WILEY-VCH

One-Carbon Homologation of α,β-Unsaturated Aldehydes: Access to α-Tertiary β,γ-Unsaturated Aldehydes

Arnaud Delbrassinne,[a] Boris Junior Takam Mba,[a] Laurent Collard[a] and Raphaël Robiette*[a]

[a] Dr A. Delbrassinne, B. J..Takam Mba, L. Collard, Prof. R. Robiette
Institute of Condensed Matter and Nanosciences
Université catholique de Louvain
Place Louis Pasteur 1 box L4.01.02, 1348 Louvain-la-Neuve, Belgium 1
E-mail: raphael.robiette@uclouvain.be
Homepage : https://perso.uclouvain.be/raphael.robiette

Supporting information for this article is given via a link at the end of the document.

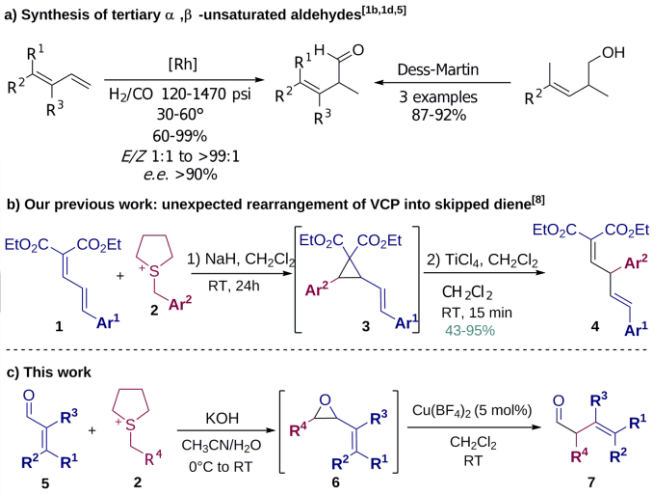
Abstract: An efficient protocol for the synthesis of enolizable α-substituted β,γ-unsaturated aldehydes is reported. The developed strategy involves two steps, epoxidation and Meinwald rearrangement, to result in a one-carbon homologation of α,β-unsaturated aldehydes enabling the insertion of a CHR unit

Introduction

Despite their versatility as intermediates in total synthesis,[1] the preparation of β,γ-unsaturated aldehydes is still a challenge in organic chemistry, in particular in the case of enolizable aldehydes. [2] Indeed, the obtaining and isolation of α-tertiary β,γ-unsaturated aldehydes is facing the difficulty of their high propensity to isomerize into their conjugated α,β-unsaturated analogues. [3] One synthetic strategy consists in the rhodium(I) catalyzed hydroformylation of 1,3-diene (Scheme 1a). [4-5] However, these methodologies requires high-pressure in CO/H_2 and results often in mixtures of targeted β,γ-unsaturated aldehydes along with isomerization product (α,β-unsaturated aldehyde) and regioisomers. Another method involves the oxidation of corresponding alcohols; [1b,1d,3] the limitation being here the access to primary homoallylic alcohols. [6]

We surmised that an alternative strategy could be the one-carbon homologation of widely available α,β-unsaturated aldehydes. However, despite the fact that one-carbon chain extension of alkyl aldehydes has long history, [7] a literature search showed no example of homologation of α,β-unsaturated aldehydes.

We recently reported the synthesis of skipped diene (**4**) from 1,3-diene (**1**) and sulfonium ylide (**2**) via the rearrangement of vinylcyclopropane **3** (Scheme 1b). [8] We envisaged that, applied to α,β-unsaturated aldehydes (**5**), this sequence would enable a short and efficient access to enolizable α-tertiary β,γ-unsaturated aldehydes **7** (Scheme 1c). [9,10]

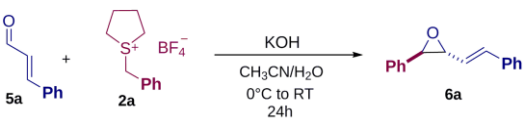


Scheme 1. Synthesis of α,β-unsaturated aldehydes, rearrangement of vinylcyclopropane **3** into skipped diene **4** and our one-carbon homologation of α,β-unsaturated aldehyde strategy

Results and Discussion

We started our investigation with cinnamaldehyde (**5a**) and the benzylic sulfonium salt **2a** as reference substrates to confirm that epoxidation reaction works as reported by others. [11] Formation of the sulfonium ylide by deprotonation of **2a** in the presence of cinnamaldehyde (**5a**) led to vinyl epoxide **6a** in a good yield and, according to reaction conditions, a moderate to a good *trans/cis* ratio (Table 1).

