ChemPubSoc Europe

DOI: 10.1002/ejoc.201600365

EurJOC European Journal of Organic Chemistry

Communication

Lithiation Chemistry

Toward Customized Tetrahydropyran Derivatives through Regioselective α-Lithiation and Functionalization of 2-Phenyltetrahydropyran

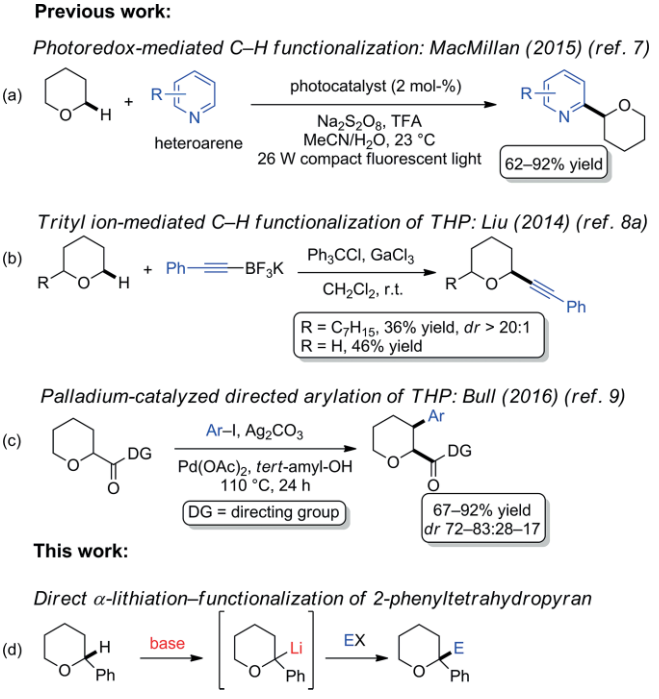
Luciana Cicco,[a] Valeria Addante,[a] Andrea Temperini*[b] Carsten Adam Donau,[c] Konstantin Karaghiosoff,[c] Filippo Maria Perna*[a] and Vito Capriati*[a]

Dedicated to Professor Achille Umani-Ronchi on the occasion of his 80th birthday

Abstract: In this contribution, the first direct and efficient functionalization of the preformed 2-phenyltetrahydropyran (2-PhTHP) nucleus by electrophilic interception of the corresponding α-lithiated derivative by employing *s*BuLi as the base and THF as the solvent at –78 °C was explored. The presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) proved to be critical to governing reaction feasibility both in polar and apolar solvents and for improving the yield of the reaction. Both carbon- and heteroatom-based halides were found to be competent electrophiles for this transformation, as well as aliphatic and aromatic aldehydes and ketones, isocyanates, and carboxylic acid derivatives. The combination of hexane/TMEDA lowered the rate of racemization of α-lithiated optically active 2-PhTHP, which thereby enabled calculation of its barrier to inversion at –78 °C.

Introduction

Saturated oxygen heterocycles, such as functionalized tetrahydropyran (THP) rings, are common structural motifs that are widely distributed across bioactive natural compounds and are also representative of the skeleton of new synthetic therapeutic agents.[1] Given the wealth of THP-containing products, it is not surprising that several efficient methodologies for the stereoselective construction of variously substituted THPs have been developed throughout the years.[2] Recent examples also include (organo)catalytic methodologies[3,4] and 6-*exo*-*tet* cyclizations of phenylseleno alcohols.[5a] A novel one-pot multistep synthetic procedure for isochromane derivatives, on the basis of the addition of *ortho*-lithiated aryloxiranes to enaminones, was also reported.[6] However, despite advances in synthetic methodologies, direct functionalization processes of pre-existing THP nuclei remain challenging and rare. In this context, significant success was recently achieved by MacMillan and Jin, who developed an efficient photoredox-mediated α-arylation of both cyclic and acyclic ethers with electron-deficient heteroarenes (Scheme 1, a).[7] Liu and co-workers showed that the reactivity of the trityl ion can be successfully tuned to promote chemoselective C–H functionalization of various cyclic ethers



Scheme 1. Direct functionalization of THP derivatives; TFA = trifluoroacetic acid.

[a] *Dipartimento di Farmacia-Scienze del Farmaco, Università di Bari "Aldo Moro", Consorzio C.I.N.M.P.I.S., Via E. Orabona 4, 70125 Bari, Italy*
E-mail: filippo.perna@uniba.it
vito.capriati@uniba.it
http://www.farmacia.uniba.it
[b] *Dipartimento di Scienze Farmaceutiche, Università di Perugia, Via del Liceo 1, 06123 Perugia, Italy*
E-mail: andrea.temperini@unipg.it
[c] *Department Chemie, Ludwig-Maximilians-Universität München, Butenandtstrasse 5–13, Haus F, 81377 München, Germany*
Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under http://dx.doi.org/10.1002/ejoc.201600365.

