivity of the reductive eliminations from rapidly equilibrating isomeric $\lambda^3$-iodanes derived from a diaryl iodonium salt and a nucleophile. The chemoselectivity is mainly determined by the partial charge at the ipso-carbon atom involved in the 3-center−4-electron bond.**

DiMagno and co-workers extensively studied the reaction of diaryl iodoniums with different nucleophiles.[1,2] In general, the selectivity of the reaction is determined by electronic effects, resulting in the functionalization of the less electron-rich aryl group via reductive elimination. Apparently, the electron-rich ligands play the role of directing groups and therefore govern the selectivity by means of electronic control.[3]

However, the fact that different selectivities are observed for electronically similar ligands (see Scheme 1) indicates that steric effects also operate.[4] DiMagno and co-workers suggested that steric hindrance will affect the transition state geometry and therefore determine the selectivity of the reaction. These authors also showed that electronic and steric effects can be combined to enhance selectivity of the reductive elimination reaction. By introducing sterically demanding aryl ligands, a unidirectional selectivity was achieved (see concept of Stereoelectronic Control of Unidirectional Reductive Elimination (SECURE) in ref 1).

The reactive species is a hypervalent iodine derivative ([10-I-3], $\lambda^3$-iodane), containing a 3-center−4-electron bond (3c−4e bond).[5] This bond is perpendicular to a classical 2-center bond, thus giving rise to the characteristic T-shaped geometry of the iodanes. The linear combination of the $\sigma$-type atomic orbitals (AOs) of the three centers results in three molecular orbitals (MOs) with a bonding, a nonbonding, and an antibonding character, the two lower-energy MOs beeing occupied (see Figure 1). In principle, these four electrons are delocalized over these three centers, but due to the node at the iodine center in the nonbonding MO, the 3c−4e bond is highly polarized toward the ligands. The polarization results in the localization of a near unit partial charge at the iodine center

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[1] Wang, B.; Graskemper, J. W.; Qin, L.; DiMagno, S. G. *Angew. Chem., Int. Ed.* **2010**, *49*, 4079–4083.

[2] Graskemper, J. W.; Wang, B.; Qin, L.; Neumann, K. D.; DiMagno, S. G. *Org. Lett.* **2011**, *13*, 3158–3161.

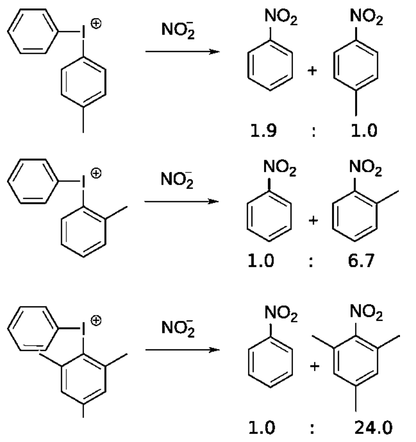
[3] Carroll, M. A.; Martín-Santamaría, S.; Pike, V. W.; Rzepa, H. S.; Widdowson, D. A. *J. Chem. Soc., Perkin Trans. 2* **1999**, 2707–2714.

[4] Grushin, V. R. *Acc. Chem. Res.* **1992**, *25*, 529–536.

[5] Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299–5358.

10.1021/ol3014039

**Scheme 1.** Different Selectivities for the Conversion of Electronically Similar Diaryl Iodoniums with $NO_2^-$[4]



($\delta_I \approx +1$) and the corresponding negative charges on both ligand atoms ($\delta_{L^1} + \delta_{L^2} \approx -1$). This bonding pattern favors the participation of electron withdrawing ligands in the 3c−4e bond. This feature is crucial for the reactivity of the hypervalent bond, in particular in view of the reductive elimination reaction (vida infra).

In principle, the T-shaped iodane structure, formed upon an addition of the nucleophile $X^-$ to the diaryl iodonium salts, allows for three configurations (see Scheme 2). However, closer inspection showed that only two isomers are of relevance, namely those with the nucleophile involved in the 3c−4e bond. In addition, an equilibrium between the two isomers will be established. From each of these an intramolecular ipso-attack of ligand X is possible leading to the reductive elimination of the corresponding functionalized arene (see Scheme 2).[3,7,8]

