Drastic Enhancement of Activity in Iodane–Based α–Tosyloxylation of Ketones: Iodine(III) Does the Hypervalent Twist

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Drastic Enhancement of Activity in Iodane-based α-Tosyloxylation of Ketones: Iodine(III) does the Hypervalent Twist.

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KEYWORDS catalysis • hypervalent compound • iodane • mechanistic study • tosyloxylation.

Supporting Information Placeholder

ABSTRACT: A drastic enhancement in catalytic activity was observed by the introduction of steric hindrance ortho to the iodine atom of catalysts used for the α-tosyloxylation of ketones. Through structural analysis and density functional theory calculations, we explain the origin of this acceleration effect and show its significance through a first example of a chiral catalyst exploiting this feature.

The field of hypervalent iodine-mediated synthetic transformations has received a growing attention in recent years.[1-4] This is not surprising considering that these reagents are polyvalent electrophiles and mild oxidants. They are a great alternative to toxic transition metals often used to effect similar transformations.[5-8] Accordingly, substantial efforts have been made towards the development of enantioselective methodologies based on these reagents.[9-10] Current stoichiometric and catalytic iodine(III)-based enantioselective systems mostly rely on iodoaryl derivatives that introduce chirality through a group ortho to the iodine atom, which either covalently or datively binds the iodane center (Figure 1). Chirality is thus expected to project efficiently on the reactive iodine(III) atom. They have been used in varied chemistry such as: a) α-tosyloxylation of ketones (**1** and **2**),[11-15] b) hydroxylative phenol dearomatization (**3** and **4**),[16] and c) dearomatizing naphthol spirolactonization (**5**[17] and **6**[18-19]).

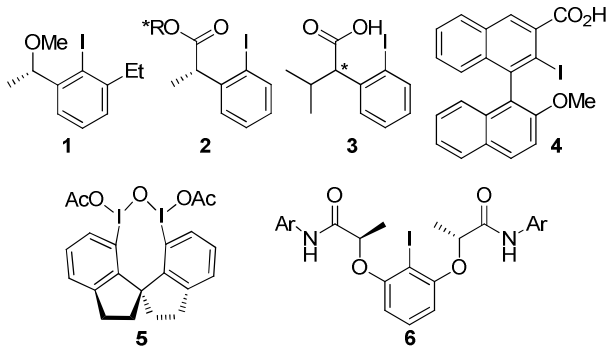
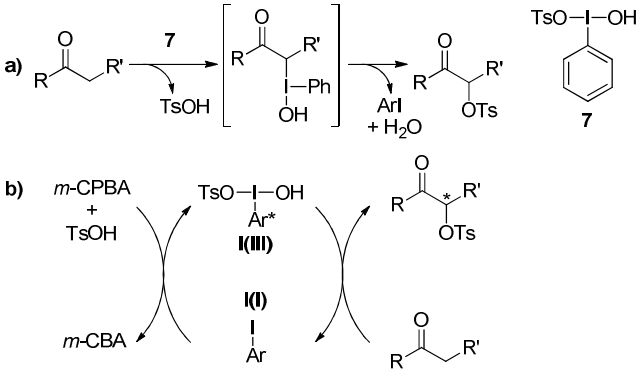


Figure 1. Examples of chiral iodanes and catalysts relying on tethered chirality.

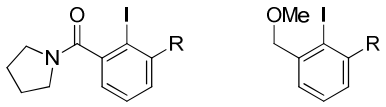
Despite constant progress in this field, efficient chiral induction remains a daunting challenge. It is thus of particular interest to open a path to new chiral catalysts. We report herein a drastic enhancement of activity effect for a family of catalysts that rely on tethered Lewis bases. Our results promise to broaden the currently narrow variety of Lewis bases used.

Our work is primarily focused on the iodine(III)-based α-tosyloxylation of carbonyl compounds.[9,11-15] The transformation is a particularly powerful one, as it yields α-tosyloxy ketones - versatile chiral synthons that enable rapid access to numerous α-chiral ketones through nucleophilic displacement. The reaction has been popularized by Koser *et al.* using hydroxy(tosyloxy)iodobenzene (Scheme 1a, **7**).[20-21] The reaction can be rendered catalytic, through the in situ oxidation of an iodine(I) pre-catalyst by a co-oxidant (Scheme 1b).[2-3,22] The best catalytic enantioselective results for the α-tosyloxylation of propiophenone were reported by Wirth *et al.*, using catalysts **1** (78%, 27% *ee*) and **2** (R* = Menthyl: 42%, 39% *ee*).[12]

Scheme 1. Iodine(III)-based α-oxidation of ketone derivatives.



