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Enantiospecific Synthesis of Nepetalactones by One-Step Oxidative NHC Catalysis

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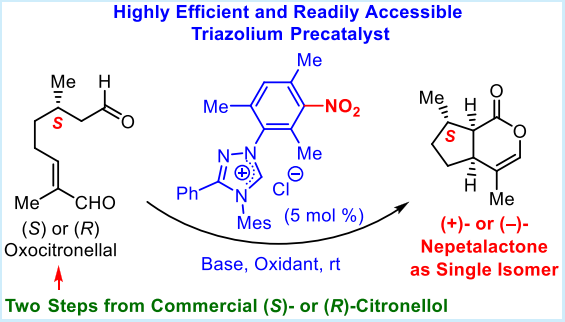
Supporting Information

ABSTRACT: An efficient oxidative NHC-catalyzed one-step transformation of (*S*)- or (*R*)-8-oxocitronellal to nepetalactone (NL) in enantio- and diastereomerically pure form has been developed. Several new and "easy to make" N-Mes- or N-Dipp-substituted 1,2,4-triazolium salts carrying nitroaromatic groups on N1 were synthesized and evaluated as precatalysts in combination with base and stoichiometric organic oxidant. Under optimized conditions, NLs are accessible in very good yields and diastereomerically pure under mild conditions. The oxidant used could be recovered and recycled under operationally simple conditions.



Nepetalactones (NLs, **1**)[1] are essential oils in a class of monoterpenoids produced by plants of the genus *Nepeta* in the mint family (Lamiaceae).[2] Generally, the (7*S*)-nepetalactones are found in natural sources and exist as a mixture of varying amounts of diastereomers, predominantly **1a** and **1b**, depending on the *Nepeta* species and the specific source (Figure 1).[2,3] For example, the oils obtained from the

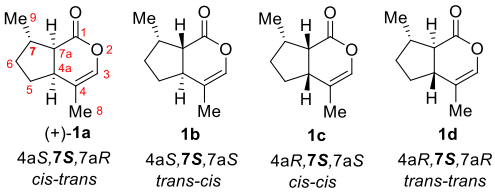


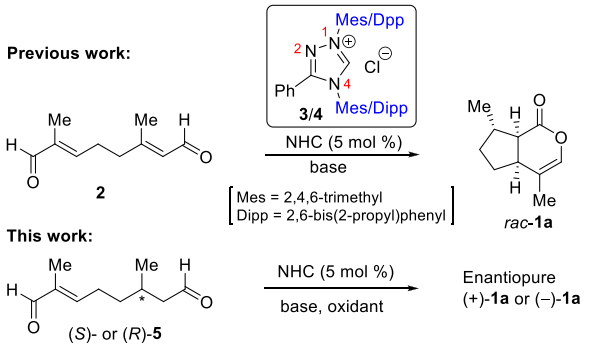
Figure 1. Four possible diastereomeric forms of (7*S*)-nepetalactones.

steam distillation of catmint plants (*N. cateria*) from different suppliers contain different ratios of *cis*−*trans*-nepetalactone (**1a**) and *trans*−*cis*-nepetalactone (**1b**).[4,5] Notably, the *trans*-fused lactone **1b** readily epimerizes to the thermodynamically more stable *cis*-fused lactone **1a** upon heating with base (DBU, Cs_2CO_3, K_2CO_3).[3,5]

Nepetalactones are known to cause a euphoric effect in cats;[6] they are also components of aphid sex pheromones[7] and insect and mosquito repellents.[4,8] In addition, (+)-**1a** has been used by Christmann et al. as starting material in the total synthesis of the highly biologically active englerin A, albeit its antipode, (+)-englerin A, was obtained.[9] To gain access to the natural (−)-englerin A, (−)-**1a** is thus required. It is noteworthy that (−)-**1a**, the enantiomer of (+)-**1a**, has never been isolated from natural sources. Several methods for the synthesis of optically active nepetalactone from citral, citronellal, pulegone, or limonene have been reported, all of which required several synthetic steps.[10]

Recently, we reported the first NHC-catalyzed one-step bicyclization of 8-oxocitral (**2**) to *rac*-nepetalactone, using 1,4-bis-Mes/Dipp-1,2,4-triazolium salts (**3**/**4**, Scheme 1) as