(Scheme 1, b)[8a] and also disclosed effective, oxidative cross-dehydrogenative coupling protocols for chromenes, benzylic ethers, and benzopyran.[8b–8d] An efficient palladium-catalyzed stereoselective arylation protocol at the unactivated 3-position of THP was recently described by Affron and Bull (Scheme 1, c).[9]

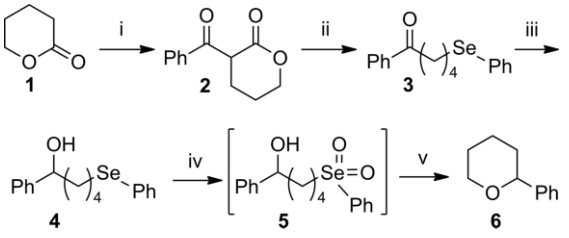
Organolithium compounds (RLi) are known to react with ethers to promote either "protophilic" (i.e., proton abstraction at the α- or β-carbon atom of the ether) or "nucleophilic" (i.e., replacement of an alkoxy group) fission reactions. The rate of these processes is dependent on the nature of the RLi and that of the ether and on the temperature.[10] In addition, α-lithiated ethers are typical Li/OR carbenoids that are able to exhibit carbanionic/carbene-like behavior.[11]

The burgeoning field of oxygen heterocycles has seen significant breakthroughs over the last 10 years, because of the development of new lithiation methodologies for the preparation of more functionalized derivatives.[12] In particular, as for cyclic ethers, both protophilic and nucleophilic fissions have been observed quite frequently with oxiranes, oxetanes, and tetrahydrofurans.[10,13–15] THP is more resistant than THF to both protophilic and nucleophilic fissions: for example, the half-life of *n*BuLi in THF is 1.78 h versus 21.0 h in THP at +20 °C.[14] By treating *s*BuLi with THP at –20 °C, a ring-opening reaction followed by polymerization was assumed to take place.[14,16] Most likely, the first stage of such "protophilic ether cleavage" is α-metalation rather than β-metalation; the latter is instead typical of larger rings (e.g., oxepane) that can easily assume the required conformation for an E2 elimination reaction.[13] This statement is consistent with the recent isolation and characterization of a crystalline α-zinc-substituted THP adduct by Mulvey and co-workers.[17] α-Lithiation of 2-(phenylsulfonyl)tetrahydropyran was reported to be feasible with *n*BuLi at –78 °C in THF, although spontaneous β-elimination of phenylsulfinic acid occurred, which thereby afforded the corresponding α,β-unsaturated adducts as the final products.[18] The reductive lithiation of both α-phenylthioTHF and THP derivatives set up by Cohen and Lin in the 1980s represented the first general method for the preparation of nontransient α-lithio cyclic ethers from carbon radicals (as precursors to the anions) formed in the rate-determining step.[19]

Herein we wish to report the first successful direct α-lithiation of 2-PhTHP as a means to obtain 2,2-disubstituted THP derivatives with a quaternary stereogenic center (Scheme 1, d). An assessment of the configurational stability of the α-lithiated THP intermediate was also undertaken.

Results and Discussion

We began our study by conducting a large series of experiments on 2-PhTHP **6**, which was prepared according to a new attractive route that is complementary to the others already described for arylTHPs[5a] and arylTHFs.[5b] Commercially available δ-valerolactone (**1**) was first α-deprotonated with lithium diisopropylamide (LDA; 2 equiv., THF, –70 °C) and then treated with benzoyl chloride (1 equiv.) to give β-ketolactone **2**, which was used without further purification. The latter, upon treatment with sodium phenyl selenolate (obtained from in situ reduction of diphenyl diselenide by the addition of sodium),[20] underwent clean nucleophilic alkyl–oxygen bond cleavage with concomitant loss of CO_2 to afford straightforwardly δ-phenylseleno ketone **3** in an overall yield of 56 %. The reduction of **3** by using $NaBH_4$ in THF/MeOH furnished the expected δ-phenylseleno alcohol **4** in 90 % yield. Finally, oxidation of **4** with an excess amount of *m*-chloroperoxybenzoic acid (*m*-CPBA) and dipotassium hydrogen phosphate occurred smoothly at room temperature to give the corresponding phenylselenone intermediate **5**, which cyclized in the presence of powdered KOH according to a 6-*exo*-*tet* ring pattern to deliver the desired 2-PhTHP **6** in 80 % yield (Scheme 2).

