Stereoselective Rearrangement

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Stereoselective Rearrangements with Chiral Hypervalent Iodine Reagents**

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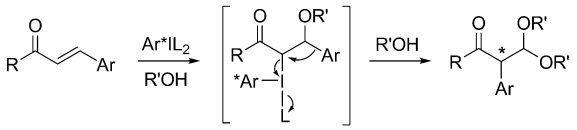
Organic molecules bearing hypervalent iodine moieties have fascinated chemists over the years. Mild reaction conditions and environmentally friendly behavior through replacement of toxic heavy metals have led to their recent renaissance in organic synthesis.[1] Their use not only as selective oxidants[2] but also as enantiomerically pure reagents[3] make them versatile reagents for many organic transformations, such as the oxidation of sulfides to sulfoxides,[4] the α-oxygenation[5] and α-arylation of carbonyl compounds,[6] the dearomatization of phenols,[7] and the dioxygenation,[8] diamination,[9] aminohydroxylation,[10] and aminofluorination[11] of alkenes. The nature of hypervalent iodine(III) compounds to react as electrophiles and then act as excellent leaving groups make them highly suitable reagents for generating cationic intermediates, which can either directly react with nucleophiles or lead to rearranged products[12] under ring expansion,[13] ring contraction,[14] or aryl migration.[8d,15] Similar rearrangements have been performed with much more toxic thallium reagents.[16]

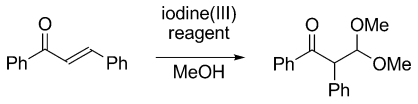
We recently reported a novel oxidative rearrangement of aryl substituted unsaturated carboxylic acids for the facile access of furanones.[17] Calculations were conducted to investigate the interplay of various cationic intermediates. Other studies have also confirmed the involvement of aryl moieties in cationic intermediates of rearrangement reactions.[18] The use of chiral hypervalent iodine reagents in asymmetric rearrangement reactions seems to be a very promising area of research and, to our knowledge, no reactions of this type have been reported to date. Herein, we describe the first stereoselective rearrangements of aryl substituted alkenes with high enantioselectivites mediated by chiral hypervalent iodine reagents. We have investigated chalcones of type **1**, which are easily accessible through an aldol condensation between methyl ketones RCOMe and aryl aldehydes ArCHO. Oxidative rearrangements of such compounds to α-arylated carbonyl compounds have been known for some time.[19] The reaction of aryl-substituted alkenes **1** with electrophilic chiral iodine reagents results in the formation of phenyliodinated intermediates **2**, which can be stabilized by the formation of phenonium ions[20] followed by the reaction with a second alcohol nucleophile to give the 1,2-migration products **3** (Scheme 1).



Scheme 1. Rearrangement of **1** to **3** via phenyliodinated intermediate **2** using hypervalent iodine reagents Ar^*IL_2.

Initially the reaction of (*E*)-1,3-diphenyl prop-2-en-1-one **1a** with only (diacetoxyiodo)benzene [$PhI(OAc)_2$] was investigated, but its reactivity with **1a** is too low and no conversion was observed (Table 1, entry 1). As already described,[19] an activation of the hypervalent iodine(III) reagent is necessary, and addition of 50% aqueous H_2SO_4 as a Brønsted acid to the reaction mixture[21] resulted in the rearranged product in 64% yield. When using [bis(trifluoroacetoxy)iodo]benzene as an iodine(III) source, the yield increased to 82% (Table 1, entries 2 and 3).

Table 1: Different hypervalent iodine reagents for the migration of **1a**.



