Organic LETTERS

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Enantioselective Iodine(III)-Mediated Synthesis of α-Tosyloxy Ketones: Breaking the Selectivity Barrier

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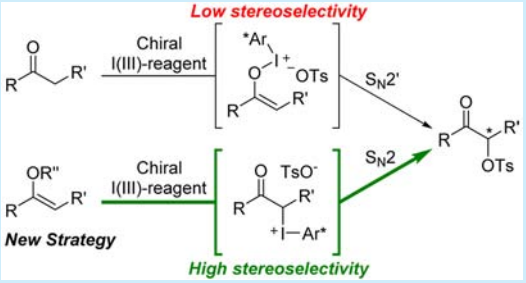
Supporting Information

ABSTRACT: The development of practical methods to access chiral nonracemic α-substituted ketones is of particular importance due to their ubiquitous nature. Unprecedented levels of enantioselectivity are reported for the synthesis of α-tosyloxy ketones, using enol esters and chiral iodine(III) reagents. The reaction can be performed under both stoichiometric and catalytic conditions. These results suggest widely different reaction mechanisms for the reaction of ketones versus enol esters, supporting recent computational insights.



The development of synthetic methodologies involving hypervalent iodine reagents has become an increasingly important field of research.[1] This can be explained by the fact that they give access to a broad range of oxidative transformations.[2] They are considered environmentally benign and can often replace toxic metal-based reagents and catalysts. In this field, the development of enantioselective methods is particularly active and flourishing.[3] Obtaining high selectivities is still a feat. Efforts from numerous groups have yielded notable success, for example, in phenolic dearomatizations[4] and alkene functionalizations.[5]

The α-functionalization of ketones has been one of the most studied reactions.[6] This is a simple yet important method, as hypervalent iodine reagents enable the introduction of nucleophiles to the α-position of carbonyls.[7] Wirth and Mizar have recently reported a very promising strategy involving silyl enol ethers to broaden the scope of nucleophiles available for the α-oxidation reaction.[8] Reaching synthetically relevant enantioselectivities remains an ongoing challenge. The α-tosyloxylation of ketones is one such method that has yet to achieve its full potential.[9] The enantioselectivities obtained remain modest (<58% ee), despite more than 15 years of efforts from numerous groups and the wide variety of chiral precatalysts studied (Figure 1).[10] Solving this issue is of great interest for synthetic chemistry, as it is a privileged transformation; the α-tosyloxy ketones are versatile chiral precursors that could serve as building blocks to access a wide variety of α-chiral ketone derivatives.

We have recently investigated the mechanism of α-tosyloxylation of ketones using quantum chemical calculations.[11] The results of this study suggest that low selectivities for this transformation could originate from a mechanistic pathway proceeding through an S_N2'-type reductive elimination involving an *O*-bonded iodane intermediate obtained from the iodine(III)-mediated enolization of the ketone. We envisioned

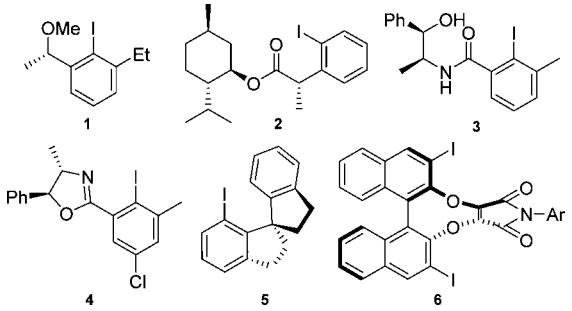
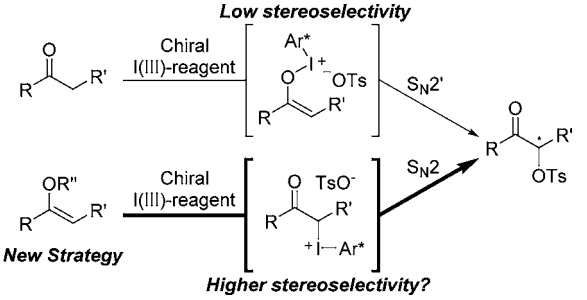


Figure 1. Best catalysts for the α-tosyloxylation of ketones.

that using substrates to which this pathway is inaccessible would also open the possibility of accessing higher enantioselectivities. With this in mind, we considered using enol derivatives to prevent passage through the *O*-bonded intermediate pathway and instead proceed through a *C*-bonded intermediate (Scheme 1).