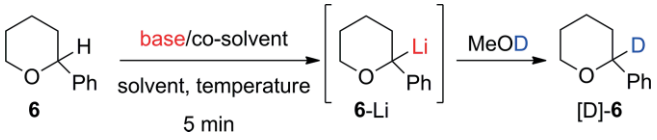


Scheme 2. Reagents and conditions: (i) 1. LDA, THF, –70 °C; 2. PhCOCl; (ii) PhSeNa, DMF, 110 °C; (iii) $NaBH_4$, THF/MeOH; (iv) *m*-CPBA, K_2HPO_4, MeCN, rt., 2 h; (v) KOH, r.t.

Such a compound was then subjected to the action of various organolithium bases, with or without *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), with varying solvents and temperatures to find the best conditions for α-lithiation. The first surprise was that subjecting **6** to the conditions reported to be effective to metalate 2-PhTHF quantitatively and that precluded at the same time its spontaneous cycloreversion (*s*BuLi/TMEDA, toluene, –78 °C),[12f] followed by quenching of the putative **6**-Li with MeOD after 5 min, afforded deuterated [D]-**6** with only 53 % deuterium incorporation (^{1}H NMR spectroscopic analysis) (Table 1, entry 1). This percentage dramatically dropped down to 4 % in the absence of such a ligand (Table 1, entry 2). The replacement of toluene by other apolar solvents such as hexane and cyclopentyl methyl ether (CPME) did not lead to any improvement, and deuterium was incorporated into **6** at –78 °C in up to 42 or in 16 % in the presence or absence of TMEDA, respectively (Table 1, entries 3–6).

The above findings are in line with recent studies reported by Capriati and co-workers on the lithiation of aryloxiranes, which showed that α-deprotonation did take place in hexane with *s*BuLi in the presence of TMEDA only, most likely thanks to the formation of more reactive ternary prelithiation complexes among tetrameric *s*BuLi, epoxides, and TMEDA.[21] Thus, it cannot be ruled out that such complexes may also play a key role in promoting deprotonation of **6**. We were pleased to find that upon switching to a more polar solvent such as THF, lithiation of **6** with *s*BuLi/TMEDA afforded, after MeOD quenching, [D]-**6** with 84 % D at –78 °C, whereas the absence of TMEDA again led to minor deuterium content (46 % D) of [D]-**1** (Table 1, entries 7 and 8). The employment of 2-MeTHF promoted a clean hydrogen–lithium exchange on **6** with *s*BuLi, although this furnished [D]-**6** with 26 or 4 % D in the presence or absence of TMEDA, respectively (Table 1, entries 9 and 10). Remarkably, a

Table 1. Optimization of the regioselective α-lithiation/deuteration of **6**.



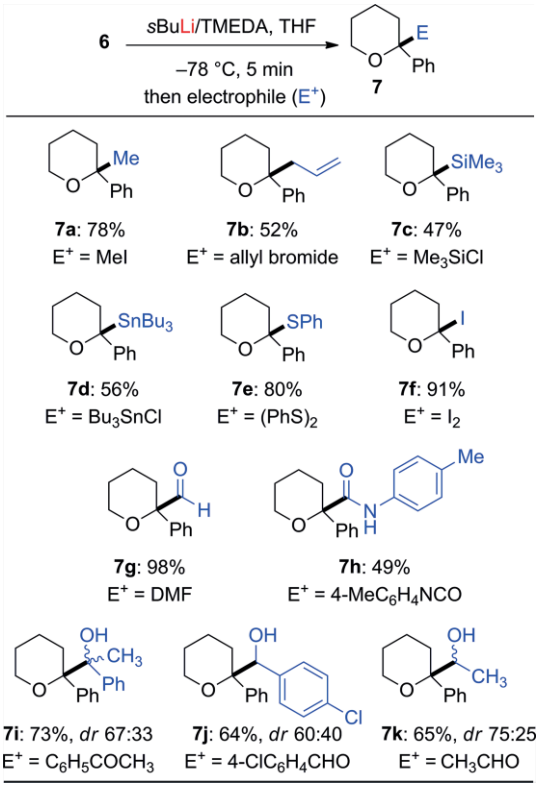
Entry	Base (equiv.)	*T* [°C]	Solvent	Co-solvent (equiv.)	D[a] [%]
1	*s*BuLi (2)	–78	toluene	TMEDA (2)	53
2	*s*BuLi (2)	–78	toluene	–	4
3	*s*BuLi (2)	–78	CPME	TMEDA (2)	42
4	*s*BuLi (2)	–78	CPME	–	16
5	*s*BuLi (2)	–78	hexane	TMEDA (2)	40
6	*s*BuLi (2)	–78	hexane	–	0
7	*s*BuLi (2)	–78	THF	TMEDA (2)	84
8	*s*BuLi (2)	–78	THF	–	46
9	*s*BuLi (2)	–78	2-MeTHF	TMEDA (2)	26
10	*s*BuLi (2)	–78	2-MeTHF	–	4
11	*s*BuLi (3)	–78	Et_2O	TMEDA (3)	80
12	***sBuLi (3)***	***–78***	***THF***	***TMEDA (3)***	***94***
13	*s*BuLi (3)	–98	THF	TMEDA (3)	0
14	*s*BuLi (3)	0	THF	TMEDA (3)	47[b]
15	*n*BuLi (3)	–78	THF	TMEDA (3)	20
16	$Me(CH_2)_5Li$ (3)	–78	THF	TMEDA (3)	0
17	*t*BuLi (3)	–78	THF	TMEDA (3)	88