Table 1. Epoxidation reaction.

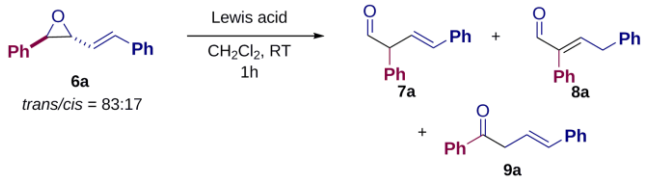


Entry	Reaction conditions	Yield (%)	*trans/cis*
1	NaH, CH_2Cl_2, RT, 24h	89	94:6

2	KOH, CH_3CN/H_2O (9/1), 0°C to RT, 24h	88	83:17
3	LHMDS, CH_2Cl_2, -78°C to RT, 16h	89	71:29

The second step of our methodology consists of a Meinwald rearrangement[12] of **6a**. Screening of reactions conditions showed that a series of Lewis acids catalyzes the conversion of vinyl epoxide **6a** into β,γ-unsaturated aldehydes **7a** (Table 2). However, in many cases, the feared isomerization of the double bond is observed yielding aldehyde **8a** as a side-product. Formation of ketone **9a** originating from the migration of hydrogen atom instead of phenyl group is another observed side-product. Fortunately, we found that catalysis by 5 mol% of $Cu(BF_4)_2$ enables a high selectivity of migration (**7a/9a** = 95/5) and prevents isomerization of the double bond (formation of **8a**).[13] We thus selected $Cu(BF_4)_2$ to develop further our methodology. Interestingly, we found that epoxide 6a obtained using KOH conditions could be engaged in the rearrangement without any purification besides a work-up.[14] Test reactions showed also that the stereochemistry of the epoxide has no impact on the outcome of the rearrangement (see SI).

Table 2. Optimization of reaction conditions for the Meinwald rearrangement.

