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Enantioselective Organocatalytic Iodination-Initiated Wagner—Meerwein Rearrangement

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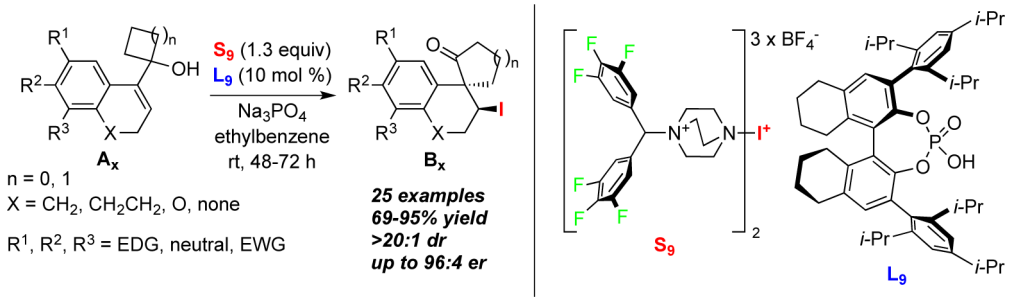
ABSTRACT



The present manuscript describes a high-yielding enantioselective semipinacol transposition, initiated by an electrophilic iodination event. The title transformation makes use of the anionic phase-transfer catalysis (PTC) paradigm for chirality induction. Thus, when combined appropriately, the insoluble cationic iodinating reagent S_9 and the lipophilic phosphoric acid L_9 act as an efficient source of chiral iodine that performs the semipinacol transposition of strained allylic alcohols A_x to β-iodo spiroketones B_x in good yields and with high levels of diastereo- and enantioinduction. The product β-iodo spiroketones could be derivatized stereospecifically and without stereoerosion, giving rise to products inaccessible directly from a semipinacol rearrangement.

The regio- and stereocontrolled functionalization of carbon—carbon double bonds is of primordial importance in organic synthesis. Transition-metal-free electrophilic activation of olefins has been largely dominated by halofunctionalization reactions.[1] These reactions involve the capture of transient haliranium ions, formed from olefin/dihalogen association, by inter- or intramolecular nucleophiles.[2] By far, the halocyclization process (intramolecular nucleophile) represents the most studied halofunctionalization reaction.[3] In sharp contrast to the exhaustively studied bromocyclization process,[4,7a,7b] engineering enantioselectivity in fluoro-,[5] chloro-,[6] and iodocyclization[7] reactions remains challenging and lacks generality in terms of substrate scope. This constitutes an important handicap to the synthetic community due to the primordial role of iodinated organic molecules in natural products, pharmaceuticals, and agrochemicals.[8a—d] Iodinated compounds are also valuable precursors that provide access to more complex molecular frameworks.[8e]

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Far less studied is the related halogenation/semipinacol rearrangement cascade.[9] In this last reaction, the transiently formed haliranium ion undergoes a Wagner–Meerwein alkyl migration, leading to the formation of synthetically valuable β-halogenated ketones (Figure 1). Whereas the chlorination- and bromination-initiated Wagner–Meerwein rearrangements of electron-rich cyclic enol ethers were shown to be amenable to asymmetric catalysis,[10] the development of enantioselective catalytic fluorination- and iodination-initiated variants remains underexplored.[11] Very recently, we have proposed a solution to the above problem by adapting the anionic phase-transfer catalysis (PTC) protocol to the fluorination/semipinacol case.[12] In the present manuscript, we wish to report a new achiral-reagent/chiral-counterion catalytic system that enables a highly stereoselective iodination/semipinacol transposition sequence to take place. To the best of our knowledge, a catalytic asymmetric protocol for the iodination-initiated Wagner–Meerwein rearrangement is unprecedented in the literature.