Entry	Reagents	Reaction Conditions[a]	3a Yield [%]	3a *ee* [%][b]
1	1.05 equiv $PhI(OAc)_2$	RT, 12 h	0	–
2	1.05 equiv $PhI(OAc)_2$ 1.4 equiv 50% H_2SO_4	RT, 3 h	64	–
3	1.05 equiv $PhI(OCOCF_3)_2$ 1.4 equiv 50% H_2SO_4	RT, 3 h	82	–
4	1.2 equiv $PhI(OAc)_2$ 1.4 equiv TBDMSOTf	0°C to RT, 14 h	37	–
5	1.15 equiv **4a** 1.4 equiv 50% H_2SO_4	RT, 2 h	4	17
6	1.15 equiv **4b** 1.4 equiv 50% H_2SO_4	RT, 20 h	5	5
7	1.5 equiv **4a** 3 equiv TBDMSOTf	−78°C, 12 h	–	–
8	1.5 equiv **4a** 3 equiv TBDMSOTf	−78°C to RT, 12 h	50	0

[a] Solvent: MeOH. [b] Determined by HPLC on chiral stationary phase.

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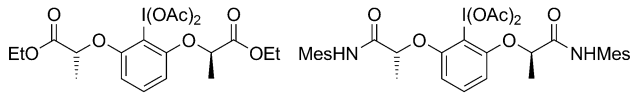
As a new stereogenic center is established in the product, lactic acid based chiral hypervalent iodine compounds, synthesized initially by Fujita et al.[8f,h,22] and further explored by various research groups[7d,9,10] in asymmetric reactions, were investigated. The reagents **4a** and **4b** (Figure 1) are diacetoxyiodo arenes and not reactive enough to induce the



4a **4b**

Figure 1. Lactate-based chiral hypervalent iodine reagents **4a** and **4b**.

rearrangement (see also Table 1, entry 1), but after addition of sulfuric acid the reaction proceeded slowly and the rearranged product was obtained in low yields and with poor enantioselectivities (Table 1, entries 5 and 6). Inspired by the successful activation of hypervalent iodine compounds with Lewis acids in asymmetric functionalizations of alkenes,[8h,10] a similar approach was investigated in these migration reactions. Unfortunately, there was either no reaction at low temperatures or only racemic product was obtained by using *tert*-butyldimethylsilyl triflate (TBDMSOTf) in MeOH (Table 1, entries 7 and 8).

Previous investigations also indicated that the solvent composition is crucial in stereoselective reactions with iodine(III) reagents.[10] Mixtures of methanol and dichloromethane did not improve the enantiomeric excess in **3a** (Table 2, entry 1). However, when the initial synthesis of the highly electrophilic hypervalent iodine reagent Ar*I(OTf)$_2$ by prior mixing of the chiral hypervalent diacetoxyiodo derivative Ar*I(OAc)$_2$ with TBDMSOTf in dichloromethane at −78 °C as evidenced by NMR studies[10,23] is followed by addition of methanol along with starting material **1a**, the product **3a** was obtained with improved enantioselectivities (Table 2, entry 2). When the reaction temperature was kept at −15 °C, the enantioselectivity rose to a promising level of 86 % (Table 2, entry 3). Also other Lewis acids have been utilized in the migration reaction in combination with different solvents and chiral hypervalent iodine reagents, as shown by entries 4–8 in Table 2.

Table 2: Conditions for the stereoselective rearrangement of **1a** to **3a**.

Entry	Reagents[a]	Solvent	**3a** *ee* [%]
1	**4b**, TBDMSOTf[b]	CH_2Cl_2/MeOH (1:1)	12
2	**4b**, TBDMSOTf[b]	CH_2Cl_2, 10 equiv MeOH	43
3	**4b**, TBDMSOTf	CH_2Cl_2, 8 equiv MeOH	86
4	**4b**, $BF_3{\cdot}OEt_2$	CH_2Cl_2, 8 equiv MeOH	24
5	**4b**, TMSOTf	CH_2Cl_2, 8 equiv MeOH	88
6	**4a**, TMSOTf	CH_2Cl_2, 8 equiv MeOH	12
7	**4b**, $BF_2OTf{\cdot}OEt_2$[c]	CH_2Cl_2, 8 equiv MeOH	89
8	**4b**, TfOH	CH_2Cl_2, 8 equiv MeOH	91
9	**4b**, TfOH	CH_2Cl_2/2,2,2-trifluoroethanol (1:1), 8 equiv MeOH	95[d] 99[e]
10	**4b**, TfOH	CH_3CN, 8 equiv MeOH	92