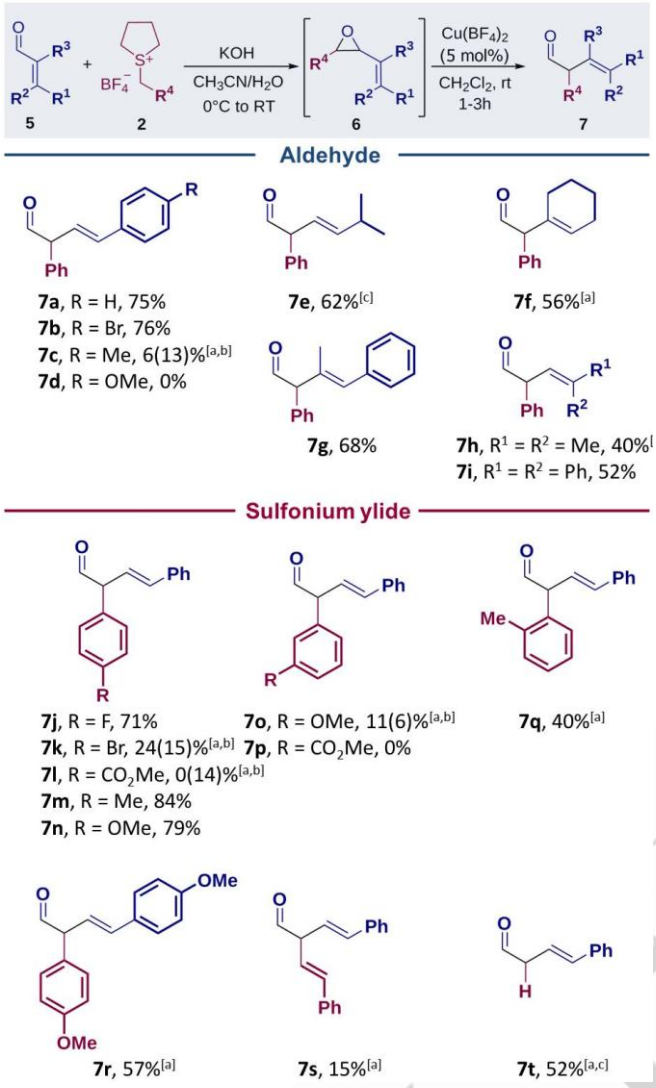


Entry	Lewis acid	Equiv.	Yield (%)[a]	**7a/8a/9a**[b]
1	$Sc(OTf)_3$	1	n.d.	46/4/50
2	$ZnCl_2$	1	81	42/0/58
3	$Yb(OTf)_3$	1	79	86/8/6
4	$Ti(Oi\text{-}Pr)_4$	1	0	/
5	$FeCl_3$	1	0	/
6	$Fe(OTf)_2$	1	0	/
7	$Cu(OTf)_2$	1	82	0/90/10
8		0.1	84	45/48/7
9		0.05	70	87/5/8
10		0.01	78	93/2/5
11	$Cu(BF_4)_2$	1	85	91/2/7
12		0.1	82	94/0/6
13		0.05	86	95/0/5
14		0.01	84	96/0/4

[a] Yield determined on the crude mixture by ^{1}H NMR using an internal standard. [b] Determined by ^{1}H NMR on the crude mixture.

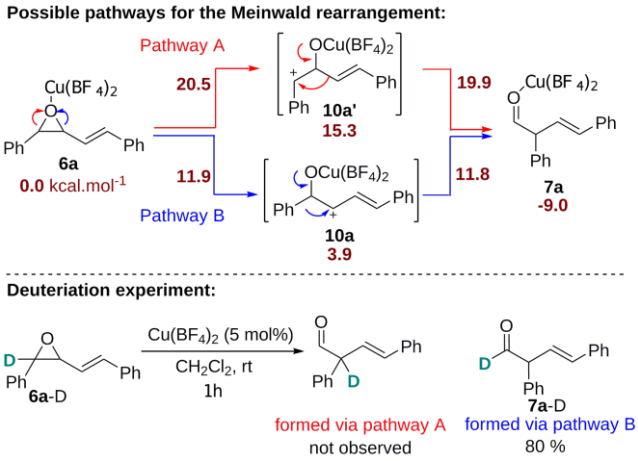
Having demonstrated the practicability and efficiency of the methodology, we next explored its scope (Scheme 2). Reaction of (electron-poor) aryl-substituted β,γ-unsaturated aldehydes worked well enabling to isolate corresponding β,γ-unsaturated aldehydes **7a-b** in good yield. Alkyl substituents could also be successfully employed (**7f-g**) and bis-substitution of the double bond is tolerated as well (see **7g-j**). However, substitution by an electron-rich aryl group emerged as a problem with the obtaining of complex mixtures after the rearrangement (**7c-d**), probably due to an excessive stabilization of the zwitterion intermediate (see SI).

Next, we turned our attention to the nature of the sulfonium salt, *i.e.* the migrating group (R^4). Substitution of the aromatic group with electron-donating substituents is well tolerated (**7m-n,q-r**) whereas in the case of electron-poor aryl groups (**7k-l,o-p**) the yield is decreased, due to the competing hydrogen migration leading instead to corresponding ketones **9**. This is in good agreement with the reported decreased migratory aptitude of electron-poor aryl groups.[8a,15] Migration of a styryl group or a hydrogen atom could also be observed (**7s-t**). The difficulty of generating alkyl substituted sulfonium ylides prevented us to consider alkyl groups;[16] these latter being reported to be poor migrating groups, they would have anyway lost the competition with the migration of a hydrogen.