[a] Deuterium incorporation as calculated by analysis of the crude reaction mixture by ^1H NMR spectroscopy; no other products were detected. [b] A complex mixture of unidentified products was detected in the crude mixture along with the starting material.

threefold excess amount of both *s*BuLi and TMEDA allowed an increase in the amount of deuterium incorporated into **1** to up to 80 and even to 94 % at –78 °C in Et_2O and THF, respectively (Table 1, entries 11 and 12). Further experimentation in THF established that a temperature as low as –98 °C precluded lithiation of **6** (Table 1, entry 13), whereas a temperature as high as 0 °C was detrimental to the chemical stability of **6**-Li, as [D]-**6** formed with 47 % D but with considerable decomposition (Table 1, entry 14). As for other bases, we found that metalation of **6** with *n*BuLi/TMEDA in THF at –78 °C did not lead to greater than 20 % deuterium incorporation (Table 1, entry 15), and surprisingly, the combination of $Me(CH_2)_5Li$/TMEDA in THF proved to be totally ineffective (Table 1, entry 16). Finally, the use of a stronger base such as *t*BuLi jointly with TMEDA in THF at –78 °C afforded [D]-**6** with 88 % D (Table 1, entry 17).

TMEDA is a commonly used ligand to modify the behavior of RLi species.[22] Such a ligand is known to have the most pronounced effects on organolithium aggregates and, thus, on their reactivity in the absence of strong donor solvents, whereas the relative affinities of TMEDA and THF for lithium seem to be highly substrate dependent.[22,23] Thus, in contrast to that observed in the case of other cyclic ethers,[12b,12f,24] the apparent beneficial influence of this ligand in all of the above-described metalations, both in polar and apolar solvents, is intriguing and deserves further consideration.[25]

Having established the optimal conditions for efficient α-lithiation of **6** (Table 1, entry 12), we next focused on evaluating the scope and generality of this methodology for the preparation of more functionalized derivatives by reaction with a broad range of structurally varied electrophiles. Alkylation with MeI and allylation with allyl bromide afforded the expected α-substituted derivatives **7a** and **7b** in reasonable yields (52–78 %, Scheme 3). The reaction of **6**-Li with Me_3SiCl, Bu_3SnCl, and $(PhS)_2$ provided the desired silyl, tin, and sulfenyl derivatives **7c**–**e** in yields of 47–80 %. Direct iodation was also successfully accomplished with I_2, which thus furnished the corresponding α-iodated adduct **7f** in high yield (91 %). The use of *N*,*N*-dimethylformamide (DMF) as a quenching agent delivered aldehyde **7g** in essentially quantitative yield (98 %), whereas trapping with 4-methylphenyl-1-isocyanate, as a more reactive electrophile, produced amide **7h** in 49 % yield.

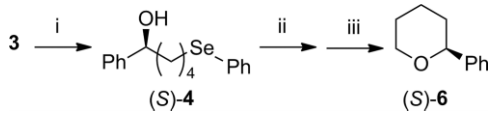


Scheme 3. Scope of electrophiles for the trapping reactions of **6**-Li. All reactions gave full conversion, yields refer to isolated products after column chromatography. Adducts **7i**–**k** were isolated as separable mixtures of diastereomers (see the Supporting Information).

As for reactions with carbonyl compounds, both an aromatic enolizable ketone such as acetophenone and aromatic and aliphatic aldehydes (e.g., 4-chlorobenzaldehyde and acetaldehyde) were competent electrophilic partners, and they afforded the expected hydroxyalkylated derivatives **7i**–**k** in good yields (64–73 %, Scheme 3).

