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Enantioselective halogenative semi-pinacol rearrangement: a stereodivergent reaction on a racemic mixture†

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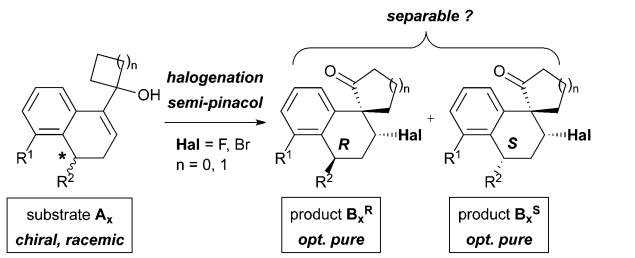
An efficient, quantitative deracemization strategy for optically inactive allylic cycloalkanols has been achieved using the biphasic halogenative semi-pinacol reaction protocol. The resultant β-halo spiroketones, containing three contiguous stereogenic centers, were easily recovered with high diastereomeric and enantiomeric purities following conventional silica gel chromatography. The optically active products could be further manipulated chemically, affording synthetically interesting scaffolds with complete preservation of stereoisomeric integrity.

Kinetic resolution (KR) describes a means of differentiating two enantiomeric substrates in a racemic mixture. As opposed to chiral resolution, which relies on different physical properties of diastereomeric products, kinetic resolution relies upon differences in reaction rates between the two enantiomers.[1] Although numerous methods that are highly efficient in terms of enantiomer discrimination have been reported in the recent years,[2] the obligation that only half of the starting material participates in the reaction compromises the productivity of the process. Furthermore, due to the fact that the two enantiomeric species react simultaneously and at different rates, the relative concentration of residual substrate enantiomers changes as the reaction proceeds. As a consequence, the enantiomeric excesses of the substrate and the product become a function of the conversion.[3] Driven by the demand of highly productive chemical processes, quantitative transformations of racemates into stereoisomerically pure products are of high value to the synthetic community.[7]

Our group has been long interested in the development of catalytic, enantioselective protocols for halogenative semi-pinacol rearrangements of strained allylic cycloalkanols.[6] More specifically, we have recently found out that the chiral phosphate anion-mediated phase-transfer procedure reprted by Toste *et al.*[8] constituted a remarkably general solution to the above problem.[4] As a subsequent challenge, we were interested in studying the influence of a pre-existing stereogenic center on the stereochemical outcome of the asymmetric halogenation/semi-pinacol reaction. In our opinion, if the level of stereoinduction by the chiral, enantiopure phosphate anion would be strong enough then the initial, optically inactive material (*rac*-$\mathbf{A}_x$) could be quantitatively deracemized and transformed into a mixture of diastereomeric, optically active β-halo spiroketones ($\mathbf{B}_x^{\mathbf{R}}$ and $\mathbf{B}_x^{\mathbf{S}}$) (Scheme 1).

Indeed, such a process would follow a stereochemical scenario where each enantiomer of the starting racemic mixture is transformed using an enantiopure catalyst into two products that do not share an enantiomorphic relationship. Moreover, if it happens that the two products would be formed in high enantiomeric excesses and would be easily separable, then the latter reaction would constitute a rare example of a stereodivergent process.[5]

To our great delight, upon subjecting the chiral, racemic allylic cyclobutanol *rac*-$\mathbf{A_1}$ to the biphasic fluorinative reaction conditions (Selectfluor, Na_3PO_4, chiral phosphoric acid $\mathbf{L_1}$,[9] and toluene) at room temperature, full consumption of the starting material was observed after two days of stirring (Table 1, entry 1). Thin-layer chromatography of the crude reaction mixture indicated the presence of two new, non-enantiomeric products with a ΔR_f of *ca.* 0.4. Facile separation of the two products by



Scheme 1 Proposed asymmetric halogenation/semi-pinacol reaction of chiral, racemic cycloalkanols *rac*-$\mathbf{A}_x$.

