DOI: 10.1002/chem.201001110

α-Arylation by Rearrangement: On the Reaction of Enolates with Diaryliodonium Salts

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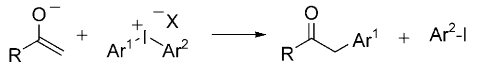
α-Substitution of enolates with various electrophiles is one of the classical reactions in organic chemistry. Asymmetric α-alkylation and α-acylation reactions are among the most important tools available for building complex chiral molecules.[1] α-Arylated carbonyl compounds are abundant substructures in natural products and pharmaceutically active compounds. Yet, there are few synthetic routes to this important compound class.[2] Direct α-arylation of enolates is much harder to realize than the corresponding alkylation reaction, and has been reported only in recent decades. These protocols are mostly based on transition-metal catalysis or stoichiometric use of heavy metal compounds, such as aryl lead reagents.[2]

Hypervalent iodine reagents have recently received considerable attention as mild, selective and non-toxic reagents in many areas of organic synthesis. Diaryliodonium salts, which are iodine(III) compounds with two aryl ligands, are versatile arylation agents for a variety of nucleophiles.[3] With the recent development of efficient and general one-pot routes to diaryliodonium salts,[3,4] the direct α-arylation of enolates with diaryliodonium salts (Scheme 1) can become an attractive alternative to the methods described above,[3,5] in particular if asymmetric versions of the reaction can be developed. So far, the only viable approaches are built on attaching a chiral aryl group as an auxiliary,[6] or by shifting the enantiodifferentiation away from the C–C bond-forming step.[7]



Scheme 1. Arylation of enolates with diaryliodonium salts.

Iodine(III) compounds have a three-coordinate T-shaped structure in the solid state, in which two of the iodine substituents participate in a hypervalent, linear 3-center 4-electron bond (an ω-bond,[8] Figure 1).[9] The two ligands in the hypervalent bond interact with the same p orbital on the central iodine, giving rise to destabilizing interactions between the two ligands, the so-called *trans* effect.[10] The two aryl groups in diaryliodonium salts both induce very strong *trans* effects, and will end up *cis* to each other, with the third ligand (X) sharing the hypervalent bond with one of the aryl groups. Iodine(III) compounds with two heteroatom ligands ($ArIL_2$) are believed to retain this T-shape in solution, with the strongly *trans*-influencing Ar moiety in the equatorial position. The structure of diaryliodonium salts in solution has been debated, and the degree of dissociation is suggested to depend both on the counterion X^- and the solvent.[9,11]

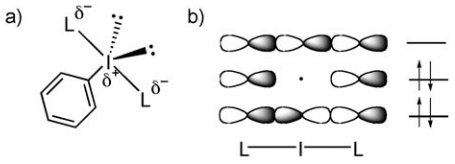


Figure 1. a) T-shaped structure. b) Orbitals in the hypervalent ω-bond.

Reactions of iodine(III) compounds with nucleophiles (Nu^-) generally take place by ligand exchange, either by an associative or dissociative mechanism.[9] In the former, initial Nu–I bond formation gives a square planar iodate intermediate $ArIL_2Nu^-$ with subsequent release of a ligand (L). Alternatively, the ligand could leave before addition of the nucleophile, forming an intermediate iodonium cation ($ArIL^+$). In either case, ArILNu is formed, and subsequent-

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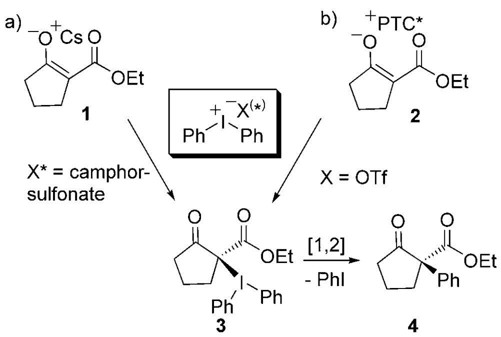
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201001110.

ly gives the product Nu–L. This could either take place by reductive elimination (also called ligand coupling),[12] by nucleophilic attack on the carbon bonded to iodine by the released ligand, with reductive loss of ArI,[9,13] or by SET mechanisms.[14]

Diaryliodonium salts are generally believed to react by the reductive elimination pathway, delivering the equatorial aryl moiety to the axially installed nucleophile.[9] Nucleophilic aromatic substitution is only expected with electron-deficient aryls or under special conditions.[15] SET mechanisms can operate,[16] but in the case of enolate arylation, product distribution studies and results using radical inhibitors argue against the involvement of radicals or benzynes.[17–19]