We were also interested in establishing whether the present protocol could be further expanded to obtain optically active derivatives. To this end, we explored the configuration stability of **6**-Li generated by deprotonation of the corresponding optically active (*S*)-**6**. The latter was prepared by preliminarily subjecting prochiral δ-phenylseleno ketone **3** to enantioselective reduction by using borane and the chiral Corey–Bakshi–Shibata (CBS) oxazaborolidine catalyst [(*S*)-MeCBS],[26] which afforded (*S*)-**4** in 84 % yield with an enantiomeric ratio (*er*) of 98:2. Final oxidation of (*S*)-**4** with *m*-CPBA followed by cyclization of the

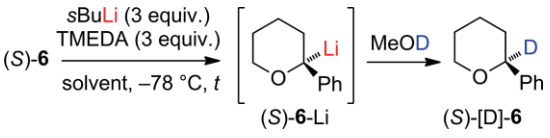
putative selenone intermediate with powdered KOH under the above-described conditions stereospecifically delivered (*S*)-**6** in an overall yield of 80 % with an *er* value of 98:2 (Scheme 4).



Scheme 4. Reagents and conditions: (i) BH_3·Me_2S, (*S*)-MeCBS, THF, 0 °C; (ii) *m*-CPBA, K_2HPO_4, MeCN, r.t., 2 h; (iii) KOH, r.t.

Exposing a 0.2 M solution of (*S*)-**6** to *s*BuLi (3 equiv.)/TMEDA (3 equiv.) in THF, followed by quenching with MeOD, essentially gave racemic [D]-**6** (60–94 % D, *er* 50:50) after a reaction time of either 5 min or 30 s at –78 °C (Table 2, entries 1 and 2). Interestingly, upon changing the solvent from THF to hexane, the rate of racemization slowed down and (*S*)-[D]-**6** was recovered with an encouraging *er* value of 60:40 (92 % D; Table 2, entry 3). Of note, a progressive increase of the *er* value up to 86:14 was observed upon aging enantiomerically enriched (*S*)-**6**-Li for shorter reaction times up to 10 s (Table 2, entries 4–6).

Table 2. Lithiation/deuteration of 2-PhTHP (*S*)-**6** with different solvents.



Entry	Solvent	*t* [s]	D [%][a]	*er*[b]
1	THF	300	94	50:50
2	THF	30	60	50:50
3	hexane	300	92	60:40
4	hexane	120	95	70:30
5	hexane	30	95	79:21
6	hexane	10	55	86:14

[a] Calculated by analysis of the crude reaction mixture by ^{1}H NMR spectroscopy and corrected for the percentage deuterium found. [b] Determined by chiral stationary phase HPLC (see the Supporting Information).

On the basis of these results, the barrier to enantiomerization of (*S*)-**6**-Li could be then calculated. The first-order plot obtained (R^2 = 0.9898) indicated a racemization half-life ($t_{1/2}$) of 2.8 min at –78 °C. Application of the Eyring equation to the estimated rate of enantiomerization (k_{enant}; calculated as the rate of racemization divided by two, i.e., $k_{rac}/2$) for (*S*)-**6**-Li furnished a barrier to inversion [$\Delta G^{\neq}$(enant)] of 13.5 ± 0.1 kcal mol^{-1} at –78 °C in hexane (see the Supporting Information).[27]

Thus, the stereochemistry of chiral nonracemic α-lithiated 2-PhTHP could be controlled in nonpolar solvents in the presence of TMEDA in line with α-lithiated styrene oxides,[21] whereas optically active α-lithiated phenyloxetane[12b] and PhTHF[12f] proved to be configurationally unstable in both polar and nonpolar solvents and underwent very fast racemization.

Conclusions

In summary, we showed for the first time that under optimized conditions and in the presence of TMEDA, regioselective and efficient functionalization of 2-PhTHP (**6**) could be successfully accomplished through a direct α-lithiation reaction performed in THF at –78 °C by using *s*BuLi as the base, followed by trapping with several electrophiles. This reaction has a broad electrophile scope and 2,2-disubstituted THP derivatives **7** can be isolated in yields up to 98 %. Optically active α-lithiated intermediate (*S*)-**6**-Li was found to be configurationally labile in THF but underwent slower racemization in hexane/TMEDA. The calculated barrier to inversion of 13.5 kcal mol^{-1} at –78 °C encourages investigation of the preparation of more functionalized optically active arylTHP derivatives, also exploiting asymmetric substitution of chiral lithiated racemic substrates that can undergo dynamic equilibration in the presence of a chiral ligand.