Scheme 1. One-Step Synthesis of Nepetalactone by NHC Catalysis



precatalysts.[11] Unfortunately, our attempts to employ chiral NHCs to effect an enantioselective transformation of 8-oxocitral (**2**) have thus far met with frustration. We therefore turned our attention to an alternative approach, namely, the use of (*S*)- and (*R*)-8-oxocitronellal (**5**) as chiral pool substrates. The latter can easily be prepared from commercially available (*S*)- and (*R*)-citronellal[10a,b,12] or (*S*)- and (*R*)-citronellol[13] (Scheme 1). This strategy would require an external stoichiometric oxidant in the NHC-catalyzed bicyclization. On the other hand, as saturated aldehydes are less functionalized and more prevalent than their respective *α*,*β*-

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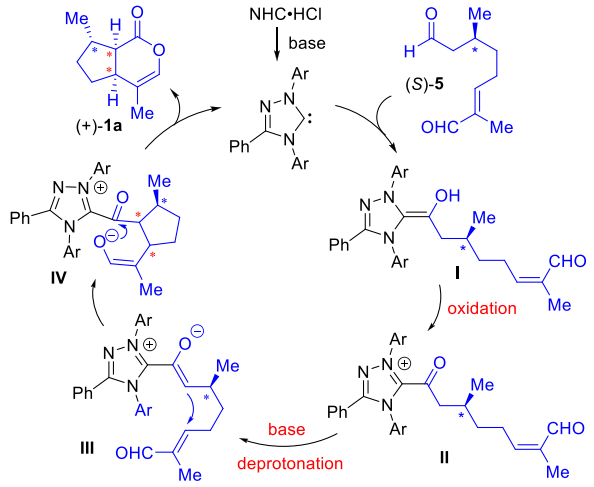
unsaturated counterparts, the resulting methodological improvement could be expected to be of broad applicability.

Our working hypothesis is demonstrated in Scheme 2. The reaction between the NHC and the aliphatic aldehyde moiety

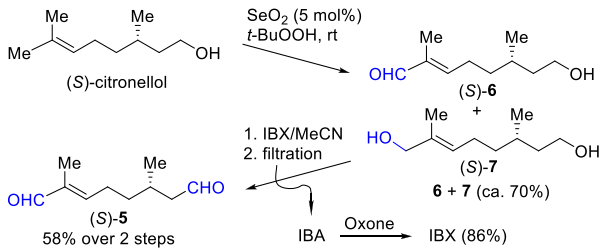
Scheme 2. Oxidative NHC-Catalyzed Bicyclization of 10-Oxocitronellal (5)



of **5** would give the Breslow intermediate **I**.[14,15] Subsequent oxidation[16,17] to the acyl azolium intermediate **II** followed by deprotonation would provide the chiral azolium enolate **III**. This key intermediate for bicyclization would induce the generation of enantiomerically pure nepetalactone possessing three chiral centers in a one-step fashion.[11] This obvious benefit prompted us to evaluate the feasibility of this concept (Scheme 2). Herein, we report the first one-step and diastereoselective conversion of (*S*)- or (*R*)-8-oxocitronellal to enantiomerically pure nepetalactones by NHC-catalysis under oxidative conditions. The stoichiometric oxidant could be easily recovered. Furthermore, several new, highly efficient, and "easy to make" triazolium precatalysts are disclosed.

Preparation of the substrate (*S*)-**5** for oxidative NHC catalysis studies was performed on multigram scale by two-step oxidation of (*S*)-citronellol, based on literature precedent (Scheme 3).[13] After allylic oxidation with SeO_2/*t*-BuOOH, the

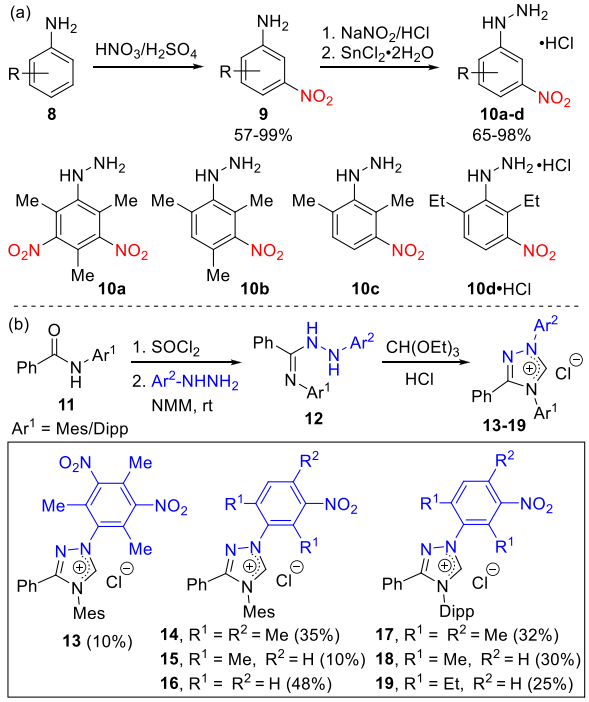
Scheme 3. Synthesis of 5 from Citronellol