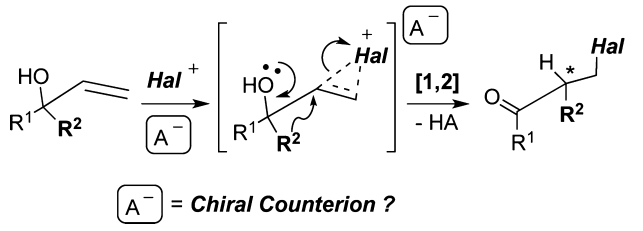
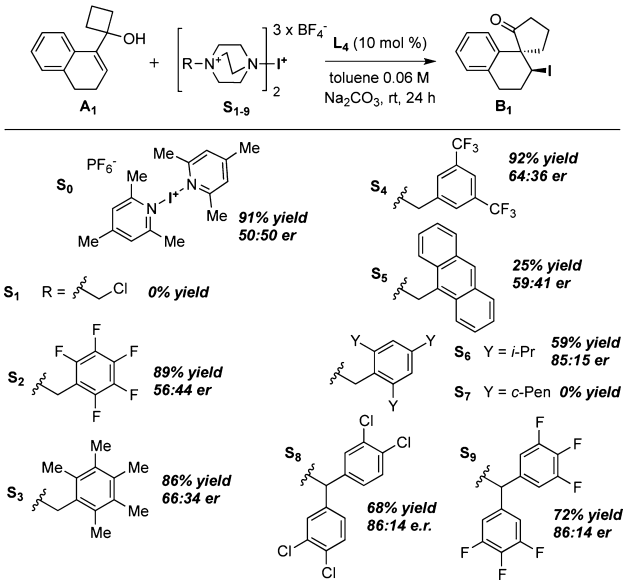


Figure 1. Concept behind enantioselective halonium ion-initiated Wagner–Meerwein transposition of allylic alcohols. Hal = F, Cl, Br, or I.

We began our studies with the reaction of allylic cyclobutanol $\mathbf{A_1}$ with $(collidine)_2I^+PF_6^-$ ($\mathbf{S_0}$) in methylene chloride at room temperature. To our great delight, the iodination/semipinacol reaction sequence took place smoothly and afforded the expected β-iodo spiroketone $\mathbf{B_1}$ as a single diastereomer and in 91% isolated yield (Scheme 1). Seeking a suitable asymmetric PTC system, we repeated the above reaction in a less polar solvent (toluene) in the presence of a base and catalytic amounts of the lipophilic chiral phosphoric acid $\mathbf{L_4}$ (TRIP).[15] Disappointingly, even though the reaction did proceed to completion, the recovered β-iodo spiroketone was racemic.

Scheme 1. Optimization of the Iodinating Reagent $\mathbf{S_{1-9}}$



Next, given the remarkable success of Selectfluor in anionic phase-transfer catalysis, we turned our attention to DABCO-derived triply charged cations ($\mathbf{S_{1-9}}$) as potential iodinating reagents (Scheme 1). These salts were readily synthesized using experimental procedures adapted from the literature.[7b] Dissapointingly, when employing $\mathbf{S_1}$, the "exact" iodo analog of Selectfluor, no reaction was observed under our previously established PTC conditions. This observation could be tentatively explained by the unfavored predissociation equilibrium of $\mathbf{S_1}$, generating insufficient amounts of the monoligated iodine(I) intermediate required for reactivity with alkenes.[13] Switching to the bulkier and more lipophilic salts $\mathbf{S_2}$ and $\mathbf{S_3}$ turned out to be beneficial for reactivity. When combined with catalytic $\mathbf{L_4}$ in toluene, both of these iodinating reagents afforded full conversion of $\mathbf{A_1}$ to $\mathbf{B_2}$, albeit with only insignificant levels of asymmetric induction (*ca.* 60:40 e.r.).