Experimental Section

Preparation of THP Derivative 7a as a Typical Procedure: A solution of 2-PhTHP (**6**; 50 mg, 0.31 mmol) and TMEDA (0.14 mL, 0.93 mmol) in dry THF (2.5 mL) was cooled to –78 °C and treated with *s*BuLi (1.25 M in cyclohexane, 0.74 mL, 0.93 mmol). The resulting red mixture was stirred for 5 min at this temperature before it was quenched with MeI (0.58 mL, 0.93 mmol). The mixture was kept at –78 °C for an additional 5 min. After this time, the mixture was slowly warmed to room temperature, and a saturated aqueous NH_4Cl solution (5 mL) was added. Then, the mixture was extracted with Et_2O (3 × 10 mL), the organic layers were combined and dried with anhydrous Na_2SO_4, and the solvent was removed under reduced pressure to leave a crude oil, which was purified by flash chromatography (silica gel; hexane/Et_2O, 20:1) to afford THP derivative **7a** (42 mg, 78 %) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (s, 3 H), 1.55–1.86 (m, 5 H), 2.29–2.33 (m, 1 H), 3.47–3.52 (m, 1 H), 3.72–3.75 (m, 1 H), 7.22–7.26 (m, 1 H), 7.33–7.43 ppm (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.1, 26.0, 32.7, 34.6, 62.8, 75.9, 125.9, 126.5, 128.4, 145.4 ppm. FTIR (neat): $\tilde{\nu}$ = 2937, 1492, 1446, 1057, 758, 701 cm^{-1}. GC–MS (70 eV): *m/z* (%) = 176 (1) [M]$^+$, 161 (100), 105 (82), 77 (20). HRMS (ESI-TOF): calcd. for $C_{12}H_{17}O$ 177.1279 [M + H]$^+$; found 177.1283.

Supporting Information (see footnote on the first page of this article): Experimental procedures, spectroscopic data, and copies of the ^{1}H NMR and ^{13}C NMR spectra of compounds **3**, **4**, **6**, and **7a**–**k**.

Acknowledgments

This work was financially supported by Ministero dell'Università e della Ricerca (MIUR) and the Interuniversities Consortium C.I.N.M.P.I.S. through the project "Sintesi di nuove molecole come farmaci per malattie rare" (code: CMPT148470). The authors would like to acknowledge Dr. Francesca Sassone for her contribution to the Experimental Section.

Keywords: Synthetic methods · Carbanions · Lithium · Oxygen heterocycles · Regioselectivity

[1] a) E. Alvarez, M. L. Candenas, R. Perez, J. L. Ravelo, M. J. Delgado, *Chem. Rev.* **1995**, *95*, 1953–1980; b) K.-S. Lee, G. Li, S. H. Kim, C.-S. Lee, M.-H.

Woo, S.-H. Lee, Y.-D. Jhang, J.-K. Son, *J. Nat. Prod.* **2002**, *65*, 1707–1708; c) T. Nakata, *Chem. Rev.* **2005**, *105*, 4314–4347; d) E. J. Kang, E. Lee, *Chem. Rev.* **2005**, *105*, 4348–4378; e) J. E. Aho, P. M. Pinko, T. K. Rissa, *Chem. Rev.* **2005**, *105*, 4406–4440; f) S. D. Roughley, A. M. Jordan, *J. Med. Chem.* **2011**, *54*, 3451–3479; g) F. Xu, M. J. Zacuto, Y. Kohmura, J. Rosen, A. Gibb, M. Alam, J. Scott, D. Tschaen, *Org. Lett.* **2014**, *16*, 5422–5425.

[2] For selected reviews, see: a) T. L. B. Boivin, *Tetrahedron* **1987**, *43*, 3309–3362; b) L. E. Titze, G. Kettschau, *Top. Curr. Chem.* **1997**, *189*, 1–120; c) P. A. Clarke, S. Santos, *Eur. J. Org. Chem.* **2006**, 2045–2053; d) I. Larrosa, P. Romea, F. Urpí, *Tetrahedron* **2008**, *64*, 2683–2723; e) N. M. Nasir, K. Ermanis, P. A. Clarke, *Org. Biomol. Chem.* **2014**, *12*, 3323–3335; f) M. A. Perry, S. D. Rychnovsky, N. Sizemore, *Top. Heterocycl. Chem.* **2014**, *35*, 43–95.

[3] M. G. Núñez, P. García, R. F. Moro, D. Díez, *Tetrahedron* **2010**, *66*, 2089–2109.

[4] R. Guo, J. Huang, H. Huang, X. Zhao, *Org. Lett.* **2016**, *18*, 505–507.