[a] 1.5 equiv **4**, 3 equiv Lewis acid, reaction temperature −78 °C to −15 °C, reaction time 14 h. [b] Reaction temperature −78 °C to RT, reaction time 14 h. [c] Prepared by a 1:1 mixture of TMSOTf and $BF_3{\cdot}OEt_2$.[24] [d] **3a**. [e] **3a′**: Bis-2,2,2-trifluoroethoxy acetal.

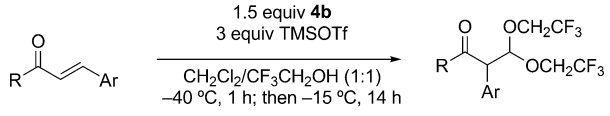
When triflic acid was used together with hypervalent iodine reagent **4b** in a 1:1 mixture of dichloromethane and 2,2,2-trifluoroethanol, a mixture of the dimethoxy acetal **3a** (95 % *ee*) and the bis(trifluoroethoxy)acetal **3a′** (99 % *ee*) was obtained (Table 2, entry 9). A close monitoring of the reaction by ^{1}H NMR revealed only a 28 % conversion into the product **3a** by employing triflic acid as Lewis acid and dichloromethane and methanol (8 equiv) as solvents (see the Supporting Information). The enantiomeric excess was found to be constant over the course of the reaction (ca. 85 % *ee*), indicating no further interaction of the chiral reagent with the product. This reaction and all the results described in Table 2 have been carried out on a sub-millimolar scale without isolation of the reaction products.

When the reaction was performed without the addition of methanol using only a 1:1 mixture of dichloromethane and 2,2,2-trifluoroethanol with triflic acid as Lewis acid, a higher yield (66 %) of the product **3a'** with moderate selectivity (69 % *ee*) was obtained. By using TMSOTf as the Lewis acid for iodine(III) activation, the asymmetric induction was found to be excellent, giving the product in 97 % *ee* (Table 3, entry 2). When TMSOTf is used as the activating Lewis acid, the same significant increase in selectivity is observed with the 4-fluorophenyl substituted chalcone **1b** (Table 3, entries 3 and 4). These reaction conditions were then applied to a wide range of substrates. Electronically withdrawing substituents on the aryl moiety at position 4 led to the expected rearranged products **3** with high selectivities, but the yields decrease with an increase in the Hammett value[25] of the halide substituents from $\sigma_p = 0.06$ (F) to $\sigma_p = 0.23$ (Br) (Table 3, entries 4 to 6). With the 4-nitro substituted chalcone **1e** ($\sigma_p = 0.78$), the starting material was completely recovered and no rearrangement took place (Table 3, entry 7). The absolute configuration of the major isomer of **3c** and **3d** was found to be *R* by anomalous dispersion scattering, and the refined Flack parameters[26] were 0.17(16) and 0.00(4), respectively, as determined by X-ray crystallography.[27]

When compounds **1** with electron-donating substituents on the aryl moiety were subjected to the rearrangement reaction conditions, products **3** were obtained in high yields and selectivities (Table 3, entries 9 and 10). Unfortunately, compounds **1** with a 4-*tert*-butyl (**1h**) and a 3-methyl substituent (**1i**) resulted in products **3h** and **3i** with only moderate selectivities (Table 3, entries 11 and 12). Compound **1j** with a 4-methoxy substituent only led to complete decomposition under different reaction conditions (Table 3, entry 13). From these results it is obvious that both steric and electronic parameters from substituents in the *para* position are strongly influencing the yield and selectivity of the reaction.