Scheme 1. New Proposed Strategy



Received: August 31, 2015
Published: September 17, 2015

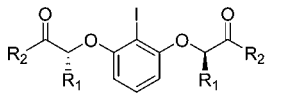
ACS Publications © 2015 American Chemical Society

DOI: 10.1021/acs.orglett.5b02501
Org. Lett. 2015, 17, 4918–4921

Computational results predict no interconversion between the *O*-bonded and *C*-bonded intermediates. Enhancement of selectivities could come from the extended interaction of the enol derivative with the chiral iodonium species. Herein, we report a high-yielding and enantioselective iodine(III)-mediated conversion of enol esters to α-tosyloxy ketones under both stoichiometric and catalytic conditions. To the best of our knowledge, these are the highest selectivities reported so far; these results finally bring a solution to this elusive stereoinduction issue.

Our initial objective was to compare the selectivity outcome of a model ketone with a corresponding enol analog to determine if an alternative mechanistic pathway is accessible. While silyl enol ethers have been reported to be proficient substrates to access α-substituted ketones using iodine(III) reagents,[8,12] they were deemed too sensitive to support catalytic conditions. We have recently reported that enol esters could be cleanly converted to α-tosyloxy ketones using [hydroxyl(tosyloxy)iodo]benzene (HTIB) under both stoichiometric and catalytic conditions.[13] Enol acetate **9a**, derived from propiophenone (**8**), was thus selected for the investigation, as it offered the best reactivity profile under screening conditions.[14] The screening protocols were optimized to provide sufficient reactivity to evaluate selectivities.

Precatalysts **4** and **7a** (Figure 2) were selected to evaluate the selectivity profiles of **8** and **9a**. Iodoarene **4** was selected as it



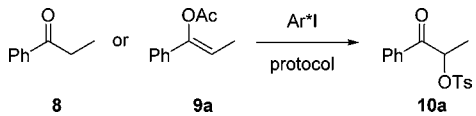
7a, R_1 = Me, R_2 = NHMes
7b, R_1 = *i*-Pr R_2 = NHMes
7c-o, R_1 = Me, R_2 : see table 2

Figure 2. Precatalysts investigated in this study.

offered one of the best selectivities for the α-tosyloxylation of ketones.[10c] Iodoarene **7a**, reported by Ishihara to provide high enantioselectivities for the oxidative spirolactonization of naphthol derivatives,[4d,e] was selected as it was found in the past years to be a privileged chiral scaffold in the field of enantioselective iodine(III)-mediated processes.[15] Both precatalysts were tested for the conversion of propiophenone (**8**) and enol acetate **9a** to the α-tosyloxy ketone product **10a**. The results are summarized in Table 1.

Both precatalysts have strikingly different selectivity profiles for the α-tosyloxylation of propiophenone, as precatalyst **7a** was

Table 1. Selectivity Profile Evaluation



8 **9a** **10a**

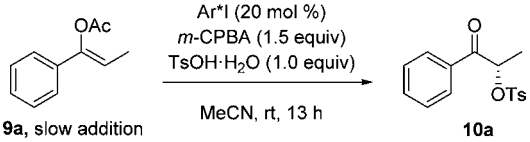
entry	Ar*I	protocol[a]	yield[b] (%)	ee of **10a**[c] (%)
1	**4**	A	80	48 (*R*)
2	**7a**	A	73	<5
3	**4**	B	50	<5
4	**7a**	B	27	78 (*S*)

[a]Protocol A: substrate **8**, Ar*I (10 mol %), *m*-CPBA (3 equiv), TsOH·H_2O (3 equiv), MeCN:CH_2Cl_2, rt, 24 h. Protocol B: substrate **9a** (slow addition), Ar*I (20 mol %), *m*-CPBA (1.5 equiv), TsOH·H_2O (1.0 equiv), MeCN, rt, 13 h. [b]Isolated yield. [c]Determined by HPLC.

found to be ineffective in inducing any selectivity. More interestingly, when subjecting the same catalysts to the conversion of enol acetate **9a** to α-tosyloxy ketone **10a**, precatalyst **4** was found to be ineffective, while precatalyst **7a** resulted in the highest selectivity so far for the iodine(III)-mediated synthesis of this product. The fact that the two precatalysts furnished widely different and inverse selectivity profiles for these two transformations strongly indicates that, while yielding the same final product, their stereochemistry-determining steps are widely different. These results support the proposal that ketones proceed through a S_N2'-type reductive elimination of an *O*-bonded iodane intermediate.[11] The enol acetate, which cannot readily lead to the *O*-bonded intermediate, would proceed through a *C*-bonded intermediate, which can then yield **10a** through an S_N2 substitution of the iodonium leaving group (Scheme 1).