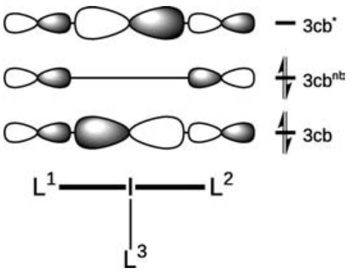
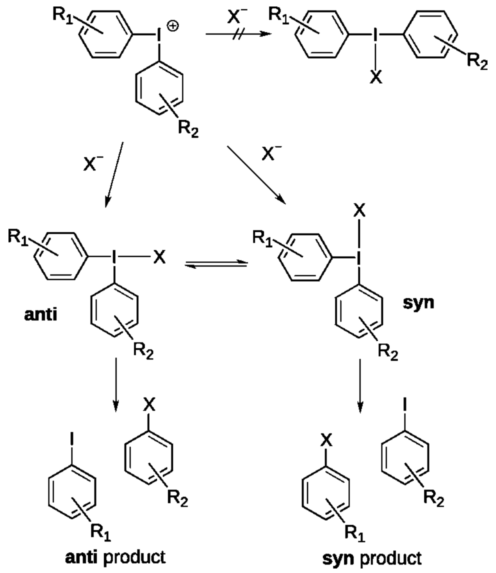


**Figure 1.** 3-Center−4-electron bond in $\lambda^3$-iodanes.[6]

As an illustrative example, the calculated stationary points on the reaction pathway of a diaryl iodonium containing a phenyl and an anisyl ligand (4-methoxyphenyl) along with a bromide as nucleophile are depicted in Figure 2. All calculations were performed with density functional theory (DFT) using the B3LYP hybrid functional[9] with the aug-cc-pVDZ basis set.[10] The energies reported are Gibbs free energies obtained from the electronic energy at 0 K plus the thermal corrections for a reference temperature of 298.15 K. The reaction of the bent diaryl iodonium with the nucleophile leads to the two T-shaped iodane isomers, which are connected by a Y-shaped transition state. The subsequent ipso-attack of the bromide either leads to the functionalization of the phenyl or the anisyl group (see Scheme 2).

**Scheme 2.** Different Selectivities for Reductive Elimination Reactions[a]



[a] Syn and anti refers to the orientation of the nucleophile $X^-$ with respect to the aryl directing group (carrying the $R_1$ group).

The reductive elimination starts from one of the two iodane isomers. Compared to the barrier for the reductive elimination step, the barrier for the isomerization is small. A scenario with a fast equilibrium between reactive species followed by the rate determining step is best represented by the Curtin-Hammett principle[11] (see Figure 2). According to the Curtin-Hammett principle, the selectivity is determined by the difference of the barriers to reductive elimination ($\Delta\Delta G^\ddagger$ in Figure 2).

The selectivity predicted for this particular reaction is in fact in qualitative agreement with the experimental result.[1] The computed barrier leading to the anti product is 2.05 kcal/mol lower in energy, showing that the anti product is favored over the syn product, and reflects the experimental ratio of 9:1 (see Table 1). The selectivity

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(6) Moss, R. A.; Wilk, B.; Krogh-Jespersen, K.; Blair, J. T.; Westbrook, J. D. *J. Am. Chem. Soc.* **1989**, *1*, 250–258.

(7) Ochiai, M. *J. Organomet. Chem.* **2000**, *611*, 494–508.

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(11) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 84–134.

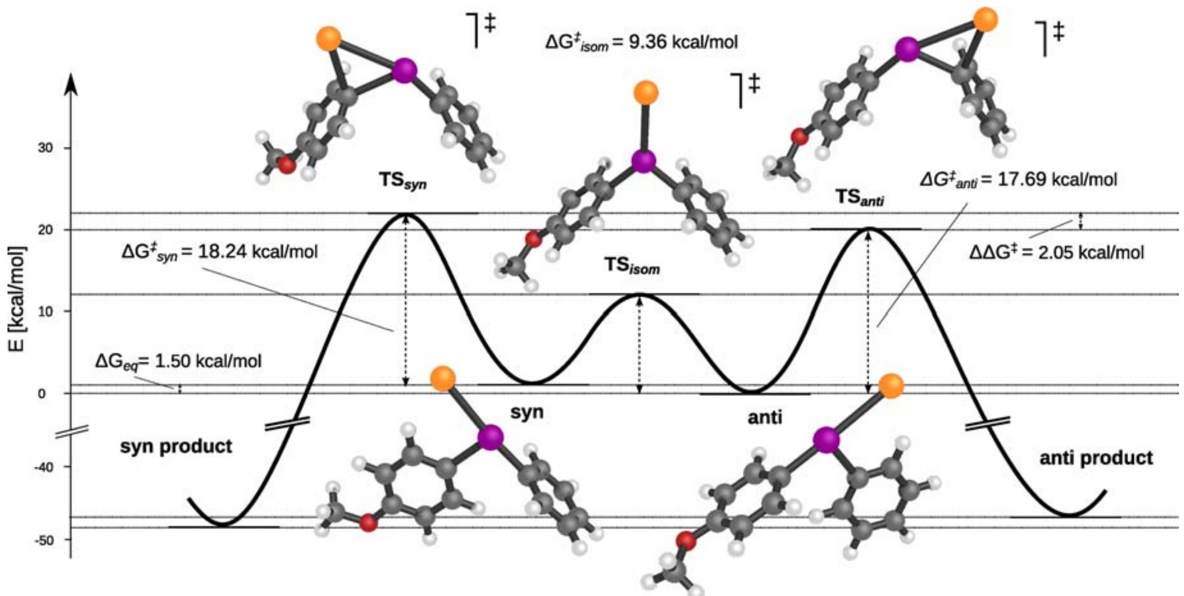
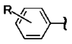