Heteroaromatic compound **1k** as well as other unsaturated carbonyl compounds such as the cinnamyl ester **1l** and the methyl-substituted ketones **1m** also underwent the rearrangement reaction with high selectivities, but only gave the reaction products **3** in low yields (Table 3, entries 14–16).

Table 3: Other substrates for the stereoselective rearrangement.[a]



1 3

Entry	Substrate	R	Ar	Product	Yield [%]	*ee* [%]
1	**1a**	Ph	Ph	**3a′**	66[b]	69
2	**1a**	Ph	Ph	**3a′**	59	97
3	**1b**	Ph	4-F-C_6H_4	**3b**	60[b]	69
4	**1b**	Ph	4-F-C_6H_4	**3b**	50	94
5	**1c**	Ph	4-Cl-C_6H_4	(*R*)-**3c**	38	92
6	**1d**	Ph	4-Br-C_6H_4	(*R*)-**3d**	17	91
7	**1e**	Ph	4-NO_2-C_6H_4	**3e**	0[c]	–
8	**1f**	Ph	4-Me-C_6H_4	**3f**	92[b]	66
9	**1f**	Ph	4-Me-C_6H_4	**3f**	80	86
10	**1g**	Ph	4-*i*Pr-C_6H_4	**3g**	68	89
11	**1h**	Ph	4-*t*Bu-C_6H_4	**3h**	65	52
12	**1i**	Ph	3-Me-C_6H_4	**3i**	42	53
13	**1j**	Ph	4-OMe-C_6H_4	**3j**	0[c]	–
14	**1k**	2-furyl	Ph	**3k**	8	83
15	**1l**	OMe	Ph	**3l**	12	96
16	**1m**	Me	Ph	**3m**	10	–[d]

[a] Reaction conditions: CH_2Cl_2/CF_3CH_2OH (1:1), 1.5 equiv **4b**, 3 equiv TMSOTf, −40 °C, 1 h; then −15 °C, 14 h. [b] Lewis acid: TfOH. [c] Hypervalent iodine reagent: $PhI(OAc)_2$, reaction temperature: 0 °C. [d] The enantiomers were inseparable on a HPLC column.

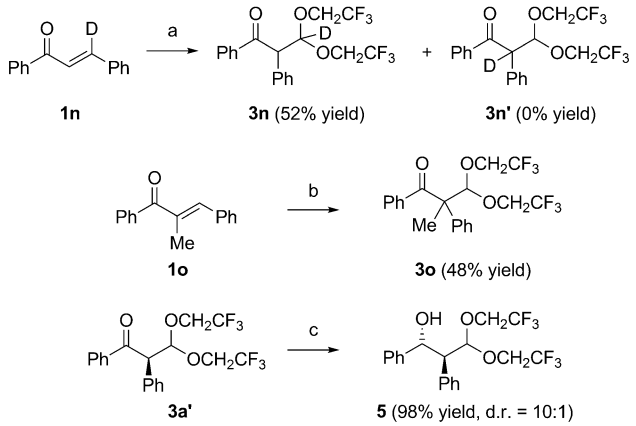
In these experiments, an excess of the hypervalent iodine reagent **4b** (1.5 equiv) is being used. About 80–85 % of the reduced aryl iodide can be recovered after the reaction without loss of optical purity and can be reoxidized.