In the course of our work to promote the α-tosyloxylation of ketones, we explored various Lewis bases adjacent to the iodine center of the catalyst. In particular, we worked with iodoarylamides derivatives (**8a-d**). Iodoethers derivatives **9a** and **9b** were also tested as achiral analogs to chiral iodoether **1**.

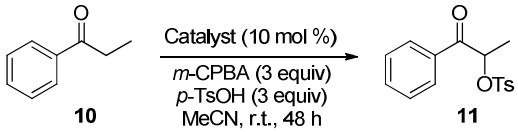


8a (R=H), **8b** (R=Me)
8c (R=Et), **8d** (R=*i*-Pr)

9a (R=H)
9b (R=Me)

Catalyst activity was evaluated using the α-tosyloxylation of propiophenone (**10**) and the results are summarized in Table 1. The conversions are due in part to background Baeyer-Villiger oxidation. The yield of **11** is however a good metric of the catalyst activity. Iodobenzene was used as a reference catalyst to evaluate activity without an adjacent Lewis base (entry 1). In contrast to **8b** and **8c**, **8a** did not display any catalytic activity (entry 2 vs. entries 3-4), suggesting that steric bulk ortho to the iodine is necessary for catalysis. This type of activity enhancement is not observed in iodoether derivatives (entries 6-7), in accord with the results reported by Wirth *et al.*[12] With respect to iodobenzene, the amide group does impart some deactivation, while the ether group does result in equally active catalysts. Interestingly, catalyst **8d**, bearing an *iso*-propyl group, is inactive (entry 5). Evaluation of the oxidation of **8d** shows that oxidation of the iso-propyl C-H bond occurs,[23] but the iodine(III) intermediate is inactive toward α-tosyloxylation.

Table 1. Evaluation of activity of iodoaryl catalysts.



10 **11**

Entry	Catalyst	R	Conv. (%)[a]	**11** (%)[a]
1	PhI	-	98	74
2	8a	H	30	<1
3	8b	Me	74	50
4	8c	Et	86	61
5	8d	*i*-Pr	35	1
6	9a	H	98	81
7	9b	Me	97	75

[a] Determined by ^{1}H NMR using an internal standard.

The effect thus depends on the nature of the Lewis base moiety. A kinetic study of the oxidation of compounds **8a** and **8b** to their corresponding λ^3-iodanes, **12a** and **12b**, was done; both oxidations showed nearly identical kinetic profiles.[24] This clearly indicates that activity enhancement occurs in the α-tosyloxylation step. Propiophenone was thus submitted to α-tosyloxylation conditions with stoichiometric quantities of **12a** and **12b**. Over a period of 24 hours, no reaction (<1%) was observed with **12a**. In contrast, **12b** did lead to product **11** (64%).[24] Both **12a** and **12b** are white crystalline solids, and crystals suitable for diffraction were obtained.[25-26] Their structural analysis was done to pinpoint the origin of the activity enhancement. As expected, both structures show complete dissociation of the tosylate anion and a strong dative bond of the amide group with the iodine(III) center. An important point to note is the planarity of the amide with respect to the aryl moiety in **12a** (Figure 2a). This is due to both the strong donating ability of the amide oxygen and its sp^2 hybridization. In contrast, the presence of the methyl group ortho to the iodine atom in **12b** effectively increases the C_α-C_I-I-O dihedral angle to over 10°. The repulsive effect of the methyl group is also observed through the lengthening of the C_I-I bond, increasing from 2.09 Å (**12a**) to 2.14 Å (**12b**). The λ^3-iodanes derived from iodoethers **9a** and **9b**, **13a** and **13b** respectively, show a similar trend.

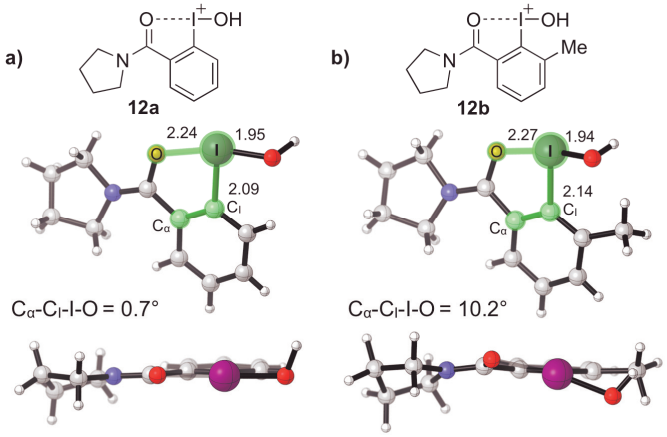


Figure 2. X-ray structures of **12a** and **12b**. The tosylate (TsO-) counterions were removed for clarity.[27]

