Sustainable Asymmetric Organolithium Chemistry: Enantio- and Chemoselective Acylations through Recycling of Solvent, Sparteine, and Weinreb "Amine"

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The well-established Hoppe–Beak chemistry, which involves enantioselective generation of organolithium compounds in the presence of (−)-sparteine, was revisited and applied to unprecedented acylations with Weinreb amides to access highly enantioenriched α-oxyketones and cyclic α-aminoketones. Recycling of the sustainable solvent cyclopentyl methyl ether, sparteine, and the released Weinreb "amine" [HNMe(OMe)] was possible through a simple work-up procedure that enabled full recovery of these precious materials. The methodology features a robust scope and flexibility, thus allowing the enantioselective preparation of scaffolds amenable of further derivatization.

Introduction

Construction of new carbon–carbon bonds with full control of stereochemistry is highly demanded in organic synthesis.[1] The conceptual simplicity of transferring an enantioenriched nucleophile to a given electrophile has emerged over the years as a reliable technique to accomplish this goal.[2] In the beginning of the 1990s, the pioneering studies by Hoppe et al.[3] and Beak et al.[4] culminated in the development of strategies for asymmetric generation of highly nucleophilic organolithium species, which could be delivered to a plethora of electrophiles with excellent stereofidelity (Scheme 1a).[5] The combination of the *Lupinus mutabili* alkaloid (−)-sparteine[6] and *s*BuLi to provide a chiral base for the deprotonation event, and the use of an apolar solvent (e.g., diethyl ether) often ensures the preservation of the stereochemical information contained in the nu-

cleophile.[7] Unfortunately, both factors pose severe limitations on the sustainability of the processes.

The full potential of this versatile methodology is limited by the scarce commercial availability of sparteine in both enantiomeric forms[8] and the inherent issues for its total synthesis methodologies.[9] Additionally, the hazards of diethyl ether (flammability, low boiling point, peroxide formation, etc.)[10] make this tactic hardly attractive from a green chemistry perspective, clearly violating the 3rd, 4th, 5th, and 7th Anastas' Principles.[11] Notwithstanding, the sparteine-mediated methodology is quite flexible and adaptable to conceptually different chemistries to access highly versatile enantioenriched building blocks (Scheme 1a), for example, Aggarwal's homologated boronates,[12] O'Brien's chiral sulfoxides,[13] and Baudoin's arenes,[14] which can be further elaborated, for example, in Aggarwal's assembly-line synthesis.[15]

During a recent study on the synthesis of thioamides from isothiocyanates and organolithium reagents,[16] we noticed that the combination of sparteine and the sustainable solvent cyclopentyl methyl ether (CPME)[17] effectively achieved a high level of stereocontrol (Scheme 1b). Additionally, this solvent promoted fast lithiations of hindered benzoate esters, as observed by Aggarwal during the synthesis of (−)-stemaphylline in the presence of the (+)-sparteine surrogate.[18]

Surprisingly, the Hoppe–Beak approach did not find application to synthesize ketones, and thus its full preparative potential was underestimated.[19] This is quite astounding because enantiomerically enriched α-substituted ketones constitute privileged frameworks across the chemical sciences. Based on our experience of chemoselective acylations of α-substituted carbanions with Weinreb amides,[20] we devised an enantio- and chemoselective methodology to reach a wide scope of α-oxyketones and cyclic α-aminoketones in high yields, without the need for column chromatography (Scheme 1c). Furthermore, a practical method for the sustainable recovery of sol-
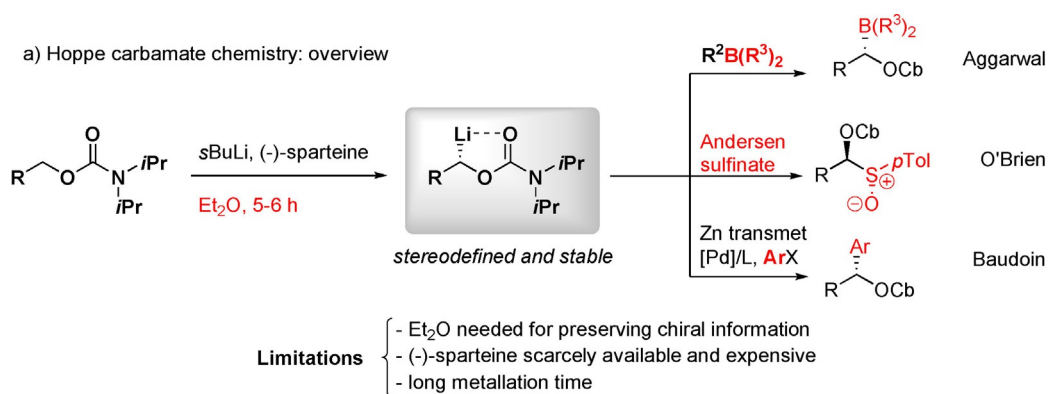
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Scheme 1. General context of the work.