Scheme 2. Rearrangement of vinylcyclopropane **3** into skipped diene **4** and our one-carbon (Yield in isolated analytically pure compound, unless mentioned otherwise). [a] Aldehyde not isolated, yield determined by ^{1}H NMR on the crude mixture; [b] β,γ-Unsaturated ketone originating from the migration of H is obtained as the main product (yield reported in brackets); [c] Rearrangment catalyzed by $Yb(OTf)_3$ (yield was lower with $Cu(BF_4)_2$; see SI). The epoxidation step was performed using Me_3SiI (see SI).

From a mechanistic point of view, DFT calculations (see SI for details) indicate that the key factor for determining regioselectivity of ring-opening and the nature of the migrating group is the relative stability of the zwitterionic intermediate **10** and not the relative migratory aptitude of the two substituents (Scheme 3). Indeed, deuterium-labeling experiments showed that the epoxide opens preferentially on the side of the most carbocation stabilizing group (*i.e.* the styryl group) and, consequently, it is the phenyl group which migrates (pathway B).



Scheme 3. Deuterium-labeling experiment and computations of the rearrangment (free energies in kcal.mol^{-1} relative to **6a**).

Next, we turned our attention to the identification of an asymmetric variant of our methodology toward β,γ-unsaturated aldehydes. Interestingly, our calculations indicate that the rearrangement should be enantiospecific (Figure 1). [17] Indeed, absolute stereochemistry of the carbon bearing the migrating group (R^4) should determine the stereochemistry of the created stereogenic center in the β,γ-unsaturated aldehyde (see SI). Accordingly, we focused our efforts on the stereocontrol of the epoxidation step. Aggarwal has already showed that high enantiocontrol could be achieved in epoxidation reactions using chiral sulfonium salt **11**, which are readily available optically pure in two steps from sulfur and limonene (Scheme 3). [18] Deprotonation of **11** in the presence of aldehyde **5a** or **5i** and subsequent rearrangement allows obtaining β,γ-unsaturated aldehydes **7a,i** in moderate yield and enantiomeric ratio (74/26 and 71/29, respectively). [19] Control experiments showed that epoxidation proceeds with a very high diastereo- and enantiocontrol (d.r. >99/1 and e.r. = 98/2). Thus, the observed moderate overall enantioselectivity is due to the partial stereospecificity of the rearrangement (see SI).

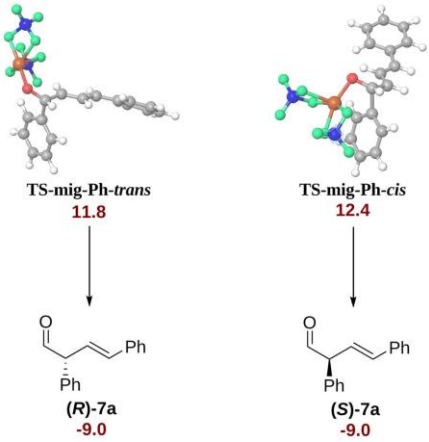
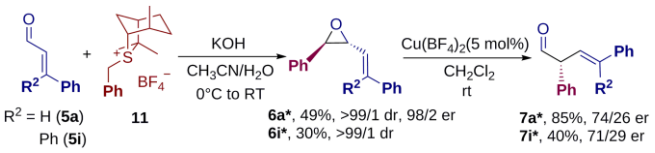


Figure 1. Structure of the two possible transition states for the migration step, leading to the two enantiomers (free energies in kcal.mol^{-1} relative to **6a**).



Scheme 4. Enantioselective synthesis of β,γ-unsaturated aldehydes (enantiomeric excess of aldehydes was measured by HPLC on the corresponding alcohol after reduction, see SI).

Conclusion

We have successfully developed a protocol for the one-carbon homologation of α,β-unsaturated aldehydes which enables the insertion of a CHAr unit. The strategy involves two steps, epoxidation and Meinwald rearrangement, and enables the synthesis of enolizable α-aryl substituted β,γ-unsaturated aldehydes. One of the key feature of the methodology is the mild reaction conditions of the rearrangement enabling to avoid isomerization of the β,γ-unsaturated aldehydes. Preliminary studies toward an enantioselective version of the methodology showed the stereospecificity of the rearrangement, providing promising results for further developments.