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We speculated that one possible rationalization for the low enantiomeric ratios observed with our PTC system gravitated around the olefin-to-olefin halogen exchange problem, known to occur between the transient iodonium cations and leading to product racemization.[14]

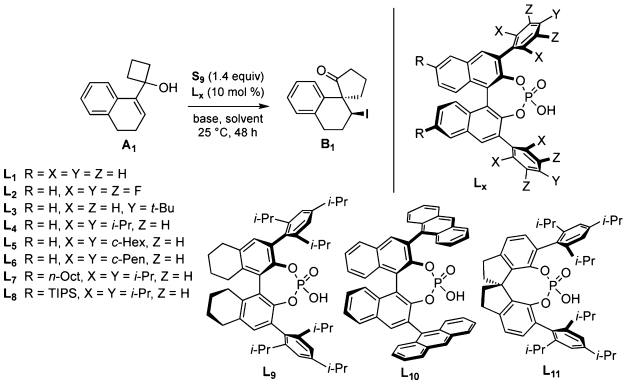
In an attempt to solve for this problem, we were intrigued by the possibility of further exploring the steric and electronic parameters of the nitrogen substituent (R) of the iodinating reagent (Scheme 1). Following this logic, further fluorination of the benzene ring of the R substituent afforded a more active reagent (**S4**), but the enantiomer ratio remained unacceptably low (64:36 e.r.). Replacing the benzene ring with the bulkier 9-anthracenyl substituent (**S5**) led to a concomitant drop in yield and in stereoselectivity. Gratifyingly, switching to the more sterically demanding 2,4,6-tris(isopropyl)phenyl substituent (**S6**) improved the enantiomeric ratio markedly (85:15 e.r.). A similar effect was obtained when employing the branched benzhydryl-based substituents (**S8** and **S9**, both 86:14 e.r.). Of note, increasing the size of the R substituent further by using the 2,4,6-tris(cyclopentyl)phenyl group (**S7**) instead of the 2,4,6-tris(isopropyl)phenyl one completely inhibited the reactivity. Encouraged by these preliminary results, we selected the iodinating reagent **S9** for further optimization studies.

A quick overview of synthetically accessible enantiopure phosphoric acids $\mathbf{L_{1-11}}$, using toluene as the solvent and Na_2CO_3 as the base, revealed **L9** as being optimal (Table 1, entry 9). Changing the base from Na_2CO_3 to Na_3PO_4 improved the enantiomeric ratio from 87:13 to 89:11, accordingly (entry 12). Fluorinated aromatic solvents such as PhF or $PhCF_3$ led to quasi racemic product mixtures (entries 13, 14). Including *n*-hexane into a binary solvent mixture with toluene, which proved to be beneficial for the related fluorination/semipinacol transposition,[12] did not increase the enantiomeric excess in the present iodination/semipinacol reaction sequence (entry 18). The switch to the less polar *para*-xylene solvent also did not increase the enantiomeric excess (entry 15). Gratifyingly, when carrying out the reaction in ethylbenzene as the solvent, an important increase of the selectivity was observed (91:9 e.r.). Further adjustments, including dilution of the reaction medium coupled with extension of the reaction time, afforded the optimal conditions for the title transformation (entry 20).

With the optimal reaction conditions being established, the substrate scope of our newly developed iodination-initiated Wagner–Meerwein rearrangement was investigated. To this end, strained allylic alcohols $\mathbf{A_{1-25}}$ were reacted with iodinating reagent **S9** and catalytic amounts of enantiopure phosphoric acid **L9** under biphasic Na_3PO_4/ethylbenzene conditions. The results are summarized in Scheme 2.

Both, three- ($n = 0$, products $\mathbf{B_{13-21}}$) and four-membered ($n = 1$, products $\mathbf{B_{1-12}}$) allylic alcohols were amenable to the enantioselective iodination/ring-expansion reaction sequence, which occurred equally well with scaffolds based on tetralone (X = CH_2, e.g. $\mathbf{B_1}$), chromanone (X = O, e.g. $\mathbf{B_8}$), and benzosuberone (X = CH_2CH_2, $\mathbf{B_{25}}$) ring systems. A distinct feature of the iodination reaction is its high tolerance toward substitution at positions C5 (e.g., $\mathbf{B_4}$), C6 (e.g., $\mathbf{B_{22}}$), and C7 (e.g., $\mathbf{B_{24}}$) of the phenyl ring. A much narrower substitution tolerance was observed for the fluorination reaction. The title enantioselective transformation was also less sensitive to substituent electronic effects when compared to the previously reported fluorination analog.