vent, sparteine, and Weinreb amine was devised, and the recovered materials were demonstrated to be equally efficient in subsequent transformations.

Results and Discussion

Hoppe's carbamate **1**[5a] and the challenging Weinreb amide **2**, featuring a potentially exchangeable bromine substituent, were selected as the model substrates (Table 1). The use of
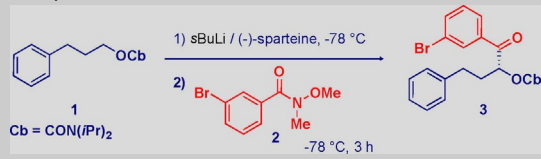
1.3 equiv. *s*BuLi and 1.3 equiv. (−)-sparteine resulted in a satisfactory isolated yield and enantiomeric ratio (e.r. = 97:3) of ketone **3** after a lithiation time of 2 h (entry 1). Increased reagent amounts only slightly improved the yield (entries 2 and 3), suggesting that the reagent loading does not play a crucial role in the process. We were delighted to find that reduced lithiation time increased the efficiency of the reaction, and an excellent 95% yield of **3** was observed after only 30 min (entries 4 and 5). Shorter lithiation times proved insufficient, and a

Table 1. Optimization of the reaction.

Entry	Solvent	1/sBuLi/(−)-sparteine [equiv.]	Lithiation time [min]	Yield of 3[a] [%]	e.r. of 3
1	CPME	1.0/1.3/1.3	120	65	97:3
2	CPME	1.5/1.6/1.6	120	70	97:3
3	CPME	1.9/2.0/2.0	120	72	97:3
4	CPME	1.5/1.6/1.6	60	78	97:3
5	CPME	1.5/1.6/1.6	30	95	97:3
6	CPME	1.5/1.6/1.6	15	45[b]	–
7	CPME	1.0/1.3/1.3	30	81	97:3
8	THF	1.5/1.6/1.6	30	55	60:40
9	toluene	1.5/1.6/1.6	30	30	80:20
10	Et₂O	1.5/1.6/1.6	30	21[b]	–
11[c]	CPME	1.5/1.6/1.6	30	–	–
12[d]	CPME	1.5/1.6/1.6	30	18	94:7
13[e]	CPME	1.5/1.6/1.6	30	91	97:3