**Figure 2.** Reaction profile of bromo-4-methoxyaryl-phenyl-iodane giving the relative barrier heights $\Delta G^{\ddagger}$ and their absolute differences $\Delta\Delta G^{\ddagger}$ expressed in terms of Gibbs free energies. Also included are the structures of the relevant stationary points.

**Table 1.** Differences between Computed Barriers in kcal/mol Compared to Observed Experimental Selectivities for the Functionalization of a Phenyl Group Using Different Directing Groups

|  | $X^-$ | $\Delta\Delta G^{\ddagger\,a}$ | exp. ratio[1] (anti:syn) |
|---|---|---|---|
| 4-($OCH_3$)Ph | $Br^-$ | -2.05 | 9:1 |
| o-tol | $Br^-$ | 2.02 | 13.3:86.7 |
| p-tol | $Br^-$ | -0.62 | 73.2:26.8 |
| p-tol | $N_3^-$ | -0.79 | 65:24 |
| SECURE[b] | $N_3^-$ | -2.27 | 96:0 |

[a] Negative values for the Gibbs free energy difference $\Delta\Delta G^{\ddagger}$ indicate a lower barrier for the functionalization of the phenyl group. [b] [2.2]Paracyclophanyl; unlike to the other cases the experimental ratio correpsonds to the functionalization of anisyl.

found for this and similar reactions support the validity of the Curtin-Hammett principle: the computed barrier height for the dominant product is consistently lower than the one of the alternative product.

With a 3c−4e bond involved in both reductive elimination reactions, its features are likely to influence the selectivity observed. One would therefore expect to see a difference in the 3c−4e bonds of the two reactive iodane isomers. Upon inspection of the partial charges of the ipso-atoms as optained from a natural population analysis (see Supporting Information), one can compare the polarity of the 3c−4e bond of the syn and anti isomers. It is remarkable that the partial charge on the iodine center is always close to +1.0 and is compensated by the negative partial charges on the ligand ipso-atoms in the 3c−4e bond. This is in line with the orbital picture presented in Figure 1.

Analyzing the example in Table 2 the result is $\Delta\delta_I = +0.99$ and $\Delta\delta_{Br} = -0.61$ in the syn as well as in the anti configuration. The relevant difference of the polarity of the 3c−4e bond lies therefore in the ipso-carbon atom of the aryl ligands (highlighted red in Table 2). Indeed, the partial charge of the ipso-carbon atom of the anisyl directing group amounts to −0.35 electrons, that is, it is 0.04 electrons more negative than the ipso-carbon atom of the phenyl ligand in the same position in the syn isomer ($\Delta\delta_{ipso}$ in Table 2). At this point it is interesting to explore whether there is a correlation between the polarity of the 3c−4e bond and the outcome of the reductive elimination reaction.

In Figure 3, the partial charge differences between the ipso-carbon atoms $\Delta\delta_{ipso}$ is plotted against the corresponding $\Delta\Delta G^{\ddagger}$ value. The plot indeed reveals a relationship between this two parameters. The greater the difference between the partial charges of the two ipso-carbons, the more pronounced the selectivity. For negative $\Delta\delta_{ipso}$ the prediction is that the reaction leans toward the functionalization of the phenyl ligand, wheras the opposite is true for the few cases with a positive difference of the partial charges. The cases where the experimental selectivity is known, actually confirm these predictions. For the anisyl directing group, the example discussed above, the partial charge difference of 0.04 electron relates to a difference in the reductive elimination barrier of 2.05 kcal/mol, thus favoring the functionalization of the phenyl group, consistent with the experimental observations of a 9:1 ratio. Further, it is important to note that the polarity correlates with experimental Hammett $\sigma$-parameters,[12] associated with the directing group.