With these promising results in hand, we undertook precatalyst optimization; the results are summarized in Table 2. The use of bulkier stereogenic centers (entry 1) leads to a drastic decrease in reactivity. Converting the amide groups to ester moieties was found to be detrimental for the selectivities, although it provided higher reactivity (entry 2).

Table 2. Precatalyst Optimization



9a, slow addition **10a**

entry	Ar*I	R_2	yield[a] (%)	ee of **10a**[b] (%)
1	**7b**	NHMes	<5	50
2	**7c**	OMe	71	43
3	**7d**	NH[3,5-$(CF_3)_2C_6H_3$]	50	36
4	**7e**	NHPh	44	60
5	**7f**	NMe(Ph)	49	83
6	**7g**	*N*-indolinyl	8	13
7	**7h**	NH(Bn)	45	74
8	**7i**	NH(*i*-Pr)	61	79
9	**7j**	NH(*n*-Bu)	60	76
10	**7k**	*N*-pyrrolidinyl	46	65
11	**7l**	*N*-(*S*)-prolinyl	39	84
12	**7m**	*N*-(*R*)-prolinyl	38	78
13	**7n**	NH[(*S*)-(α-Me)Bn]	53	79
14	**7o**	NH[(*R*)-(α-Me)Bn]	76	78

[a]Isolated yield. [b]Determined by HPLC.

Evaluation of different aryl groups on the amide moieties showed that steric bulk was not the main factor to achieve high enantioselectivies (entries 3 and 4). Surprisingly, introduction of a supplementary methyl group on the amide nitrogen atoms did lead to an enhancement in selectivity (entry 5). Attempts to constrain rotation of the phenyl group with respect to the methyl group by the use of indolinyl moieties on the amides resulted in a drastic loss of both reactivity and selectivity (entry 6). Benzylic and aliphatic groups on the amide nitrogen atoms were investigated; they resulted in good activity and acceptable selectivities (entries 7−10). These precatalysts were, however, much more difficult to obtain and purify due to a drastic increase in polarity with respect to the catalysts bearing anilines on the amides. Finally, we investigated the effect of introducing a second source of chirality on the precatalyst by creating amides from chiral amines (entries 11−14). While they gave

DOI: 10.1021/acs.orglett.5b02501
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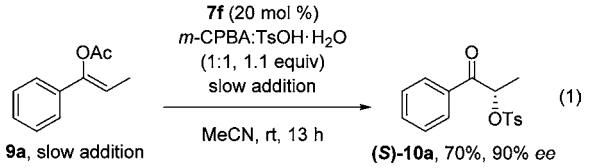
interesting activity and selectivity profiles, they suffered the same purification problems described for precatalysts **7h**–**k**. It is important to note that most precatalysts with secondary amides, bearing an hydrogen atom on the amide groups, showed slight degradation over the course of the reaction.

Iodoarene **7f** was thus selected as the best precatalyst due to its high selectivity, its stability under reaction conditions, and its ease of synthesis and purification from cheap starting materials. The catalytic conditions were optimized further; a good yield and excellent enantioselectivity were achieved (eq 1).[14]