[a] Isolated yields. [b] Byproducts were observed. [c] The corresponding ester was employed instead of **2**. [d] The corresponding acid chloride was used instead of **2**. [e] (−)-Sparteine recovered from the reaction in entry 5 was employed.
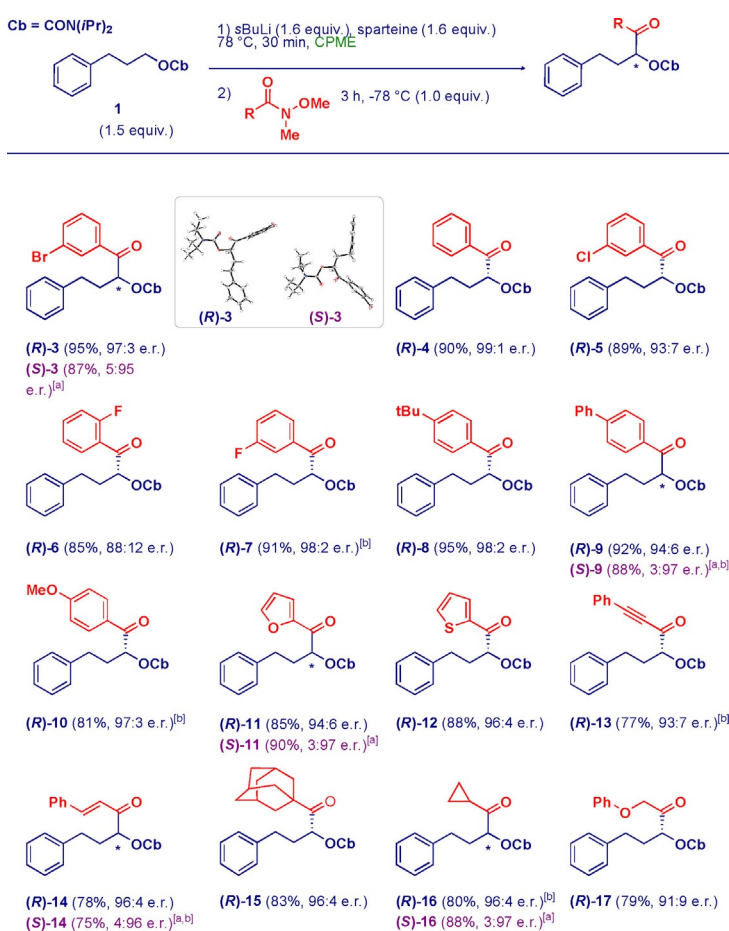
mixture of ketones **3** and different unidentified by-products were formed, presumably because of attack of sBuLi on the Weinreb amide (entry 6). The reaction proved less efficient with 1.3 equiv. of the reagents, even if 30 min lithiation time was used (entry 7).

Solvents were subsequently screened, and THF dramatically induced racemization (Table 1, entry 8), in agreement with previous studies.[5a] This was true also for toluene (entry 9), whereas lithiation in the commonly employed Et₂O was very limited within 30 min (entry 10). Clearly, the chemical stability of the lithiated carbamate is the main factor governing the transformation and its prompt generation in CPME ensures the success of the process. This solvent very efficiently preserves the stereochemical information of the nucleophile during the substitution event. CPME is a promising, apolar solvent,[21] which is highly stable under strongly basic conditions, features a low peroxide-formation tendency, and a narrow explosion range, thus fulfilling the 3rd, 4th, 5th, and 12th Green Chemistry Principles.[11] Furthermore, the use of CPME was essential to avoid chromatographic purifications. Weinreb amides proved to be crucial as acylating agents for the reaction outcome,[22] as demonstrated by the lack of reactivity of the corresponding ester (entry 11) and by the limited yield with the corresponding acid chloride (entry 12).

The sustainability elements of the process make this efficient transformation highly attractive: a) Recovering the precious (−)-sparteine according to the Aggarwal procedure[15] proved easily applicable to the presented methodology, and neither chemical

yield nor e.r. were affected if it was reused in another reaction (Table 1, entry 13). b) Analogously, the *N,O*-dimethylhydroxylamine fragment of the Weinreb amide, which is released at the end of the sequence, can easily be recycled and reused for the preparation of additional Weinreb amides.[23] c) The substantial immiscibility of CPME with water allowed avoidance of classical organic solvents (e.g., EtOAc, Et₂O) during the work-up and, more importantly, the analytically pure ketone **3** was obtained after simple recrystallization from the reaction medium. d) The CPME could be recovered by a simple distillation.