crude mixture of **6** and **7** obtained was directly subjected to IBX oxidation in DMSO, furnishing **5** in moderate isolated yield (25−44%, lit.[13] 79% crude yield). We found that some impurities from the allylic oxidation have similar R_f to that of **5**, making purification of **5** in the end by column chromatography (CC) difficult. Therefore, we applied a short CC for purification of **6** and **7** prior to the IBX oxidation. We additionally observed that performing the IBX oxidation in MeCN as solvent was advantageous.[18] After filtration, the solid IBA byproduct obtained can be oxidized with aqueous Oxone,[19] providing 86% yield of recovered IBX. The desired (*S*)-**5** was obtained in 58% yield, over two steps, after purification.

For NHC catalysts, our previous study had revealed that only 1,2,4-triazolylidenes carrying mesityl (Mes) or 2,6-bis(2-propyl)phenyl (Dipp) groups at N1 and N4 efficiently catalyzed the one-step bicyclization of 8-oxocitral (**2**) to NL **1** (*cf.* Scheme 1).[11] The synthesis of the triazolium precatalysts mentioned required the use of Mes/Dipp-hydrazine hydrochlorides as one of the starting materials (*cf.* Scheme 4b). The

Scheme 4. Synthesis of New Triazolium Salts Carrying Nitro Groups as Precatalysts



latter were typically prepared from Mes/Dipp-Br via Grignard reaction with di-*tert*-butyl azodicarboxylate (BocN=NBoc), followed by Boc-deprotection.[11,20] The low purity and poor stability (very sensitive to air) of mesitylhydrazine[20b,21] and the difficulties of purification (requiring column chromatography)[11] of the corresponding bis-Mes-triazolium salt **3**, prompted us to investigate the synthesis of new triazolium derivatives bearing a nitro group (NO_2) on the arylhydrazine moiety (Scheme 4). We envisaged that the introduction of a nitro group, owing to its electron withdrawing effect, would reduce the reactivity of the proximal N of the hydrazine, and consequently steer the condensation with imidoyl chloride to the distal N, that is, to the formation of **12** (Scheme 4b). The resulting absence of isomeric products would greatly facilitate purification of the triazolium salt.

Pleasingly, the hydrazines **10a−d** (Scheme 4a) could be conveniently prepared from the corresponding anilines **8** in two steps by nitration with nitric acid (1 or 2 equiv),[22] followed by a diazotization/reduction process.[20b,23] The free hydrazines **10a−c** are solids obtained in high purity by simply washing with Et_2O and are not sensitive to air. The free hydrazine **10d** is an oil, preferably stored as its hydrochloride salt. Next, the triazolium salts were synthesized via a simple

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three-step sequence (purification only in the final step) starting from the benzamide **11** (Scheme 4b), readily prepared in 50 g scale from Mes/Dipp-aniline (see the SI). To our delight, the new triazolium salts **13**–**19**, derived from hydrazines **10a**–**d** and the commercially available 3-nitrophenylhydazine hydrochloride, could be easily purified by simply washing the crude product with EtOAc several times.

We obtained crystalline samples of triazolium salts **14**, **16**, **17**, and **18** suitable for single crystal X-ray structural analysis, as shown in Figure 2. All crystal structures were similar in the

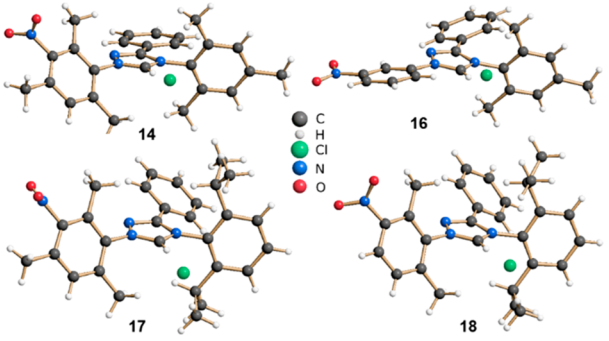


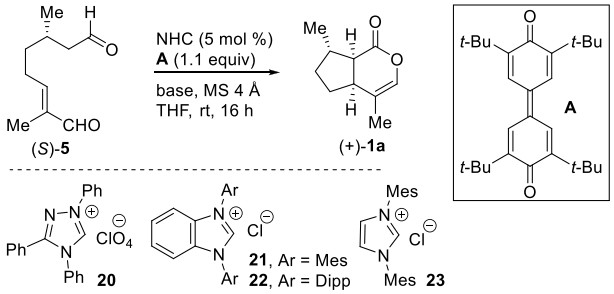
Figure 2. X-ray crystal structures of **14**, **16**, **17**, and **18**.

sense that the N-substituents carrying ortho,ortho′-disubstituents on the aryl group are almost perpendicular to the triazolium ring, while the *m*-nitrophenyl ring at N1 of **16** is almost coplanar with the triazolium core.