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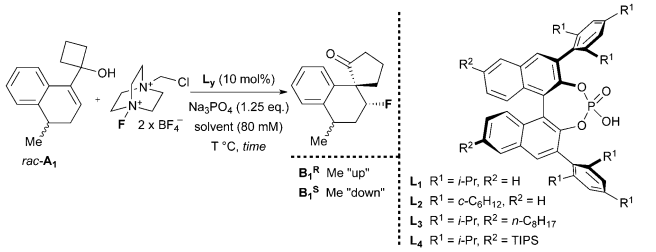
Table 1 Optimization of the conditions for the stereodivergent fluorination/semi-pinacol reaction[a]



Entry	L_x	Solvent	T (°C)	t (h)	Ratio[b] $A_1/B_1^R/B_1^S$	e.r.[c] B_1^R/B_1^S
1	L_1	Toluene	25	48	0 : 1 : 1	93 : 7/93 : 7
2	L_2	Toluene	25	48	0 : 1 : 1	88 : 12/82 : 18
3	L_1	PhF–Hex	25	48	0 : 1 : 1	94 : 6/92 : 8
4	L_1	PhF–Hex	−12	48	1 : 5.3 : 4.7	95 : 5/94 : 6[d]
5	L_3	PhF–Hex	−12	96	0 : 1 : 1	95.5 : 4.5/95 : 5
6	L_4	PhF–Hex	−12	96	0 : 1 : 1	96 : 4/96 : 4
7[e]	L_4	PhF–Hex	−12	96	0 : 1 : 1	96 : 4/96 : 4

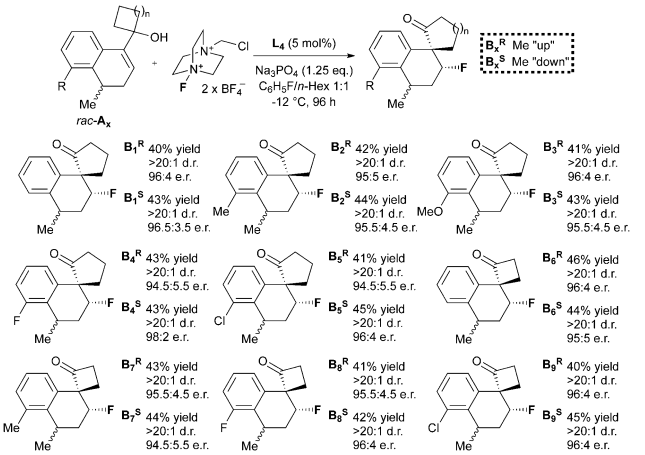
[a] Reaction conditions: see ESI. [b] Determined by ^{1}H NMR analysis of unpurified reaction mixtures. [c] Determined by chiral HPLC analysis. [d] The enantiomeric excess of unreacted A_1 was 7%. [e] 5 mol% catalyst loading was used.

conventional silica gel chromatography, followed by ^{1}H/^{13}C/^{19}F NMR analysis of the resultant pure fractions indicated that the two products were in fact diastereomers (referred to as B_1^R and B_1^S, depending on the absolute configuration of the deracemized benzylic stereogenic center). The exceptionally large R_f difference between the two diastereomers allowed the recovery of very pure compounds, with isolated yields close to the theoretical maximum of 50% for each. Most importantly, the enantiomer ratios of product β-fluoro spiroketones B_1^R and B_1^S, containing three contiguous stereogenic centers, were high (93 : 7 *e.r.* for both). The level of asymmetric induction could be improved by further optimizing the reaction conditions (Table 1).

The stereodivergent reaction displayed higher levels of asymmetric induction when carried out in the fluorobenzene–*n*-hexane mixture instead of toluene (compare entries 1 and 3). Lowering the temperature led to a slower albeit more enantioselective reaction, which in turn required longer reaction times and the use of the more lipophilic phosphoric acid catalysts (L_3 and L_4). It is interesting to note that no kinetic resolution occurred during the present fluorination/semi-pinacol reaction. As evidenced from entry 4, when stopped at incomplete conversion, the recovered unreacted allylic alcohol A_1 was quasi-racemic (7% ee). This indicates that the two enantiomers of the starting material reacted with the enantiopure catalyst at similar rates.