Computational chemistry was used to obtain the structures of these λ^3-iodanes.[28] In the case of **13a**, a torsion of 13.2° is already present. This value increases to 23.3° in **13b**. This inherent torsion is due to two factors. First, a noticeably longer O-I dative bond is observed in both compounds compared to the iodoamide derivatives. Second, the hybridization of the ether oxygen is sp^3. Still, a destabilization should be observed in these iodoether-derived λ^3-iodanes as well.

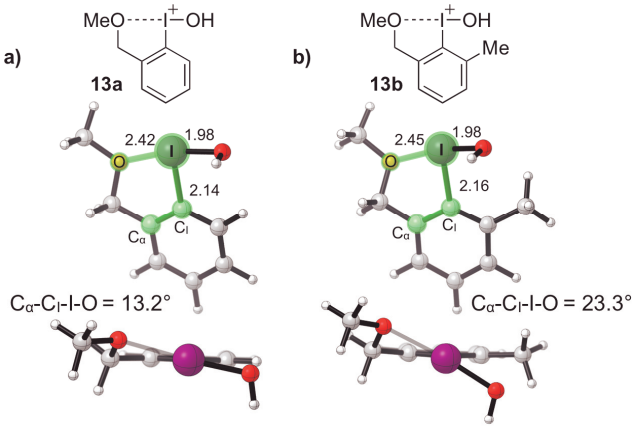
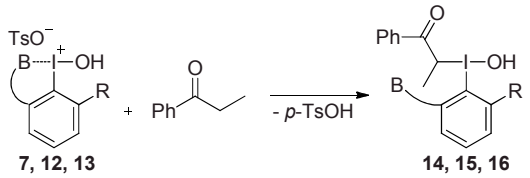


Figure 3. Optimized structures of **13a** and **13b**.[28]

But how important is the destabilization in **12b** compared to **12a**, in comparison to **13a** vs. **13b**? To quantify this, we resorted to isodesmic reactions. The destabilization energy incurred by the methyl group were computed for both the iodoamide (**12a,b**) and iodoether (**13a,b**) derivatives.[24,29] They were found to be 5.0 and 2.4 kcal/mol, respectively. The destabilization of **12b** is thus quite important and would result in a more reactive intermediate. However, no acceleration is found with **9b**, compared to **9a**, despite a non-negligible destabilization. Moreover, both iodoether derivatives are active catalysts. In this context, it seems that activity is not purely linked to the destabilization effect. It is important to look at the reaction pathway to better understand this behavior. One crucial step of the α-tosyloxylation process is the formation of the α-iodono ketone intermediate (**14**, **15** or **16**).[30] The latter results in the dissocia-

tion of the tethered Lewis base (B). The strength of the Lewis base dative bond can then influence the rate of the reaction. The free energies of formation of **14**, **15** and **16** from **7**, **12a**, **12b**, **13a**, and **13b** were computed and are reported in Table 2.

Table 2. Free energies of formation (ΔG_{rxn}) of **14**, **15** and **16**.[28]

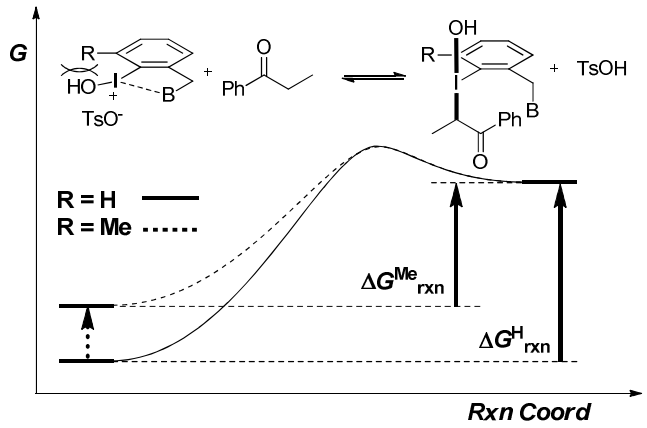


7, 12, 13 **14, 15, 16**

Entry	λ^3-iodane	R	Product	ΔG_{rxn} (kcal/mol)
1	7	-	14	17.1
2	12a	H	15a	26.2
3	12b	Me	15b	21.8
4	13a	H	16a	18.8
5	13b	Me	16b	17.1