With the optimized conditions in hand, the scope of the reaction was investigated by using a range of Weinreb amides (Scheme 2). High chemoselectivity was uniformly observed, and aromatic (**3–10**), heteroaromatic (**11,12**), conjugated (**13,14**), and aliphatic (**15–17**) ketones were formed in excellent yields and enantiomeric ratios. Substitution across the aromatic moieties of the Weinreb amides was well tolerated, except in the case of the *ortho*-fluoro analogue **6**, which resulted in a somewhat lower e.r. value. Sterically congested amides, as well as α-substituted amides, could also be employed (**15–17**). The protocol manifests genuine 1,2-selectivity with unsaturated Weinreb amides (**13,14**), which in principle could suffer from conjugate addition (see below). Gratifyingly, both enantiomers of a given ketone could be prepared in compara-


Scheme 2. Reaction scope. [a] Reaction with (+)-sparteine. [b] Reaction with recovered sparteine. See the Supporting Information for full details.

ble efficiency and enantiopurity by selecting (−)- or (+)-sparteine. Recovered (average 80%) sparteine was employed in several experiments to demonstrate the efficiency of this process. Furthermore, the protocol allowed us to recover with comparable efficiency CPME and *N,O*-dimethylhydroxylamine, which could be advantageously reused whenever necessary. Unambiguous proof of the absolute stereochemistry of **3** was ascertained through X-ray crystallographic analysis.

Cognizant of the stereochemical integrity of enantioenriched α-oxy-α-methylbenzyllithium reagents,[24] we were pleased to find that such trisubstituted carbanions were suitable for our methodology (Scheme 3). Upon deprotonation of enantiopure α-methyl carbamate **18** with *s*BuLi in CPME, a series of α-quaternary carbonyl compounds could be prepared in excellent yields and enantiomeric ratios starting from the *R* or *S* carbamates (sparteine was not required for deprotonating these chiral starting materials). The trapping with a formyl Weinreb amide provided the corresponding α-oxyaldehyde **19**, and aromatic (**20, 21**), aliphatic (**22**), or propargylic (**23**) analogues yielded the corresponding ketones.

The stereochemical course of the transformation is mainly controlled by the ability of the expelled leaving group to coordinate the lithium cation, and/or by the lowest unoccupied molecular orbital (LUMO) involved.[24] Based on the assumption that NMe(OMe) efficiently coordinates Li, in analogy to a general RO group of an ester, it is possible to affirm that Weinreb amides prefer a suprafacial attack with retention of configuration. The absolute configuration of the ketones has been assigned based on comparison with literature data for compounds **19** and **20**.

The corresponding ketone **23** was formed through a stereoinversion sequence, presumably owing to the energetically low LUMO of propargylic systems. Reactions with α,β-unsaturated Weinreb amides surprisingly resulted in selective 1,4-addition to yield amides **24** and **25** with full diastereo- and enantiocontrol, instead of the commonly observed 1,2-addition.[25] As noticed in the case of product **23**, inversion of configuration occurred at the quaternary lithiated center, whereas the configuration of the tertiary stereocenter created during the reaction was determined by the steric hindrance of the carbamate.