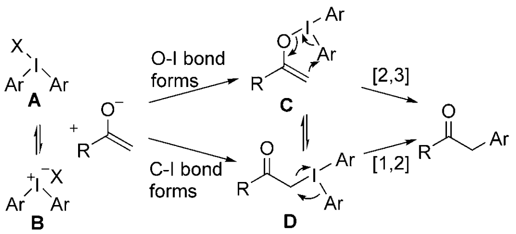
Based on the mechanism described above, we hypothesized that asymmetric induction could be achieved in several ways. Two approaches were investigated, one involving a diaryliodonium salt with a chiral anion (X^{*-}) and the other using chiral phase-transfer catalysis (PTC^{*+}). Camphorsulfonate was used as the chiral anion to direct the electrophile to one face of enolate **1** (Scheme 2a).[20] The chosen PTC^{*+} should block one face of enolate **2** as demonstrated in asymmetric S_NAr reactions of **2** (Scheme 2b).[21] Both approaches were expected to deliver the enantiomerically enriched iodane intermediate **3**, which would yield product **4** upon reductive elimination (i.e., [1,2] rearrangement).[22]



Scheme 2. Proposed asymmetric arylations of β-keto ester enolates by using a) a chiral anion and b) a chiral PTC; OTf = trifluoromethanesulfonate.

Several variations of the two approaches depicted in Scheme 2 were tested, as outlined in the Supporting Information. However, in all cases the arylation proceeded with complete absence of chiral induction in both approaches, indicating that neither X^{*-} nor PTC^{*+} stays associated in the selectivity-determining step. Motivated by these observations, we performed a theoretical study[23] of the title reaction.

The mechanistic possibilities are widened with enolates compared with other nucleophiles.[18] As discussed above, the reaction could follow associative or dissociative ligand-exchange pathways, that is, the enolate could react with neutral **A** or cationic **B** (Scheme 3). Either pathway could give intermediate **C** or **D**, with oxygen or carbon bonded to iodine.[24] These intermediates could either equilibrate rapidly, or form the product through different reductive elimination mechanisms; [2,3] rearrangement or [1,2] rearrangement, respectively.



Scheme 3. Possible intermediates in the α-arylation of enolates.

Initial B3LYP calculations[25] were performed on a model reaction of acetaldehyde enolate with diphenyliodonium chloride in the gas phase and THF, respectively. The chloride anion was chosen to ensure that any results indicating a dissociative pathway would be general also for more weakly coordinating anions, such as triflate or tetrafluoroborate.[26] The energy levels in THF are depicted in Figure 2. The structures **A** and **B** are too close in energy to ascertain whether the ligand exchange takes place by an associative or dissociative pathway. With more easily dissociated counterions, it is likely that **B** is an intermediate and forms **C** and **D** by enolate addition. Even if the anionic species **E** and **F** were formed by addition to **A**, they would quickly lose Cl^- to give **C** and **D**, respectively. These intermediates are isoenergetic, and will rapidly isomerize through an η^3 transition state (TS). Somewhat surprisingly, the preferred reductive elimination is by [2,3] rearrangement rather than the alternative [1,2] process. Direct product formation from anionic intermediates **E** and **F** is disfavored due to high calculated barriers.

The competing [1,2] and [2,3] rearrangements were also compared for the arylation of experimentally employed prochiral enolate **1** (Figure 3). Again, the [2,3] rearrangement pathway was favored over the [1,2] rearrangement, which shows that the results in Figure 2 are valid for α-arylation of various types of enolizable carbonyl compounds.

To summarize, the energy differences between the different pathways are quite small in solution, and could possibly be altered by structural variations of the enolate and/or diaryliodonium salt. Changing the solvent and/or counterion could influence the ionic part of the mechanism, but would not have any significant influence on the selectivity-determining steps in the neutral part of the reaction profile.

We can draw interesting conclusions with regards to the possibilities of making this reaction asymmetric. The low isomerization barrier between **C** and **D** (16 kJ mol^{-1}) is a clear indication that any asymmetric induction obtained in the formation of carbon-bound intermediate **F** or **D** will be lost by fast equilibration with intermediate **C**. Since **C** and **D** are neutral species, they are not expected to be influenced by a chiral anion or a chiral PTC system. This is in