Having established the appropriate experimental conditions for the stereodivergent fluorination/semi-pinacol reaction, the substrate scope of this new methodology was investigated next (Scheme 2).

The above-described fluorinative deracemization strategy worked equally well with substituted chiral, racemic cyclobutanols (A_1–A_5) and cyclopropanols (A_6–A_9), both based on the C1-methylated dihydronaphthalene scaffold. In each case, both diastereomers of the product β-fluoro spiroketones (B_x^R and B_x^S) could be isolated in high yields due to very large ΔR_f separations. The enantiomer



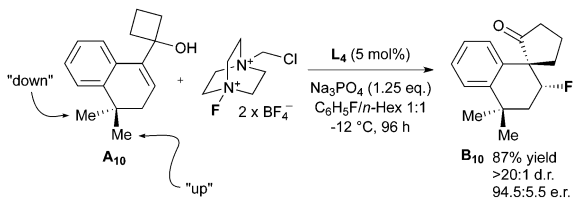
Scheme 2 Substrate scope of the fluorination/semi-pinacol reaction, performed on racemic allylic cycloalkanols *rac*-A_x.

ratios of both diastereomers were invariably high (*ca.* 95 : 5 *e.r.* in most cases), thus avoiding complications inherent to matched/mismatched combinations.

Single crystals of chiral, enantiopure β-fluoro spiroketones B_2^R, B_3^S and B_4^S were grown for X-ray diffraction analysis.[10,11] It is fascinating to note that, as predicted from solution-phase ^{1}H/^{13}C/^{19}F NMR spectral analyses,[11] both enantiomers of chiral, racemic allylic alcohols underwent the semi-pinacol rearrangement through *Re*-face fluorination. This result is consistent with reactivity trends of the "normal" prochiral allylic alcohols.[4a] Presumably, the pre-existing stereogenic center in substrates *rac*-A_x has little-to-zero influence on the reaction stereochemistry, which is in turn entirely dominated by the absolute configuration of the chiral, enantiopure phosphate anion.

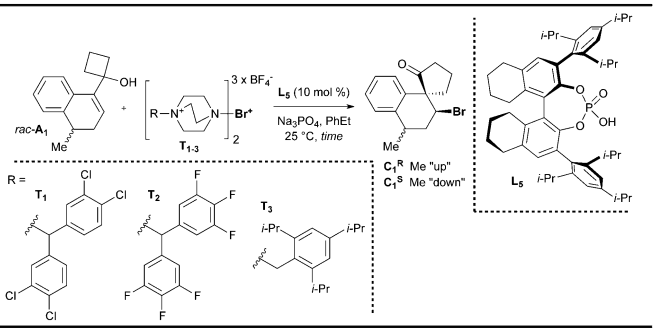
The irrelevance of the relative orientation of the benzylic methyl group for the sense of absolute induction was demonstrated by subjecting the *gem*-dimethyl-substituted allylic alcohol A_{10} to the fluorination/semi-pinacol sequence (Scheme 3). The expected β-fluoro spiroketone B_{10} was isolated with a high enantiomeric excess value (94.5 : 5.5 *e.r.*), providing evidence that both the "up" and "down" orientations of the benzylic C1-methyl group were readily accommodated into the chiral pocket of the catalyst, leading to similar reaction rates and high levels of asymmetric induction for both orientations.

Subsequently, the stereodivergent process was extended to the bromination-initiated semi-pinacol rearrangement (Table 2). To this end the chiral, racemic cyclobutanol *rac*-A_1 was reacted with DABCO-derived triply charged cations T_1–T_3 and chiral phosphoric



Scheme 3 Probing the influence of the relative orientation of the benzylic methyl group on the level of asymmetric induction.