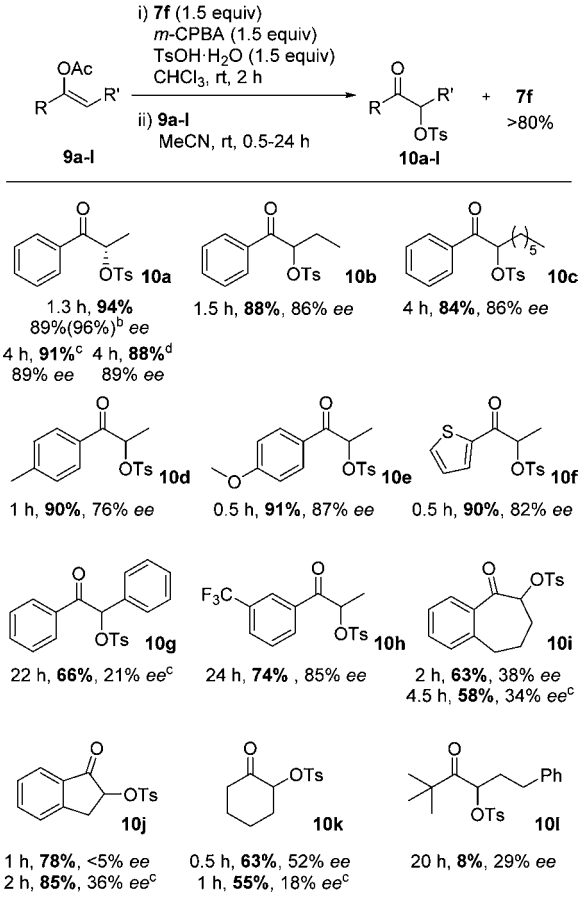


To simplify the investigation of the reaction scope, we decided to focus our efforts on the development of stoichiometric reaction conditions.[16] It was not considered a drawback, since **7f** is stable under the reaction conditions and was expected to be easily recovered. To ensure complete substrate conversion, we elected to use an excess of the chiral iodane. The latter was first obtained by oxidation of **7f** in the presence of stoichiometric amounts of *m*-CPBA and TsOH, according to a procedure reported by Togo.[17] The results are summarized in Scheme 2.

The enol acetates were cleanly converted to the α-tosyloxy ketones in usually excellent yields. The main byproducts detected were the corresponding α-hydroxy ketones in trace amounts (<5%). It is important to note that in all reactions **7f** was recovered in very good yield (>80%). Gratifyingly, the stoichiometric conditions yielded the desired product with the same level of selectivity as the catalytic conditions. Product **10a** can be recrystallized to provide an almost enantiopure (96% ee) form. We evaluated the effect of solvent on the reaction outcome. Surprisingly, it had no effect on the selectivity, although the reaction rate was clearly affected. A longer alkyl chain R′ group did not have a major effect on yield or selectivity. Exchanging R′ for a phenyl group did, however, result in a lower yield and a drastic loss in enantioselectivity.[18] The method supports variation of the electronic properties of the aromatic moiety (R group) on the enol ester. Electron-donating groups enhance the rate of the reaction and fortunately do not result in noticeable loss of selectivity. It is noteworthy to point out that such products are difficult to obtain using the α-tosyloxylation methodology, as electron-rich ketones tend to be unreactive.[10c] Surprisingly, a methyl group at the para position (**9d**) of the aromatic had a detrimental effect on selectivity, while a methoxy group (**9e**) had no such effect. Substrate **9h**, bearing an electron-deficient aromatic group, showed much lower reactivity, but the selectivity was not drastically affected.

The effect of enol ester stereochemistry was much more important. Cyclic substrates **9i** and **9k**, having an (*E*)-*O*-enol stereochemistry, afforded only modest selectivities. An even more striking result was obtained with substrate **9j**, which yielded product **10j** in racemic form. In contrast to the reaction with **9a**, selectivity for the conversion of **9j** could be improved up to 36% ee using dichloromethane as the reaction solvent. On the other hand, using this solvent for the formation of **10i** and **10k** did not improve selectivities. These are particularly

Scheme 2. Reaction Scope Evaluation[a]



[a]Isolated yields reported and enantiomeric excess determined by HPLC. [b]Enantiomeric purity of recrystallized **10a**. [c]Reaction done in CH_2Cl_2. [d]Reaction performed in $CHCl_3$.

interesting findings, as the recent methodology developed by Wirth and Mizar involved similar chiral reagents and was shown to afford very good selectivities exclusively for cyclic silyl enol ethers reminiscent of substrate **9j**.[8] Substrate **9l** was found to be almost unreactive toward the chiral iodane reagent, as only low conversion, yield, and selectivity were observed over 20 h reaction time at room temperature. Increasing reaction time or reaction temperature did not improve the yield. This is in stark contrast with the reactivity observed with HTIB[13] and demonstrates the increased steric bulk incurred by the chiral environment around the iodine center.

In summary, we have developed a highly enantioselective iodine(III)-mediated synthesis of α-tosyloxy ketones using easily accessible substrates. While they can be obtained from their ketone counterparts, the fact that enol esters can be synthesized from nonketonic substrates, such as alkynes,[19] actually expands the scope of the methodology; it has the added benefit of removing the necessity of using ketone derivatives to access α-substituted ketones with iodine(III)-mediated processes. The obtained results further support our recent computational study suggesting that the α-tosyloxylation of ketones proceeds through an iodine(III)-mediated enolization and S_N2'-type reductive elimination. With this in mind, the success of the current methodology is a stepping stone to better appreciate the requirements for efficient stereoinduction.

DOI: 10.1021/acs.orglett.5b02501
Org. Lett. 2015, 17, 4918–4921

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02501.

Experimental procedures and NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Science and Engineering Research Council (NSERC) of Canada, the Canada Foundation for Innovation (CFI), the FRQNT Centre in Green Chemistry and Catalysis (CGCC), and the Université de Sherbrooke.

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