Experimental Section

General procedure : The benzylic sulfonium salt (1.4 eq.) is dissolved in a 9/1 mixture of MeCN/H_2O (8 mL/100 mg of α,β-unsaturated aldehyde) in a round-bottom flask at 0°C. Aldehyde (1 eq., 150 mg) and KOH (1.4 eq) are added and the reaction mixture is allowed to warm up to room temperature and stirred for 24-72h. Then, the reaction mixture is concentrated under reduced pressure and dissolved in dichloromethane. Water is added and the two layers are separated. The aqueous phase is extracted twice with dichloromethane. The combined organic layers are washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Epoxide (1 eq., 100 mg) and $Cu(BF_4)_2$ are dissolved in dry dichloromethane (6 mL/100mg of epoxide). The reaction mixture is stirred at room temperature for 1-3 h. Water is added to stop the reaction. The two layers are separated and the aqueous one is extracted twice with dichloromethane. The combined organic layers are washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Characterization of **7a** : ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.76 (d, J = 2.1 Hz, 1H), 7.48–7.17 (m, 10H), 6.54–6.49 (m, 2H), 4.43 ppm (dd, J = 5.5, 2.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.3, 136.5, 135.6, 134.3, 129.2, 129.0, 128.6, 128.0, 127.8, 126.5, 124.5, 61.9 ppm; IR: $\tilde{\nu}$ = 3031, 1722, 1690, 1596, 1494, 1453 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{16}H_{15}O^+$: 223.11174 $[M+H]^+$; found: 223.11169.

Computational details : Calculations were carried out using the Orca 4.1.0 program package. Geometry optimisations were performed at the M06-2X level of theory using the 6-31G(d) basis set.[20] Solvent effects were modelled by using the SMD solvation module[21] as incorporated in Orca, using the parameters for dichloromethane. The stationary points were characterized by full calculation of vibrational frequencies at the M06-2X/6-31+G(d)(CH_2Cl_2) level. These frequency calculations provided also thermal and entropic contributions to free energy. Gas phase electronic energies were obtained after single point calculations, at the M06-2X/6-311+G(d,p) level of theory. We have made a systematic attempt to locate all possible local minima (at the M06-2X/6- 31+G(d) level), with the data presented referring to the lowest energy form.

Supporting Information

Full experimental procedures, characterization data, additional experimental observations, computational details and Cartesian coordinates for all computed structures are available in the supplementary material of this article. The authors have cited additional references within the Supporting Information.[22]

Acknowledgements

This work was supported by the Fonds Spéciaux de Recherche through a PhD fellowship to AD. Computational resources have been provided by the supercomputing facilities of the Université catholique de Louvain (CISM/UCL) and the Consortium des Équipements de Calcul Intensif en Fédération Wallonie Bruxelles (CÉCI) funded by the Fonds de la Recherche Scientifique-FNRS (F.R.S.-FNRS) under convention 2.5020.11 and by the Walloon Region. We thank S. Ouk, through the Fondation Louvain, for very kind financial support. We thank B. Tchamba Lontsi and P.-L. Lefebvre for their technical assistance. RR is a Maître de Recherche of the F.R.S.-FNRS.

Keywords: Epoxide • Homologation • Meinwald • Migration • Rearrangement

[1] a) T. E. Smith, S. J. Fink, Z. G. Levine, K. A. McClelland, A. A. Zackheim, M. E. Daub, *Org. Lett.* **2012**, *14*, 1452–1455; b) E. de Lemos, F.-H. Porée, A. Bourin, J. Barbion, E. Agouridas, M. I. Lannou, A. Commerçon, J.-F. Betzer, A. Pancrazi, J. Ardisson, *Chem. Eur. J.* **2008**, *14*, 11092–11112; c) A. Fürstner, C. Nevado, M. Waser, M. Tremblay, C. Chevrier, F. Teplý, C. Aïssa, E. Moulin, O. Müller, *J. Am. Chem. Soc.* **2007**, *129*, 9150–9161; d) A. Fürstner, E. Kattnig, O. Lepage, *J. Am. Chem. Soc.* **2006**, *128*, 9194–9204; e) P. Liu, E. N. Jacobsen, *J. Am. Chem. Soc.* **2001**, *123*, 10772–10773.