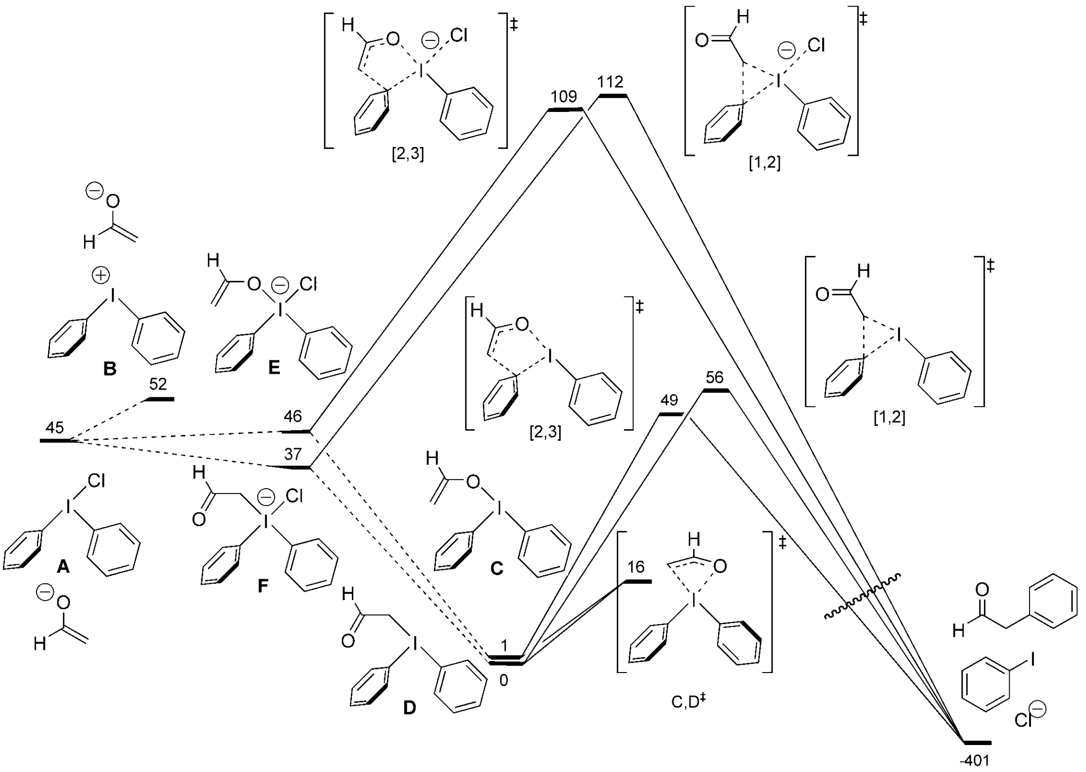


Figure 2. Energy levels (in kJ mol^{-1}) of possible intermediates and TS structures in the reaction of acetaldehyde enolate with Ph_2ICl in THF. Dotted lines indicate rapid association/dissociation equilibria.

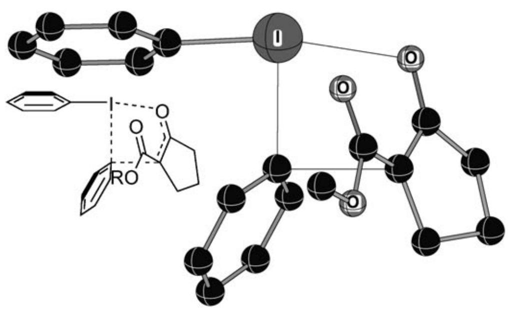


Figure 3. Favored [2,3] rearrangement TS in the arylation of enolate **1** with Ph_2ICl (hydrogen atoms are hidden).

good agreement with the lack of selectivity observed in the experimental work (Scheme 2 and Supporting Information).

Thus, asymmetric induction in the arylation of enolates by diaryliodonium salts could either be obtained by influencing the neutral, prochiral complex **C**,[6] by differentiation of the enantiotopic faces irreversibly during the enolate formation,[7] or by increasing the barrier to interconversion of the O–I and C–I intermediates. Ionic species are not expected to have any beneficial interactions with neutral **C**. Chiral Lewis bases could coordinate to the iodine in a similar manner to chiral anions and give complexes like **E** and **F**, but rearrangements of those species have too high barriers to be competitive. Potentially fruitful approaches could either be based on covalently linked auxiliaries, or on chiral Lewis acids that could associate with and favor reactions via C-linked intermediate **D**. We are currently investigating such systems[27] and will report the results in due time.

Experimental Section

Experimental procedures, analytical data, and computational details are available in the Supporting Information.

Acknowledgements

This work was financially supported by the Swedish Research Council, Carl Trygger Foundation, and K&A Wallenberg Foundation.

Keywords: arylation • density functional calculations • hypervalent compounds • iodanes • reaction mechanisms

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Received: April 27, 2010
Published online: June 16, 2010