

SYNTHESIS OF HIGHLY FUNCTIONALIZED NON-RACEMIC CHIRAL ALKYL HALIDES USING KHARASCH ADDITION

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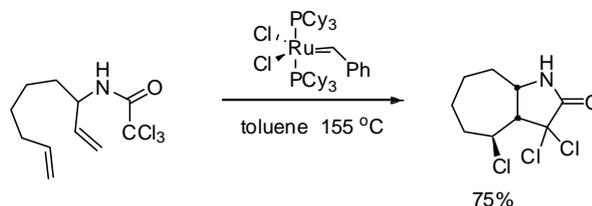
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■ ABSTRACT

We have developed a new catalytic asymmetric method for the synthesis of highly functionalized non-racemic chiral alkyl halides using Kharasch addition in good yields and moderate enantioselectivities.

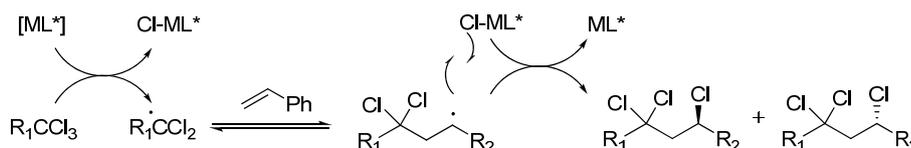
■ INTRODUCTION

The addition of polyhalogenated alkanes to carbon-carbon double bonds (Kharasch reaction) has been of interest during the last years.¹ In our group, this reaction has been applied to the synthesis of highly functionalized halogenated compounds.² Although the Kharasch reaction offers a powerful tool to functionalize olefins with a high level of atom economy, most of the successful examples are limited in terms of stereoselectivity. Therefore, the control of the absolute configuration in this reaction constitutes an important goal in organic synthesis.



■ RESULTS AND DISCUSSION

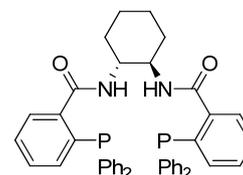
In this communication we present our preliminary results on the asymmetric Kharasch addition of halogenated compounds to olefins. Considering the mechanism of the transition metal-catalyzed Kharasch addition, enantioselective control could be expected by using a chiral metal catalyst that transfers a halogen in the stereo-determining step (*Scheme 1*).



Scheme 1. Asymmetric atom transfer radical cyclization.

In order to perform enantioselective synthesis of highly functionalized, non-racemic, chiral alkyl halides by catalyzed Kharasch reaction we studied the trichloroacetonitrile and styrene reaction. We explored the influence the role of concentration, solvents, time, temperature, additives as well as different metal complexes on the efficiency and selectivity of this reaction.

Ligand effect: Several peptide and phosphine ligands were tested by using as model the addition of trichloroacetonitrile to styrene at room temperature. Despite the conversion is complete in all cases, only using (*R,R*)-Troost ligand (15% mol) in presence of Cu₂S (10% mol) gave non-racemic product.



Effect of copper salt: To determine which Cu(I) salt provided the best selectivity, different salts were evaluated including: CuCl, CuI, CuCN, Cu₂S, etc... At room temperature, no substantial differences in the enantioselectivity were observed, but Cu₂S provided better conversion in the same reaction time.

Loading of trichloroacetonitrile: Possible competition between enantioselective donation of the halogen by the chiral metal-ligand complex and non enantioselective donation by extra trichloroacetonitrile was not observed varying the loading of trichloroacetonitrile.

Effect of stoichiometry: By using a catalyst/ligand Cu₂S/Troost ligand in a ratio 1:5, 1:4, 1:2 and 1:1 no substantial difference in the *e.e.* was observed.

Effect of solvent: THF, CH₂Cl₂ and toluene gave the desired product in good yields but without enantioselectivity. Furthermore, no product was observed using Et₂O, presumably due to the lack of solubility.