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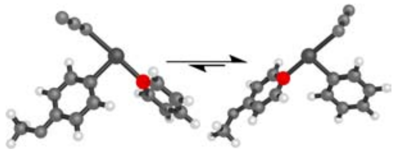
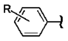
[12] Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *97*, 165–195.

**Table 2.** Natural Charges of the Ligand Ipso-atoms $\delta_{\text{ipso}}$ in the Syn and Anti Isomers of a Series of Diaryliodanes (with $X = N_3$, Br)[a]



|  | $\Delta\delta_{ispo}(X = N_3)$[b] | $\Delta\delta_{ispo}(X = Br)$ |
|---|---|---|
| 4-($OCH_3$)Ph | -0.04 | -0.04 |
| 4-($NH_2$)Ph | -0.04 | -0.06 |
| o-tol | 0.00 | 0.00 |
| m-tol | 0.00 | 0.01 |
| p-tol | -0.01 | -0.02 |
| 4-($CF_3$)Ph | 0.02 | 0.03 |
| 4-($C_3H_5$)Ph[c] | -0.02 | -0.02 |
| mesyl | -0.02 | -0.02 |

[a] One of the aryl ligands is a phenyl group present in all compounds and the other ligand is referred to as directing group. The highlighted atoms correspond to the aryl ipso-atoms involved in the 3c–4e bond. [b] Negative values of $\Delta\delta_{\text{ipso}}$ indicate a dominating directing group. [c] 4-Cyclopropyl phenyl.

However, there are a number of cases that do not follow this pattern (empty diamonds in Figure 3). Closer inspection shows that these involve aryl ligands with bulky substituents. In these cases steric hindrance plays a role resulting in functionalization of the directing group rather than the phenyl ligand. Apparently, the barrier for the funtionalization of the mesyl group is lower than the one for the phenyl.

Figure 3 can be divided into 2 × 2 sectors, namely two sectors containing cases where the outcome of the reaction appears to be controlled by the 3c–4e bond polarity, that is, phenyl functionalization along with negative charge differences, and directing group functionalization with positive charge differences. The two off-diagonal sectors show cases where other effects determine the selectivity. Obviously, in the case of small or zero polarity difference electronic control is absent, and the outcome of the reaction is determined by different factors.

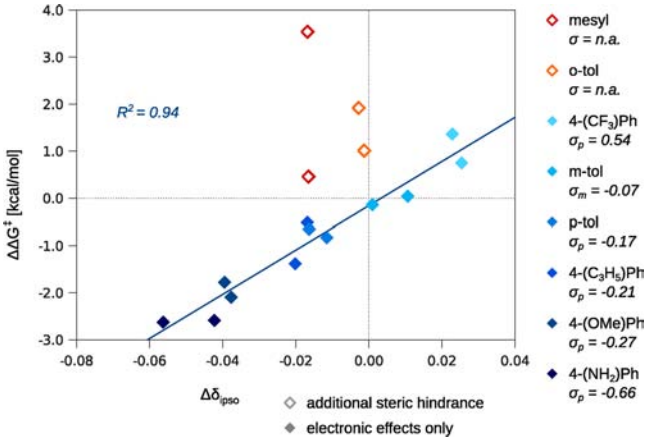


**Figure 3.** Theoretical selectivity $\Delta\Delta G^{\ddagger}$ for the functionalization of a phenyl group using different directing groups (with $X = N_3$, Br) plotted versus the natural charge differences $\Delta\delta_{\text{ipso}}$ of the ipso-carbon atoms of the aryl ligands in the 3c–4e bond. For each directing group, the Hammett $\sigma$-parameters are also listed.[13]

In summary, by means of a computational study we have shown that the mechanism of the iodine guided functionalization of arenes follows a Curtin-Hammett type reaction profile, with the reductive elimination as the rate determining step. In absence of strain, the overall reaction is determined by the electronic features of the 3c–4e bond in the iodane intermediates formed upon the addition of a nucleophile to a diaryl iodonium salt. A relation between the polarity of the 3c–4e bond and the computed reductive elimination barrier, and therefore the selectivity of the overall reaction, is established. These observations are in agreement with previously reported experimental results.

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**Supporting Information Available.** Description of computational methods, tables of Cartesian coordinates, of computed structures, reaction energies, and natural charges. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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