With the new triazolium precatalysts in hand, we set out to investigate the one-step transformation of (*S*)-**5** to nepetalactone (+)-**1a** (Table 1). With K_2CO_3 as the base, among the oxidants examined (MnO_2, phenazine, riboflavin derivatives), quinone **A**, an oxidant pioneered by Studer and co-workers for NHC catalysis,[24] was identified as the most effective one. In the presence of 5 mol % triazolium **3** or **4**, the desired (+)-**1a** was obtained in excellent yields and diastereoselectivities (entries 1 and 2). Various NHCs were then tested under identical conditions. To our delight, all of the new triazolium precatalysts **13**–**15** and **17**–**19** provided the product (+)-**1a** in excellent yields and diastereoselectivities (entries 3–5 and 7–9). On the other hand, the mono-Mes-substituted triazolium salt **16** gave moderate yield and diminished diastereoselectivity (entry 6), indicating the important role of the ortho,ortho′-disubstitution of the N1-aryl group of the triazolium precatalysts. The parent *N*-phenyl triazolium salt **20** (protonated Enders–Teles carbene)[25] showed moderate activity and poor diastereoselectivity (entry 10). The bis-Mes/Dipp-benzimidazolium salts **21** and **22**[15d] also displayed excellent diastereoselectivities, yet reactivities were lower than those of the triazolium analogues (entries 11 and 12 versus entries 1 and 2). For this transformation, IMes (**23**) was catalytically inactive (entry 13).

Interestingly, excellent diastereoselectivities were observed with the group of N4-Mes-substituted precatalysts **3**, **13**–**15**, and **21**, affording (+)-**1a** as the only product isomer (entries 1, 3–5, and 11), while the group of N4-Dipp-substituted precatalysts **4**, **17**–**19**, and **22** delivered slightly lower selectivities (entries 2, 7–9, and 12). From the group of N4-Mes-triazolium salts, **14** emerged as the catalyst of choice, due to the ease of its purification and synthesis in high yield. With **14**, we examined the effect of different bases. At higher substrate concentration of 0.4 M in THF, K_2CO_3 showed low

Table 1. Screening of Reaction Conditions for the NHC-Catalyzed Transformation of (*S*)-5 to (+)-1a[a]



entry	catalyst	base (equiv)	yield[b] (%)	1a ds[b] (%)
1	**3**	K_2CO_3 (0.5)	92	>99
2	**4**	K_2CO_3 (0.5)	95	97
3	**13**	K_2CO_3 (0.5)	90	>99
4	**14**	K_2CO_3 (0.5)	92	>99
5	**15**	K_2CO_3 (0.5)	92	>99
6	**16**	K_2CO_3 (0.5)	60	88
7	**17**	K_2CO_3 (0.5)	93	97
8	**18**	K_2CO_3 (0.5)	92	96
9	**19**	K_2CO_3 (0.5)	92	96
10	**20**	K_2CO_3 (0.5)	45	44
11	**21**	K_2CO_3 (0.5)	68	>99
12	**22**	K_2CO_3 (0.5)	82	95
13	**23**	K_2CO_3 (0.5)	0	
14[c]	**14**	K_2CO_3 (0.2)	59	>99
15[c]	**14**	NaOAc (0.2)	91	>99
16[c]	**14**	LiOAc (0.2)	90	>99
17[c,d]	**14**	LiOAc (0.2)	79	>99
18[c]	**14**	DIPEA (0.2)	92	>99
19[c,d]	**14**	DIPEA (0.2)	91	>99

[a]Reaction was performed with 0.1 mmol of (*S*)-**5** in THF (0.5 mL), unless noted otherwise. For entries 1, 2, 4, 5, and 7–9, the substrate was completely consumed after ca. 6 h, whereas in the cases ofentries 6, 10–12, the reactio did not go to completion after 16 h. "MS" stands for molecular sieves. [b]Determined by GC using dodecane as internal standard; "yield" denotes to the sum of all diastereoisomers obtained; "diastereoselectivity" indicates the percentage of (+)-**1a** present in the total yield. [c]Solvent = 0.25 mL, reaction time 5 h; in the cases of entries 14 and 17, the reaction did not reach completion. [d]The reaction was performed in toluene.

activity, presumably because of poor solubility (entry 14), whereas the use of NaOAc, LiOAc, and DIPEA resulted in excellent yields (entries 15, 16, and 18). Changing the solvent to toluene led to no noticeable change in results when DIPEA was used as the base (entry 19). Lower reactivity was observed with LiOAc, presumably because of lower solubility (entry 17).