[2] For the synthesis of α-quaternary β,γ-unsaturated aldehydes, see a) Z. Wang, Z. P. Yang, G. C. Fu, *Nat. Chem.* **2021**, *13*, 236-242. b) V. Pace, L. Castoldi, E. Mazzeo, M. Rui, T. Langer, W. Holzer, *Angew. Chem. Int. Ed.* **2017**, *56*, 12677–12682; c) M. Simaan, P.-O. Delaye, M. Shi, I. Marek, *Chem. Int. Ed.* **2015**, *54*, 12345–12348.

[3] For examples where obtained β,γ-unsaturated aldehyde is immediately (*in situ*) engaged into a subsequent transformation due to its instability under reaction conditions, see ref. 2b. and L. Wavrin, J. Viala, *Synthesis* **2002**, *3*, 326–330.

[4] a) P. Neubert, S. Fuchs, A. Behr, *Green Chem.* **2015**, *17*, 4045–4052; b) A. Behr, S. Reyer, N. Tenhumberg, *Dalton Trans.* **2011**, *40*, 11742–11747; c) S. Bertozzi, N. Campigli, G. Vitulli, R. Lazzaroni, P. Salvadori, *J. Organomet. Chem.* **1995**, *487*, 41–45; d) B. Fell, W. Rupilius, *Tet. Lett.* **1969**, *32*, 2721–2723.

[5] a) G. W. Wong, C. R. Landis, *Aldrichimica Acta* **2014**, *47*, 29–38; b) A. L. Watkins, C. R. Landis, *Org. Lett.* **2011**, *13*, 164–167; c) T. Horiuchi, T. Ohta, E. Shirakawa, K. Nozaki, H. Takaya, *Tetrahedron* **1997**, *53*, 7795–7804.

[6] L. Rycek, T. Hudlicky, *Angew. Chem. Int. Ed.* **2017**, *56*, 6022–6066.

[7] For reviews, see: (a) A. R. Katritzky, S. Bobrov, *Arkivoc* **2005**, *10*, 174–188; b) S. F. Martin, *Synthesis* **1979**, *9*, 633–665.

[8] a) A. Delbrassinne, M. Richald, J. Janssens, R. Robiette, *Eur. J. Org. Chem.* **2021**, 2862–2868; b) M. Richald, A. Delbrassinne, R. Robiette, *Eur. J. Org. Chem.* **2019**, 3779–3782.

[9] In fact, the obtaining of enolizable β,γ-unsaturated aldehydes from vinylepoxide, via a Meinwald rearrangement, has already been reported but the aldehyde is systematically not isolated and made reacted *in situ*. See a) J. Xu, Y. Song, J. He, S. Dong, L. Lin, X. Feng, *Angew. Chem. Int. Ed.* **2021**, *60*, 14521–14527; b) B. M. Trost, J. S. Tracy, *Chem. Eur. J.* **2015**, *21*, 15108–15112; c) M. L. Maddess, M. Lautens, *Org. Lett.* **2005**, *7*, 3557–3560; d) M. Lautens, S. G. Ouellet, S. Raeppel, *Angew. Chem. Int. Ed.* **2000**, *39*, 4079–4082. Only one example could be found in which enolizable β,γ-unsaturated aldehydes were isolated but substitution is restricted to TMS (only four examples), see X.-M. Deng, X.-L. Sun, Y. Tang, *J. Org. Chem.* **2005**, *70*, 6537–6540.

[10] For some examples of Meinwald rearrangement toward non-enolizable β,γ-unsaturated aldehydes (or ketone), see ref 2b and a) D. W. McCullough, T. Cohen, *Tet. Lett.* **1988**, *29*, 27–30; b) W. Adam, A. Berkessel, K. Hildenbrand, E.-M. Peters, K. Peters, H. G. von Schnering, *J. Org. Chem.* **1985**, *50*, 4899–4909; c) B. Bardili, H. Marschall-Weyerstahl, P. Weyerstahl, *Liebigs Ann. Chem.* **1985**, 275–300.