Table 1. Optimization of the Reaction Conditions[a,f]



entry	$\mathbf{L_x}$	base	solvent	yield[b] [%]	er[c]
1	$\mathbf{L_1}$	Na_2CO_3	PhMe	64	59:41
2	$\mathbf{L_2}$	Na_2CO_3	PhMe	8	n.d.
3	$\mathbf{L_3}$	Na_2CO_3	PhMe	78	54:46
4	$\mathbf{L_4}$	Na_2CO_3	PhMe	68	86:14
5	$\mathbf{L_5}$	Na_2CO_3	PhMe	0	n.d.
6	$\mathbf{L_6}$	Na_2CO_3	PhMe	22	87:13
7	$\mathbf{L_7}$	Na_2CO_3	PhMe	66	82:18
8	$\mathbf{L_8}$	Na_2CO_3	PhMe	67	79:21
9	$\mathbf{L_9}$	Na_2CO_3	PhMe	73	87:13
10	$\mathbf{L_{10}}$	Na_2CO_3	PhMe	52	66:34
11	$\mathbf{L_{11}}$	Na_2CO_3	PhMe	60	37:63[d]
12	$\mathbf{L_9}$	Na_3PO_4	PhMe	76	89:11
13	$\mathbf{L_9}$	Na_3PO_4	PhF	86	53:47
14	$\mathbf{L_9}$	Na_3PO_4	$PhCF_3$	88	52:48
15	$\mathbf{L_9}$	Na_3PO_4	*p*-Xyl	74	88:12
16	$\mathbf{L_9}$	Na_3PO_4	PhH	79	84:16
17	$\mathbf{L_9}$	Na_3PO_4	$(i\text{-Pr})_2O$	82	85:15
18	$\mathbf{L_9}$	Na_3PO_4	PhMe/*n*-Hex 1:1	70	87:13
19	$\mathbf{L_9}$	Na_3PO_4	PhEt	85	91:9
20[e]	$\mathbf{L_9}$	Na_3PO_4	PhEt	87	93:7

[a] Reaction conditions: see Supporting Information. [b] Isolated yield after flash chromatography. [c] Determined by chiral HPLC. [d] The opposite enantiomer was obtained. [e] Molar concentration decreased to 0.05 M; reaction time increased to 72 h; **S9** reduced to 1.3 equiv. [f] A single diastereoisomer was obtained in each case. *p*-Xyl = *para*-xylene. *n*-Hex = *n*-hexane. n.d. = not determined.

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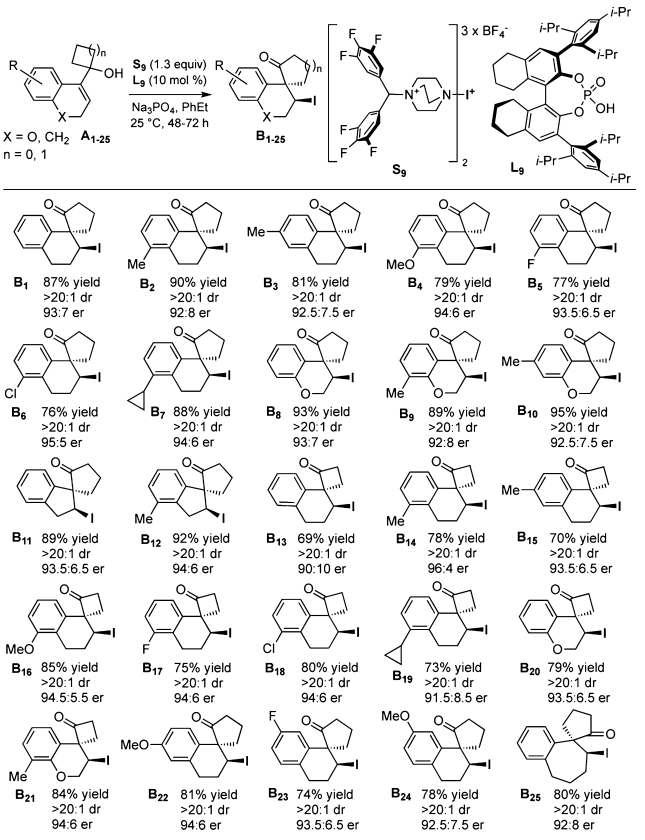
(16) The stereochemistry of compound $\mathbf{B_8}$ was confirmed by X-ray diffraction analysis. CCDC 965243 contains all of the crystallographic data for this paper. These data are available free of charge from The Cambridge Crystallographic Data Centre under www.ccdc.cam.ac.uk/data_request/cif.