We have recently reported the isolation of tetrahedral intermediates formed upon the addition of racemic functionalized organolithium reagents to Weinreb amides.[26] To our delight, the reaction with an optically active organolithium reagent to form product (*R*)-**4** could be intervened by addition of trimethylsilyl-imidazole (ImTMS). Thus, the enantiomerically enriched tetrahedral intermediate could, for the first time, be isolated as *O*-TMS hemiaminals **27** and **28** (Scheme 4a). However, the high chemical instability of this species did not allow an efficient separa-
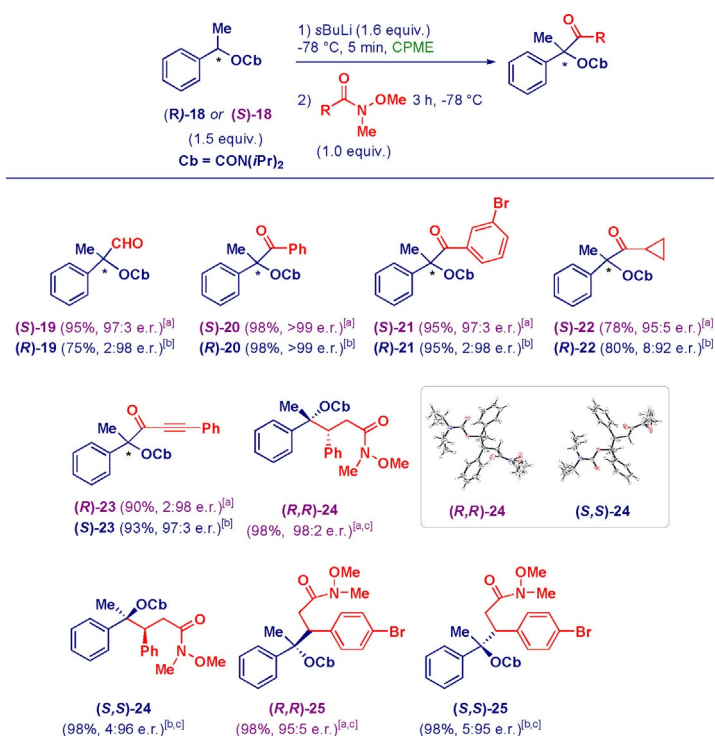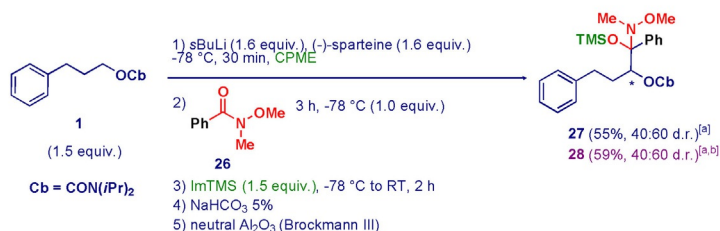

Scheme 3. Reactivity of α-oxy-α-methylbenzyllithiums with Weinreb amides. [a] Reaction performed with (*S*)-**18**. [b] Reaction performed with (*R*)-**18**. [c] Only one diastereoisomer observed.

tion of the diastereomers (40:60 d.r. mixture) by flash chromatography or preparative HPLC.

N-Acylpyrroles[27] form highly stable carbinols upon reactions with carbon nucleophiles according to studies by Evans et al.[28] and Brandänge et al..[29] Pleasingly, the reaction of the lithiated Hoppe's carbamate with *N*-acylpyrrole **29** resulted in the isolable, diastereopure tetrahedral intermediates **30** and **31** with excellent e.r. and d.r. values (Scheme 4b). By performing the reaction in the presence of either enantiomer of sparteine,
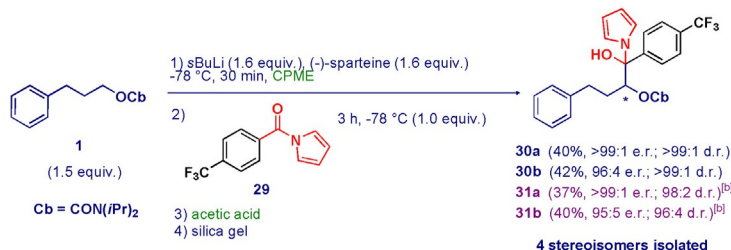
Scheme 4. Isolation of hemiaminal-type optically active tetrahedral intermediates. [a] Diastereomeric ratio determined by ¹H NMR analysis. [b] Reaction with (+)-sparteine.

four stereoisomers were formed and easily separated through chromatography on silica gel. Subsequent HPLC analysis of each of the stereoisomers confirmed the enantiopurity of each single stereoisomer.

To further expand the synthetic potential of the methodology, it was applied to the synthesis of chiral α-pyrrolidynyl ketones, which also constitute biologically active substances.[30] Enantioselective lithiation of N-Boc pyrrolidine[31] (**32**) in CPME followed by treatment with a range of Weinreb amides delivered the targeted scaffolds with excellent enantiocontrol (Scheme 5). The scope includes (hetero)aromatic (**33–35**), unsa-

subjected to reduction with L-selectride. Alcohol **44** was obtained as a single diastereoisomer in excellent yield with very high enantiopurity (Scheme 6b).