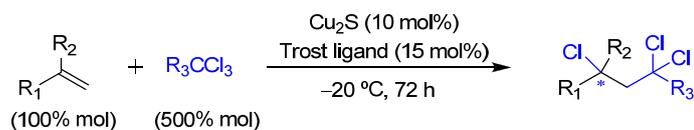
Effect of temperature: We examined the influence of the temperature in the reaction. Higher temperatures (45°C), lead to same yield but poor enantioselectivity as the reaction at room temperature. Experiments at lower temperature provided better results. Different temperatures were screened and the better result was obtained at -20°C during 72 hours, affording the desired product with 51% *e.e.*

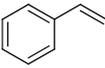
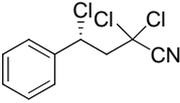
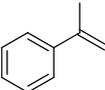
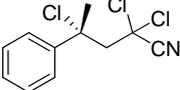
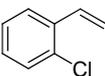
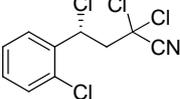
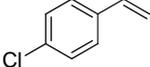
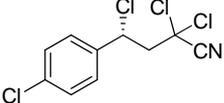
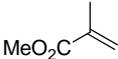
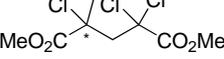
°C	yield (%)	<i>e.e.</i> (%)
-28	42	50
-20	88	51
-10	98	45
0	99	35
r.t.	99	20
45	99	14

Effect of additives: The addition of catalytic amount of water could lead to disproportionation of [Cu(I)] in [Cu(0)] and [Cu(II)] but led to racemic compound.

The use of 10 mol% of a Lewis acid (InCl₃, ZnCl₂, Pd(OAc)₂, etc...) decrease the *e.e.*

Both electron rich and deficient olefins were tested. In addition, the influence of sterics in both trihaloalkane and alkene were evaluated in this asymmetric transformation. The best results were obtained on using (*R,R*)-Troost ligand (15 mol %) and Cu₂S (10 mol %) as copper source at -20 °C for 72 hours. Under these conditions, the reaction of alkenes with trihaloalkanes afforded the corresponding polyhalogenated product in good yields (76-96%). Likewise, modest levels of enantioselectivity (41–51% *e.e.*) have been achieved. Some examples are summarized below.



entry	alkene	trichloroalkyl	Kharasch product	yield (%)	e.e. (%)
1		Cl ₃ CCN		88	50
2		Cl ₃ CCN		81	51
3		Cl ₃ CCN		94	42
4		Cl ₃ CCN		92	41
5		Cl ₃ CCO ₂ Me		73	n.d.

■ GENERAL EXPERIMENTAL PROCEDURE

Considering the mechanism of the reaction and the sensibility of the copper salts to oxidation, every trace of moisture must be avoided during the process. Consequently, all reactions were set up in a glovebox system. Inside the glovebox, at room temperature, copper disulfide (10% mol, 0.1 mmol), Trost ligand (15% mol, 0.015 mmol) and fresh distilled trichloroacetonitrile (15 equiv., 1.5 mmol) were added into a sealed tube and cooled at -46°C. After 5 minutes, fresh distilled α-methylstyrene (1 equiv., 0.1 mmol) was added and the vial was again capped and sealed. The reaction was kept outside the glovebox, stirring at -20°C for 72 hours. The reaction was quenched by opening the vial to the air. Purification by column chromatography on silica gel (Hexanes/Et₂O 10:1) gave the desired compound (81%) as a colourless oil.

The corresponding racemic product used for analysis on HPLC were obtained with good yield following the same experimental procedure and using triphenylphosphine as ligand instead of Trost ligand.

HPLC analysis Chiracel OD(C) column (1% isopropanol/hexanes); 0.5 mL/min, showed a mixture of enantiomers (51% *e.e.*).

¹H NMR (300 MHz, CDCl₃) δ/ppm: 2.2 (s, 3H, CH₃), 3.4 (m, 2H, CH₂), 7.2-7.36 (m, 3H, ArH), 7.45 (d, 1H, ArH).

^{13}C NMR (75 MHz, CDCl_3) δ /ppm: 30.9 (CH_3), 61.1 (CH_2), 65.0 (C), 69.1 (C), 114.6 (CN), 126.5 (CH), 128.5 (CH), 128.7 (CH), 141.7 (C).

HRMS (ESI⁺): calcd. for $\text{C}_{11}\text{H}_{11}\text{Cl}_3\text{N}$: 261.99571 [M^+]; found: 261.99616.

■ REFERENCES

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2. (a) Lee, B. T.; Schrader, T. O.; Martin-Matute, B.; Kauffman, C. R.; Zhang, P.; Snapper, M. L. *Tetrahedron* **2004**, 60, 7391–7396. (b) Seigal, B. A.; Fajardo, C.; Snapper, M. L. *J. Am. Chem. Soc.* **2005**, 127, 16329–16332. (c) Seigal, B. A. PhD Thesis: “The Development of new Ruthenium-Catalyzed Tandem Reaction” Boston College, 2005.

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