Table 2 Optimization of the conditions for the stereodivergent bromination/semi-pinacol reaction[a]



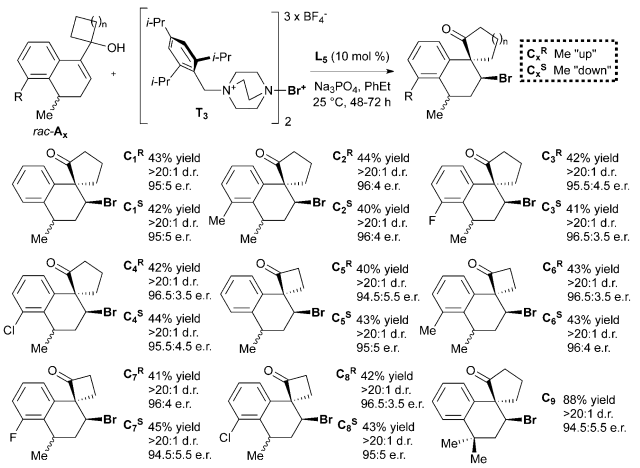
Entry	$\mathbf{T}_x$	Solvent	t (h)	Ratio[b] $\mathbf{A_1}/\mathbf{C_1}^{\mathbf{R}}/\mathbf{C_1}^{\mathbf{S}}$	e.r.[c] $\mathbf{C_1}^{\mathbf{R}}/\mathbf{C_1}^{\mathbf{S}}$
1	$\mathbf{T_1}$	PhEt	24	1 : 1.5 : 1.7	93 : 7/93 : 7
2	$\mathbf{T_2}$	PhEt	24	1 : 1.9 : 2.3	92.5 : 7.5/93.5 : 6.5
3	$\mathbf{T_3}$	PhEt	24	1 : 4.6 : 4.9	95 : 5/95:5[d]
4	$\mathbf{T_3}$	PhEt	72	0 : 1 : 1	95 : 5/95 : 5
5[e]	$\mathbf{T_3}$	PhEt	72	1 : 2.2 : 3.9	89 : 11/93 : 7

[a] Reaction conditions: see ESI. [b] Determined by ^{1}H NMR analysis of unpurified reaction mixtures. [c] Determined by chiral HPLC analysis. [d] The enantiomeric excess of unreacted $\mathbf{A_1}$ was 5%. [e] 5 mol% catalyst loading was used.

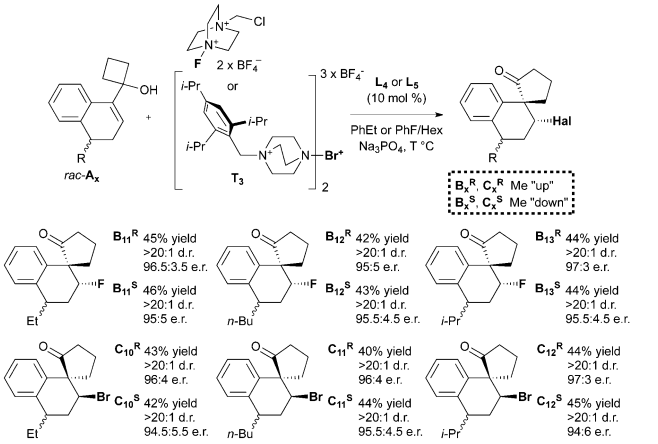
acid (R_a)-H_8-TRIP ($\mathbf{L_5}$), under reaction conditions similar to those reported recently for the iodination/semi-pinacol reaction.[4b]

As can be seen from Table 2, upon employing the brominating reagent $\mathbf{T_3}$ in ethylbenzene at room temperature (entry 4), the bromination/semi-pinacol reaction provided a successful platform for performing the stereodivergent reaction. As already observed for the fluorination case, the moderately large ΔR_f separations (*ca.* 0.2–0.3) between the two diastereomeric products ($\mathbf{C_1}^{\mathbf{R}}$ and $\mathbf{C_1}^{\mathbf{S}}$) allowed the recovery of very pure materials. Furthermore, the products were formed with very high levels of asymmetric induction (up to 97 : 3 *e.r.*), and with isolated yields close to the theoretical maximum of 50%. Once again, no kinetic resolution was observed during the present bromination/semi-pinacol rearrangement sequence (entry 3).