Formation of **14** from iodane **7** is easily accessible, with a ΔG_{rxn} of 17.1 kcal/mol. In contrast, formation of **15a** is not readily possible at room temperature, due to a ΔG_{rxn} of 26.2 kcal/mol. However, the free energy of formation of **15b** is smaller by over 5 kcal/mol, making it easily accessible at room temperature. **16a** and **16b**, both derived from iodoether derivatives, possess smaller free energies of formation (entries 4 and 5), which explains the activity of catalysts **9a** and **9b** and the lack of effect of the ortho-methyl group. The free energies calculated for **7**, **13a** and **13b** is in very good correlation with the relative activities of the corresponding catalysts (PhI vs. **9a** vs **9b**). From these results, it is now possible to draw a clear picture of the origin of the effect. With catalysts involving a tethered Lewis base, the strength of the dative bond is very important. With stronger Lewis bases, such as amide groups, the energy required to dissociate the base can become rate limiting and even prevent reaction. In such cases, it is necessary to introduce tension to destabilize the bound conformation so that dissociation can occur at an acceptable rate. The Lewis base in the iodoamide derivative is a sp^2 oxygen atom, favoring the formation of a dative bond planar to the aromatic ring system. Introduction of a sterically demanding group ortho to the iodine center forces the λ^3-iodane hydroxyl group to be out of plane, resulting in a noticeable destabilization of the λ^3-iodane intermediate (Scheme 2).

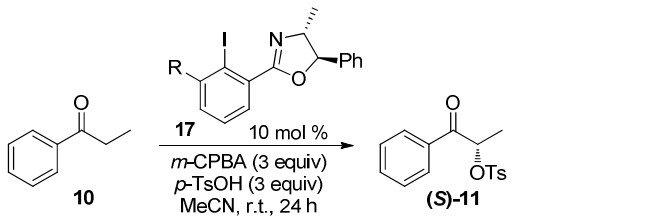
Scheme 2. Rational of the iodine(III) hypervalent twist.



This type of destabilization to accelerate a key reaction step in hypervalent iodine chemistry is reminiscent of the hypervalent twist found in iodine(V) chemistry and described by Goddard et al., related to the oxidation of alcohols using IBX.[31-33] Our work provides the first evidence that this type of torsion-induced activation can exist in iodine(III) species and can be exploited in a more general fashion to attain enhanced reactivity, even in catalytic systems.

The question remains, whether this type of torsion-induced destabilization is general? Chiral Lewis bases with similar donating ability and sp^2-hybridized donor atom should present this behavior. Accordingly, we developed chiral iodoaryl oxazolines **17a** and **17b** as new catalysts for the α-tosyloxylation of propiophenone (Scheme 3). Similar compounds have been used to create chiral iodine(V) reagents that have shown good chiral induction potential for the oxidation of *o*-alkylphenols.[34] To our delight, an even stronger enhancement of activity is observed with these catalysts. While **17a** is almost inactive, **17b** shows levels of activity and enantioselectivity that favorably compare to the currently best catalysts for this transformation.[11-12]

Scheme 3. Enantioselective α-tosyloxylation of **10**.[35]



In conclusion, we discovered and explained a drastic activation effect in the catalytic λ^3-iodane-based α-tosyloxylation reaction. It shows that the use of a torsion-induced destabilization in iodine(III) chemistry can have a large impact on reactivity. The results described herein expand the applicability of the hypervalent twist concept initially proposed by Goddard in iodine(V) chemistry. We project that this behavior will have significant consequences on the creation of novel chiral catalysts for iodine(III)-mediated systems as it opens the path to numerous Lewis bases that would otherwise result in inactive catalysts. We can envision the introduction of chiral amides, oximes, and hydrazones as sp^2 Lewis bases at position ortho to the iodine. The exploitation of this effect in the design of more efficient catalytic enantioselective methodologies is currently underway and will be reported in due course.

ASSOCIATED CONTENT

Characterization and NMR spectra for all new compounds. Full Gaussian reference, cartesian coordinates, electronic and zero-point vibrational energies. This material is available free of charge via the Internet at http://pubs.acs.org.

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(28) Structures optimized at the B3LYP level, with PCM solvation model for acetonitrile, using 6-31+G(d,p) basis set for light atoms and LANL2DZdp(ECP) basis set for iodine. This level of theory gives structures in good agreement with the X-rays structures of **12a** and **12b**. See Supporting Information for details.

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(35) Product **11** does not racemize in the reaction conditions, as confirmed by resubmitting the enantioenriched product to the reaction conditions.

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