The propargylic ketone (R)-**13** was used as a platform for the asymmetric construction of 1,2,3-triazole **45** through a 1,3-dipolar cycloaddition in the presence of diethyl aluminumazide[34] in CPME (Scheme 6c). Moreover, the same ketone underwent an efficient chemoselective homologation with a lithium carbenoid to produce the α-oxyepoxydes **46** (1:1 d.r.) with excellent enantiopurity (Scheme 6d).[35]

Conclusions

We have disclosed a conceptually new, flexible, versatile, and high-yielding acylation of enantiopure organolithium reagents (Hoppe's carbamates and N-Boc pyrrolidine) en route to new α-oxyketones and cyclic α-aminoketones. The combination of Weinreb amides and cyclopentyl methyl ether (CPME) as an environmentally benign reaction medium enables access to the targeted compounds with excellent stereofidelities within short reaction times. Both enantiomers of a given scaffold are accessible by simply selecting the appropriate sparteine enantiomer. Analogously, configurationally stable α-oxy-α-methyl-benzyllithiums, prepared without requirement of sparteine, can be added to Weinreb amides for enantioselective synthesis of α-quaternary ketones.
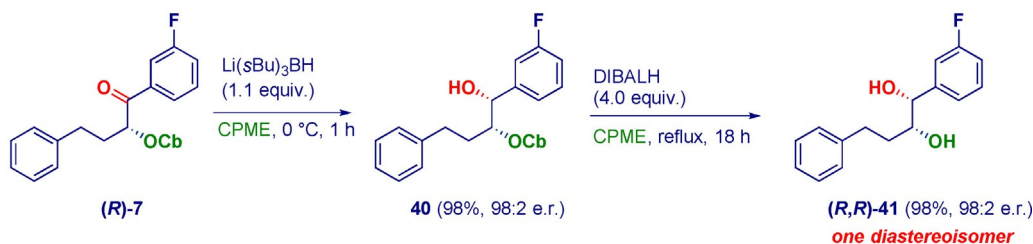
Furthermore, several sustainable features of these new transformations have been developed to meet the drawbacks related to the use of the necessary substrates and reagents. The precious sparteine ligand was efficiently recycled (80% average) in a practical fashion that also enabled recovery of the Weinreb amine and the solvent. The beneficial effect of CPME is further showcased by its excellent ability as a recrystallization medium to obtain analytically pure compounds, thus avoiding purification by column chromatography.

Scheme 5. Enantioselective synthesis of α-pyrrolydinyl ketones. [a] Reaction with (+)-sparteine. [b] Reaction with recovered sparteine. See the Supporting Information for full details.

turated (**36**, **37**), and aliphatic (**38**, **39**) α-aminoketones. Remarkable chemoselectivity was observed in reactions with Weinreb amides presenting additional electrophilic sites, leading to products with cyano (**34**), cinnamoyl (**36**), and propargyl (**37**) substituents. Aliphatic Weinreb amides with an acidic α-proton are also suitable substrates for the transformation, delivering cyclic α-aminoketones **38** and **39**. The latter compound was obtained with perfect diastereoselectivity starting from an optically active Weinreb amide, and the stereochemistry was unambiguously assigned by X-ray analysis. Again, the opposite enantiomers were prepared with equally excellent stereofidelity by use of (+)-sparteine.