A recent publication showed the potential of an aryl ketone to migrate in boron trifluoride catalyzed epoxide opening reactions.[28] To confirm that the reaction mechanism proceeds with aryl ring migration, the deuterium-labeled compound **1n** was treated with $PhI(OAc)_2$ together with TfOH. The phenyl ring migrated product **3n** was obtained exclusively alongside unreacted starting material. The product **3n′**, which would result from an aryl ketone migration, was not observed in this reaction. We also investigated compound **1o** in an attempt to generate quaternary carbon centers in this process. No reaction was observed in attempted stereoselective rearrangement with **4b**, but the reaction proceeded by using (diacetoxyiodo)benzene and TMSOTf as activating reagent to give the expected rearranged product **3o** in 48 % yield. Photoisomerization of (*E*)-**1a**[29] led to an inseparable mixture of (*E*)-**1a** and (*Z*)-**1a** (4:10), which was subjected to the rearrangement conditions using reagent **4b**. Product **3a′** was obtained in 31 % yield and with 55 % *ee*; the recovered starting material **1a** showed an altered *E*/*Z* ratio of about 10:2. This indicates that (*Z*)-**1a** reacts much faster than (*E*)-**1a**, but the enantiomeric excess obtained in the product **3a′** is lower.

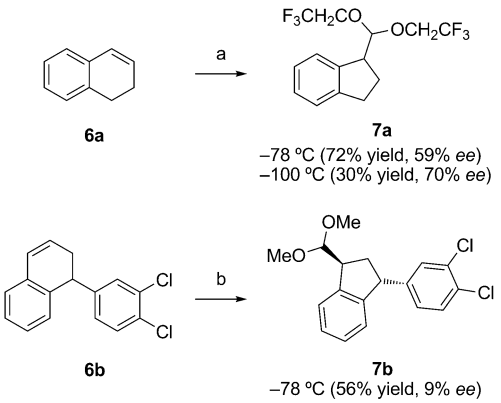
Compound **3a′** was reduced with sodium borohydride to obtain the corresponding alcohol **4** with good diastereoselectivity (Scheme 2). Products of type **4** are versatile building blocks for further manipulations. Moreover, this asymmetric method allowed the synthesis of fluorinated acetals, which have many applications in biological chemistry and industry.[30]

Ring contraction reactions of tetralone derivatives have also been performed using this method.[14] When compound **6a** was subjected to the rearrangement reaction conditions, rearranged product **7a** was obtained in 59 % *ee*. The selectivity was improved at lower temperature to 70 % *ee* but with decreased yields. Further functionalization of compound **7a** can lead to the synthesis of compounds of biological importance.[31] Unfortunately, substrate **6b** gave a very low selectivity in product **7b** when methanol was used as nucleophile. The use of 2,2,2-trifluoroethanol in this ring-contraction reaction resulted in a complex mixture of products (Scheme 3).

In conclusion, we have developed an efficient and highly stereoselective method for the α-arylation of a wide range of



Scheme 2. Isotope labeling and generation of quaternary centers. Reaction conditions: a) 1.5 equiv $PhI(OAc)_2$, 3 equiv TfOH, CH_2Cl_2/CF_3CH_2OH (1:1), −40 °C, 1 h; then 0 °C, 3 h. b) 1.5 equiv $PhI(OAc)_2$, 3 equiv TMSOTf, CH_2Cl_2/CF_3CH_2OH (1:1), −40 °C, 1 h; then −15 °C, 14 h. c) 2 equiv $NaBH_4$, MeOH, 0 °C, 30 min.



Scheme 3. Ring-contraction reactions of tetralone derivatives **6**. Reaction conditions: a) −78 °C: 1.5 equiv **4b**, 3 equiv TfOH, CH_2Cl_2/CF_3CH_2OH (4:1), 14 h; −100 °C: 1.5 equiv **4b**, 3 equiv TMSOTf, $CH_2Cl_2/CF_3CH_2OH/Et_2O$ (3:1:4), 3 h. b) 1.5 equiv **4b**, 3 equiv TfOH, 8 equiv MeOH, CH_2Cl_2, −78 °C, 14 h.

carbonyl compounds by an oxidative rearrangement procedure. These results are noteworthy as they are the first examples of chiral hypervalent iodine(III) reagents in highly stereoselective rearrangement reactions. Further investigations for developing a catalytic reaction and for the synthesis of enantiomerically enriched building blocks using this approach are currently in progress.

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