[11] a) V. K. Aggarwal, I. Bae, H.-Y. Lee, J. Richardson, D. T. Williams, *Angew. Chem. Int. Ed.* **2003**, *42*, 3274–3278; b) D. W. Lupton, D. K. Taylor, *Tetrahedron* **2002**, *58*, 4517–4527; c) A. Solladié-Cavallo, L. Bouérat, M. Roje, *Tet. Lett.* **2000**, *41*, 7309–7312.

[12] For the original paper, see: J. Meinwald, S. S. Labana, M. S. Chadha, *J. Am. Chem. Soc.* **1963**, *85*, 582–585. For reviews, see: a) R. E. Parker, N. S. Issacs, *Chem. Rev.* **1959**, *59*, 737–799; b) A. S. Rao, S. K. Paknikar, J. G. Kirtane, *Tetrahedron* **1983**, *39*, 2323–2367; c) J. G. Smith, *Synthesis* **1984**, 629–656; d) Z. Wang, in *Comprehensive Organic Name Reactions and Reagents*, John Wiley & Sons, Inc., New York, **2010**, pp. 1880–1882.

[13] M. W. C. Robinson, K. S. Pillinger, A. E. Graham, *Tet. Lett.* **2006**, *47*, 5919–5921.

[14] One-pot reaction conditions to perform the epoxidation and the rearrangement in a single step were attempted but the rearrangement proved to be non-compatible with the presence of tetrahydrothiophene.

[15] a) Z. Feng, D. J. Tantillo, *J. Am. Chem. Soc.* **2021**, *143*, 1088–1097; b) H. C. Brown, C. J. Kim, *J. Am. Chem. Soc.* **1968**, *90*, 2082–2096.

[16] C. G. Kokotos, E. M. McGarrigle, V. K. Aggarwal, *Synlett* **2008**, *14*, 2191–2195.

[17] For an example of stereospecific Meinwald rearrangement, see: M. E. Jung, K. L. Anderson, *Tet. Lett.* **1997**, *38*, 2605–2608.

[18] a) O. Illa, M. Namutebi, C. Saha, M. Ostovar, C. C. Chen, M. F. Haddow, S. Nocquet-Thibault, M. Lusi, M. E. McGarrigle, V. K. Aggarwal, *J. Am. Chem. Soc.* **2013**, *135*, 11951–119566; b) O. Illa, M. Archad, A. Ros, M. E. McGarrigle, V. K. Aggarwal, V. K. *J. Am. Chem. Soc.* **2010**, *132*, 1828–1830.

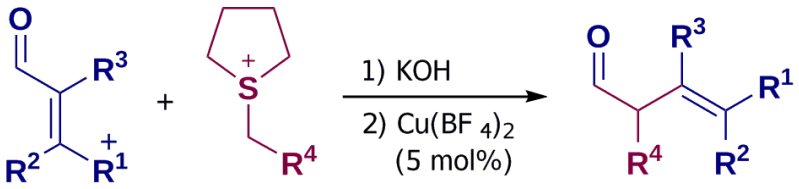
[19] Absolute stereochemistry of epoxide **6a** was determined in ref. 17. The absolute stereochemistry of β,γ-unsaturated aldehydes **7a,i** was attributed according to the model derived from our DFT study (see SI).

[20] W. J. Hehre, R. Ditchfield, J. A. Pople, *J. Chem. Phys.* **1972**, *56*, 2257–2261.

[21] A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem. B* **2009**, *113*, 6378–6396.

[22] Y. Li, J. Han, H. Luo, Q. An, X.-P. Cao, B. Li, *Org. Lett.* **2019**, *21*, 6050–6053.

Entry for the Table of Contents



An efficient two-step no purification protocol for the synthesis of enolizable α-subtituted β,γ-unsaturated aldehydes is reported. The developed strategy involves two steps, epoxidation and Meinwald rearrangement, to result in a formal one-carbon homologation of α,β-unsaturated aldehydes enabling the insertion of a CHR unit.