Scheme 2. Substrate Scope of the Iodination/Semipinacol Reaction Sequence



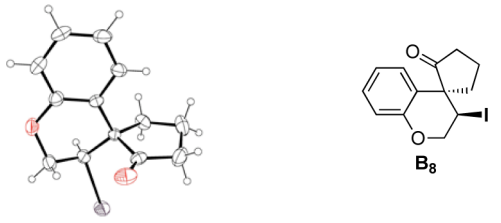
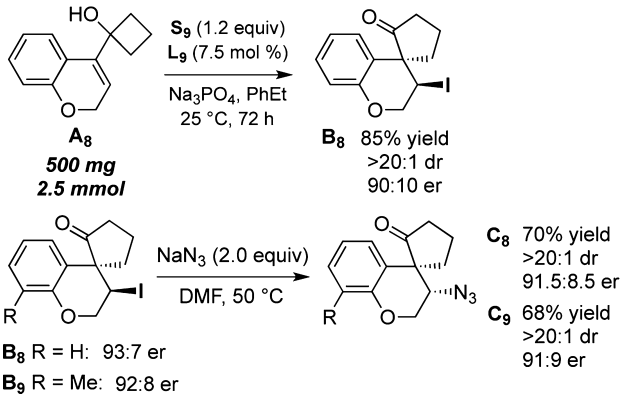


Figure 2. X-ray crystal structure of $\mathbf{B_8}$ (ellipsoids set at 50%).[16]

Single crystals of $\mathbf{B_8}$ were grown for X-ray diffraction analysis (Figure 2).[16] It is fascinating to note that, for an identically configured enantiopure phosphoric acid, the sense of absolute induction is opposite to that observed for the related fluorination-initiated Wagner–Meerwein rearrangement.[12] The relative configuration was consistent with selective migration of the C–C bond that is *anti* to the iodonium bridge.

Scheme 3. Stereospecific Derivatization of the Products



Very importantly, the hereby disclosed transformation was readily amenable to scale-up. Thus, allylic alcohol $\mathbf{A_8}$ was converted into the corresponding spiro β-iodoketone $\mathbf{B_8}$ in excellent yield and without a drop in the enantioselectivity (Scheme 3). Furthermore, two product β-iodoketones ($\mathbf{B_8}$ and $\mathbf{B_9}$) were subjected to an S_N2 reaction with sodium azide. Under optimized experimental conditions, the reaction took place stereospecifically and products $\mathbf{C_{8-9}}$ were recovered in respectable yields.

In conclusion, we have shown that an enantioselective iodination-initiated Wagner–Meerwein transposition of strained allylic alcohols is feasible under phase-transfer conditions, when employing an appropriate achiral-reagent/chiral-counterion catalytic system. The observed stereoselectivities reported to date are the best for this type of reaction. Kinetic and computational studies, aimed at shining light on the stereodivergency between the iodination and the fluorination reactions, are currently underway in our laboratory.

Supporting Information Available. Detailed experimental procedures, spectroscopic characterization of newly synthesized compounds, and chiral HPLC and SFC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.