[5] a) A. Temperini, A. Barattucci, P. M. Bonaccorsi, O. Rosati, L. Minuti, *J. Org. Chem.* **2015**, *80*, 8102–8112; b) L. Minuti, A. Barattucci, P. M. Bonaccorsi, M. L. Di Gioia, A. Leggio, C. Siciliano, A. Temperini, *Org. Lett.* **2013**, *15*, 3906–3909.

[6] A. Salomone, F. M. Perna, F. C. Sassone, A. Falcicchio, J. Bezenšek, J. Svete, B. Stanovnik, S. Florio, V. Capriati, *J. Org. Chem.* **2013**, *78*, 11059–11065.

[7] J. Jin, D. W. C. MacMillan, *Angew. Chem. Int. Ed.* **2015**, *54*, 1565–1569; *Angew. Chem.* **2015**, *127*, 1585–1589.

[8] a) M. Wan, Z. Meng, H. Lou, L. Liu, *Angew. Chem. Int. Ed.* **2014**, *53*, 13845–13849; *Angew. Chem.* **2014**, *126*, 14065–14069; b) Z. Meng, S. Sun, H. Yuan, H. Lou, L. Liu, *Angew. Chem. Int. Ed.* **2014**, *53*, 543–547; *Angew. Chem.* **2014**, *126*, 553–557; c) W. Chen, Z. Xie, H. Zheng, H. Lou, L. Liu, *Org. Lett.* **2014**, *16*, 5988–5991; d) F. Li, Z. Meng, J. Hua, W. Li, H. Lou, L. Liu, *Org. Biomol. Chem.* **2015**, *13*, 5710–5715.

[9] D. P. Affron, J. A. Bull, *Eur. J. Org. Chem.* **2016**, 136–149.

[10] a) G. Köbrich, A. Baumann, *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 856–858; *Angew. Chem.* **1973**, *85*, 916–918; b) A. Maercker, *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 972–989; *Angew. Chem.* **1987**, *99*, 1002–1019.

[11] For reviews on lithium carbenoids, see: a) G. Boche, J. C. W. Lohrenz, *Chem. Rev.* **2001**, *101*, 697–756; b) V. Capriati, S. Florio, *Chem. Eur. J.* **2010**, *16*, 4152–4162, and references cited therein; c) V. Capriati, *Modern Lithium Carbenoid Chemistry*, in: *Contemporary Carbene Chemistry* (Eds.: R. A. Moss, M. P. Doyle), Wiley, Hoboken, NJ, **2013**, p. 327–362.

[12] For α-lithiated aryloxiranes, see: a) V. Capriati, S. Florio, A. Salomone, *Top. Stereochem.* **2010**, *26*, 135–164; for lithiated oxetanes, see: b) D. I. Coppi, A. Salomone, F. M. Perna, V. Capriati, *Chem. Commun.* **2011**, *47*, 9918–9920; c) D. I. Coppi, A. Salomone, F. M. Perna, V. Capriati, *Angew. Chem. Int. Ed.* **2012**, *51*, 7532–7536; *Angew. Chem.* **2012**, *124*, 7650–7654; d) J. V. Geden, B. O. Beasley, G. J. Clarkson, M. Shipman, *J. Org. Chem.* **2013**, *78*, 12243–12250; e) K. F. Morgan, I. A. Hollingsworth, J. A. Bull, *Chem. Commun.* **2014**, *50*, 5203–5205; for lithiated aryltetrahydrofurans, see: f) R. Rosmara, V. Mallardo, F. M. Perna, A. Salomone, V. Capriati, *Chem. Commun.* **2013**, *49*, 10160–10162; g) F. C. Sassone, F. M. Perna, A. Salomone, S. Florio, V. Capriati, *Chem. Commun.* **2015**, *51*, 9459–9462; for recent reviews, see: h) F. M. Perna, A. Salomone, V. Capriati, *Oxygen-Bearing Lithium Compounds in Modern Synthesis*, in: *Lithium Compounds in Organic Synthesis – From Fundamentals to Applications* (Eds.: R. Luisi, V. Capriati), Wiley-VCH, Weinheim, Germany, **2014**, p. 153–189; i) F. M. Perna, A. Salomone, V. Capriati, *Recent Developments in the Lithiation Reactions of Oxygen Heterocycles*, in: *Advances in Heterocyclic Chemistry* (Eds.: E. F. V. Scriven, C. A. Ramsden), Elsevier/Academic Press, Cambridge, MA, **2016**, vol. 118, p. 91–127.

[13] R. B. Bates, L. M. Kroposki, D. E. Potter, *J. Org. Chem.* **1972**, *37*, 560–562.