The optimal conditions being established, the substrate scope of the stereodivergent, brominative semi-pinacol reaction was probed next (Scheme 4).



Scheme 4 Substrate scope of the bromination/semi-pinacol reaction, performed on racemic allylic cycloalkanols *rac*-$\mathbf{A_x}$.



Scheme 5 Investigation of the influence of the size of the benzylic substituent on the enantioselectivity of the stereodivergent halogenation/semi-pinacol reaction.

Single crystals of the chiral, enantiopure β-bromo spiroketone $\mathbf{C_2}^{\mathbf{S}}$ were grown for X-ray diffraction analysis.[10,11] This allowed the assignment of the relative and absolute configurations of products.

It is interesting to note that electrophilic bromination takes place through the *Si*-face of the starting allylic alcohol *rac*-$\mathbf{A_2}$, as opposed to the *Re*-face fluorination discussed above. This switch in the sense of absolute induction when moving from fluorine to the heavier halogens, while keeping the absolute configuration of the phosphate anion intact, is consistent with our earlier observations made by studying the iodination of "normal" prochiral allylic alcohols.[4b]

The importance of the size of the benzylic substituent in the substrate allylic alcohols was addressed next. To this end, a set of dihydronaphthalene-based cyclobutanols containing either an ethyl ($\mathbf{A_{10}}$), a *n*-butyl ($\mathbf{A_{11}}$), or an isopropyl ($\mathbf{A_{12}}$) substituent at the benzylic position were synthesized and subjected to the stereodivergent halogenative reaction, under our previously described optimized conditions (Scheme 5).

As can be seen from Scheme 5 above, the steric size of the benzylic substituent had only an insignificant effect on the yield and enantioselectivity of the stereodivergent halogenation/semi-pinacol reaction. A small increase in the level of asymmetric induction for the more sterically congested congeners was nevertheless noted. Thus, upon comparing the ethyl-($\mathbf{B_{11}}$) and isopropyl-substituted ($\mathbf{B_{13}}$) β-fluoro spiroketones, a slightly higher enantiomer ratio (about 2%) was observed for the latter. A similar trend was also noted for the brominative reaction as well (compare β-bromo spiroketones $\mathbf{C_{10}}$ and $\mathbf{C_{12}}$).

Furthermore, the synthetic utility of β-halo spiroketones was proven by carrying out a set of derivatization reactions. Synthetic manipulation of products involved a stereospecific Baeyer–Villiger oxidation of spiro-cyclobutanone $\mathbf{B_8}^{\mathbf{R}}$, as well as diastereoselective reduction of spiro-cyclopentanones $\mathbf{B_2}^{\mathbf{R}}$, $\mathbf{B_5}^{\mathbf{R}}$ and $\mathbf{C_4}^{\mathbf{S}}$. Details of these transformations are given in the ESI.†[11]

In the context of the halogenation/semi-pinacol rearrangement sequence, the interaction between a chiral, enantiopure

phosphate anion and a chiral, racemic allylic cycloalkanol displayed two salient features that allowed its use in a successful stereodivergent reaction. First, both enantiomers of the starting material reacted at similar rates. Second, the relative orientation of the benzylic substituent in the substrate had little-to-zero influence on the level of asymmetric induction. These "abnormalities", combined with the fortuitously large ΔR_f separations of the diastereomeric products for a broad range of substrate cycloalkanols, led to a very efficient deracemization technique described in this communication. The product β-halo spiroketones were recovered with very high stereochemical purities and could be further manipulated chemically.

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11 See the ESI† section for details.