With the optimized reaction conditions at hand, we further developed the procedure for the synthesis of (+)-**1a** from (*S*)-**5** on gram scale, at the same time aiming at recovering the oxidant **A**/**A**-H_2 from the reaction mixture to overcome potential drawbacks of its stoichiometric use. Note that the oxidant **A** was readily prepared from 2,6-di-*tert*-butylphenol on 50 g scale, simply by stirring open to air in the presence of KOH in H_2O/*t*-BuOH.[26] The synthesis of (+)-**1a** was performed on 10 mmol scale of (*S*)-**5** using the triazolium salt **14** (5 mol %), DIPEA (20 mol %), and the oxidant **A** (1.1 equiv) in THF at rt (Scheme 5). After completion of the reaction, **A**-H_2/**A** could be readily isolated by precipitation in MeOH–H_2O and filtration. Gratifyingly, the recovered **A**-H_2 could be recycled to **A** in 90% yield (after recrystallization) by

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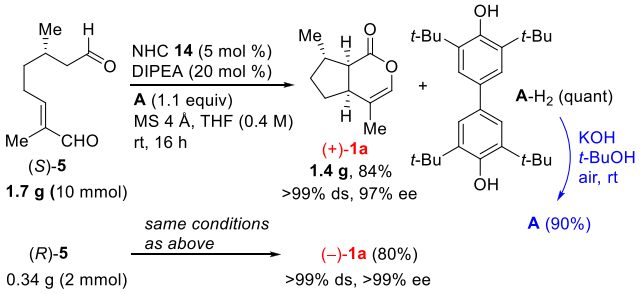
Scheme 5. Enantiospecific Synthesis of the Nepetalactone Enantiomers (+)-1a and (−)-1a



applying the same method as described for the synthesis of **A**. The nepetalactone was isolated by extraction and purified by the Kugelrohr distillation, affording (+)-**1a** in 84% yield with ds > 99% and ee = 97% {chiral GC; $[\alpha]^{20}_{D}$ +21.9 (*c* 0.25, Et_2O); lit.[10b] +20.6 (*c* 0.24, Et_2O; > 95% ee by NMR)}. (−)-**1a** was prepared in the same manner starting from (*R*)-**5** on 2 mmol scale and obtained in 80% yield with ds > 99% and ee > 99% {chiral GC; $[\alpha]^{20}_{D}$ −22.4 (*c* 0.25, Et_2O); lit.[10b] −21.0 (*c* 0.17, Et_2O; > 95% ee by NMR)}. Note that the lower ee of (+)-**1a** (97%) relative to the ee of (−)-**1a** (>99%) does not result from an erosion of enantiopurity in the course of the preparation of the dialdehyde (*R*)-**5** or the oxidative bicyclization of the latter to (+)-**1a**. Instead, analysis of the commercial citronellol enantiomers used as starting materials revealed 97% ee for the (*S*)-enantiomer, and >99% ee for its (*R*)-antipode (see SI for the details of the analysis). In other words, the enantiomeric compositions of the nepetalactone products (−)-**1a** and (+)-**1a** correspond exactly to those of the citronellol starting materials.

In conclusion, we have developed a novel triazolylidene-catalyzed one-step transformation of 8-oxocitronellal to nepetalactone under oxidative conditions. A new series of "easy to make" triazolium salts carrying nitroaromatic substituents on N1 was synthesized and evaluated. It was found that ortho,ortho′-disubstituted aryl groups on both N1 and N4 of the triazolium precatalyst played an important role in enhancing the catalytic activity, presumably due to dispersive stabilization of reaction intermediates.[11,27] The best diastereoselectivity for the transformation of **5** to **1a** was obtained with N4-Mes-substituted triazolium catalysts. From the latter, **14** emerged as the catalyst of choice, owing to the ease and high yield of its preparation. With our newly developed method, both natural (+)-nepetalactone **1a** and its unnatural (−)-enantiomer could be synthesized at will in diastereomerically pure form, starting from commercially available (*S*)- and (*R*)-citronellol, respectively. We expect that the convenient methodology presented herein can be extended to the synthesis of structurally related targets.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04034.

Detailed experimental procedures, spectral and X-ray data (PDF)

Accession Codes

CCDC 1961413−1961416 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

†J.-M.N. performed X-ray crystallography.

Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to the late Prof. Dieter Enders.

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