[14] P. Stanetty, M. D. Mihovilovic, *J. Org. Chem.* **1997**, *62*, 1514–1515.

[15] R. L. Letsinger, D. F. Pollart, *J. Am. Chem. Soc.* **1956**, *78*, 6079–6085.

[16] J. Langer, M. Köhler, R. Fischer, F. Dündar, H. Görls, M. Westerhausen, *Organometallics* **2012**, *31*, 6172–6182.

[17] A. R. Kennedy, J. Klett, R. E. Mulvey, D. S. Wright, *Science* **2009**, *326*, 706–708.

[18] S. V. Ley, B. Lygo, A. Wonnacott, *Tetrahedron Lett.* **1985**, *26*, 535–538.

[19] T. Cohen, M.-T. Lin, *J. Am. Chem. Soc.* **1984**, *106*, 1130–1131.

[20] Previous examples of the in situ preparation of PhSeNa by reduction of diphenyl diselenide employed $NaBH_4$ in DMF at 110–120 °C or Na in THF/hexamethylphosphoric triamide (HMPA) at reflux; see: a) R. N. Scarborough Jr., A. B. Smith III, *Tetrahedron Lett.* **1977**, *18*, 4361–4364; b) D. Liotta, H. Santiesteban, *Tetrahedron Lett.* **1977**, *18*, 4369–4372.

[21] F. M. Perna, A. Salomone, M. Dammacco, S. Florio, V. Capriati, *Chem. Eur. J.* **2011**, *17*, 8216–8225.

[22] a) D. B. Collum, *Acc. Chem. Res.* **1992**, *25*, 448–454; b) B. L. Lucht, D. B. Collum, *J. Am. Chem. Soc.* **1995**, *117*, 9863–9874; c) B. L. Lucht, M. P. Bernstein, J. F. Remenar, D. B. Collum, *J. Am. Chem. Soc.* **1996**, *118*, 10707–10718; d) D. B. Collum, D. Hoffmann, *J. Am. Chem. Soc.* **1998**, *120*, 5810–5811.

[23] a) H. J. Reich, W. S. Goldenberg, A. W. Sanders, K. L. Jantzi, C. C. Tzschucke, *J. Am. Chem. Soc.* **2003**, *125*, 3509–3521; b) H. J. Reich, W. S. Goldenberg, A. W. Sanders, *ARKIVOC* **2004**, *xiii*, 97–129.

[24] TMEDA was also shown to be necessary to preserve the chemical integrity of α-lithiated styrene oxide once generated in THF and to mitigate its carbene-like reactivity, see: a) V. Capriati, S. Florio, R. Luisi, A. Salomone, *Org. Lett.* **2002**, *4*, 2445–2448; b) V. Capriati, S. Florio, F. M. Perna, A. Salomone, A. Abbotto, M. Amedjkouh, S. O. Nilsson Lill, *Chem. Eur. J.* **2009**, *15*, 7958–7979.

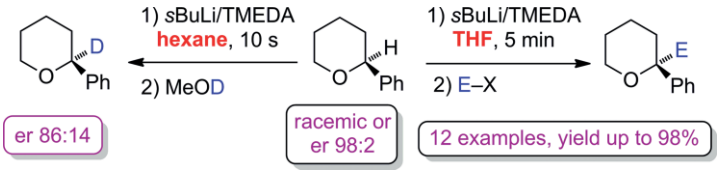
[25] Solution and solid structure investigation of **6**-Li are underway and results will be reported in due course.

[26] E. J. Corey, R. K. Bakshi, S. Shibata, *J. Am. Chem. Soc.* **1987**, *109*, 5551–5553.

[27] Activation free energy for the enantiomerization ($\Delta G^{\neq}_{enant}$, kcal mol^{-1}) was calculated by application of the Eyring equation, in which T is the absolute temperature and k_{enant} is the rate constant [s^{-1}] ($k_{enant} = k_{rac}/2$): $\Delta G^{\neq}_{enant} = 4.574\ T\ [10.318 + \log_{10}(T\,k_{enant})]$: H. Eyring, *Chem. Rev.* **1935**, *17*, 65–77.

Received: March 23, 2016
Published Online: ■

Lithiation Chemistry



2-Phenyltetrahydropyran is easily functionalized in up to 98 % yield in THF by using a *s*BuLi-mediated lithiation-trapping method in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA). The rate of racemization of the optically active intermediate is slowed down in hexane/TMEDA, which thereby paves the way for the preparation of enantiomerically enriched tetrahydropyran derivatives.

DOI: 10.1002/ejoc.201600365