The synthetic potential of selected compounds is illustrated in Scheme 6. The reduction of the enantiomerically pure α-oxyketone (R)-**7** with L-selectride efficiently afforded the monoprotected 1,2-diol **40** (Scheme 6a). Subsequent removal of the carbamate moiety under O'Brien's conditions[32] delivered the challenging 1,2-diol (R,R)-**41** as a single diastereoisomer with excellent enantiopurity. The relative configuration was determined to be *syn* by diagnostic nuclear overhauser enhancement and exchange spectroscopy (NOESY) experiments on the corresponding acetonide.[33] Analogously, the reaction of Hoppe's carbamate with the chiral Weinreb amide **42** yielded a diastereopure α,α'-disubstituted ketone **43**, which was directly
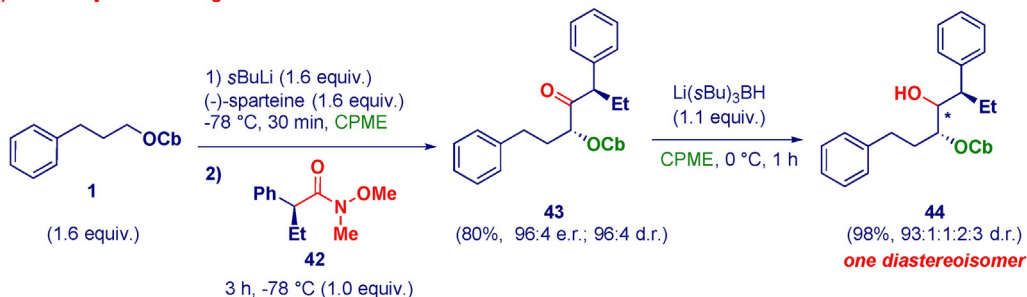
Experimental Section

General procedure for synthesis of compound 3

A solution of 3-phenylpropyl diisopropylcarbamate (**1**, 0.077 g, 0.294 mmol, 1.5 equiv.) and (−)-sparteine (0.073 g, 0.313 mmol, 1.6 equiv.) under argon in anhydrous CPME (2.0 mL) was cooled to −78 °C. A solution of sBuLi (1.4 M in cyclohexane/hexane 92:8, 0.022 mL, 0.313 mmol, 1.6 equiv.) was added dropwise and the reaction mixture was stirred for 30 min, then 3-bromo-N-methoxy-N-methylbenzamide (**2**, 0.048 g, 0.196 mmol, 1.0 equiv.) in CPME was added slowly. The reaction mixture was quenched after 3 h with HCl (1 N solution, 5 mL) and stirred 1–2 min before the two phases were separated. The pure compound was recrystallized from the same solvent. Compound **3** was obtained in 95% yield (0.087 g) as a white solid (m.p.: 75–82 °C). CPME (b.p.: 106 °C) was redistilled and could be reused. The acidic aqueous layer was basified with NaOH (20% aq.) and extracted with CPME (5 mL). The organic layer was distilled to recover N,O-dimethylhydroxylamine (b.p.: 43 °C), CPME (b.p.: 106 °C), and sparteine (137–138 °C, 1.33 mbar). Recovery data for CPME, sparteine, and N,O-dimethylhydroxylamine are presented in Tables S1, S2, and S3 in the Supporting Information.
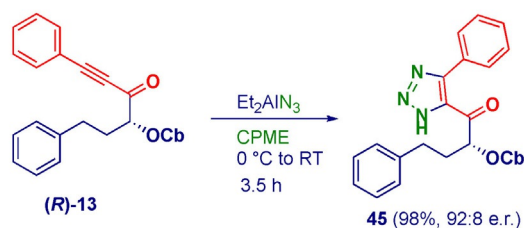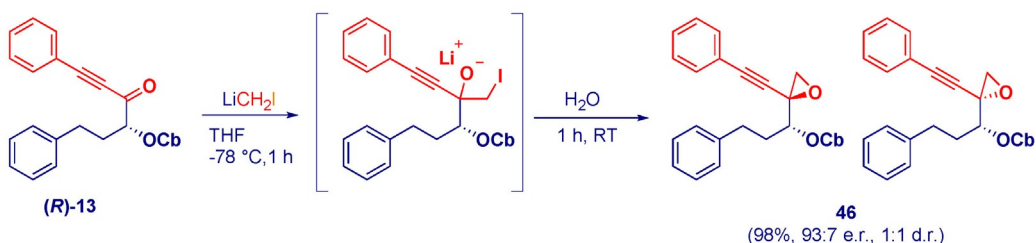
Scheme 6. Synthetic manipulations of enantiopure α-oxyketones.

Crystallography

Acknowledgements

Conflict of interest

The authors declare no conflict of interest.

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