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Access to Benzylic Quaternary Carbons from Aromatic Ketones

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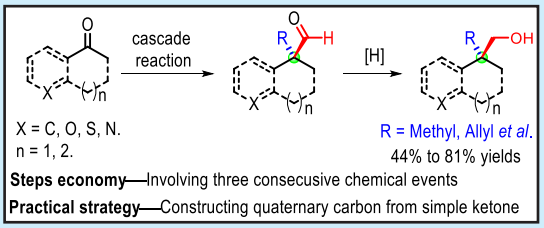
Supporting Information

ABSTRACT: The construction of benzylic all-carbon quaternary stereocenters, which are ubiquitous in biomolecules and drugs, is a task of high practical significance. Herein, we disclose a highly efficient one-pot method of constructing all-carbon quaternary structural units from aryl ketones, revealing that the entire process involves three consecutive chemical events, namely nucleophilic addition, Meinwald 1,2-hydrogen migration, and alkylation. Interestingly, dimerization of acetophenones results in formation of 2,4-diarylfurans under the employed conditions rather than the quaternary carbon products.



Substituent change is an effective way to increase the biological activity of drugs.[1] In particular, all-carbon quaternary stereocenters, i.e., those featuring carbon bonded to four carbon substituents, can address a myriad of structural diversity and conformational constraint issues in medicinal chemistry. However, such stereocenters are difficult to synthesize in view of the spatial congestion around the central carbon, which highlights the need for the development of new synthetic strategies.[2] As indicated in Figure 1a, many of the recently developed strategies construct quaternary carbon centers from sp^2-hybridized carbon-containing substrates such as substituted olefins,[3] enolate equivalents,[4] and carbenoids;[5] however, the synthesis of these substrates is trivial and usually involves multiple functional group interconversions. Thus, the development of general methods for the rapid and direct conversion of simple widespread groups into core structural units is a task of high practical significance.

The development of a method allowing the construction of all-carbon quaternary stereocenters from ketones would obviate lengthy and laborious substrate syntheses; nonetheless, the corresponding research remains rare. Trost and co-workers pioneered the construction of quaternary carbons via the condensation of ketones with diphenylsulfonium cyclopropylides.[6] However, this transformation is limited to the preparation of α-quaternary carbon cyclobutanones and is rarely used in other aspects. Recently, Pace and co-workers have accessed allylic all-carbon quaternary stereocenters utilizing an impressive and highly efficient cascade reaction limited to α,β-unsaturated ketones as substrates.[7] Thus, strategies using the carbonyl group for the construction of quaternary stereocenters need to be further developed.

Benzylic all-carbon quaternary units are ubiquitous in many natural products and pharmaceuticals (Figure 1b) and often serve as versatile building blocks to access bioactive molecules.[8] For example, galanthamine is used for the early treatment of Alzheimer's disease,[9] and carinatine A, isolated from the traditional Chinese medicine *Phlegmariurus carinatus*, is used to treat rheumatism, swelling, and pain,[10] while sporochnol, isolated from the Caribbean marine alga *Sporochnus bolleanus*, is a herbivorous fish deterrent.[11]

Inspired by the ubiquity of the keto group and the pharmaceutical importance of benzylic all-carbon quaternary stereocenters, we herein developed a highly efficient and practical strategy of directly constructing benzylic quaternary stereocenters from aryl ketones via three consecutive transformations. The first of these transformations, namely the reaction of aromatic ketones with CH_2I_2 and MeLi, affords epoxides,[12] LiI, and MeI (Figure 1c). Subsequently, epoxides are converted into aldehydes via LiI-catalyzed Meinwald-type 1,2-H migration,[13] and α-alkylation of these aldehydes affords the desired quaternary carbon centers. The above three-steps reaction can be conducted in a one-pot manner; however, several side reactions and problems may occur, i.e., the formation of tertiary alcohols via the nucleophilic attack of carbonyl groups by MeLi; generation of carbonyl α-methylation products in the presence of MeLi and CH_3I; and low alkylation yields due to the steric hindrance of α-benzylic aldehydes.

To examine the feasibility of the hypotheses, the α-tetralone (**1a**) served as a model substrate to commence our studies (Table 1). Fortunately, α-tetralone (**1a**) was converted successfully into the desired aldehyde (**2a′**) in the presence of 1.2 equiv CH_2I_2 in THF when MeLi (1.2 equivlents) was added at 0 °C and warmed up to room temperature stirred for 6 h. Considering the lability, the aldehyde (**2a′**) was isolated by flash column chromatography and reduced to alcohols (**2a**) (Table 1, entry 1). The yield of **2a** could be improved by adding MeLi at −78 °C (entry 2), and a further yield improvement (to 75%) was achieved by increasing the amount

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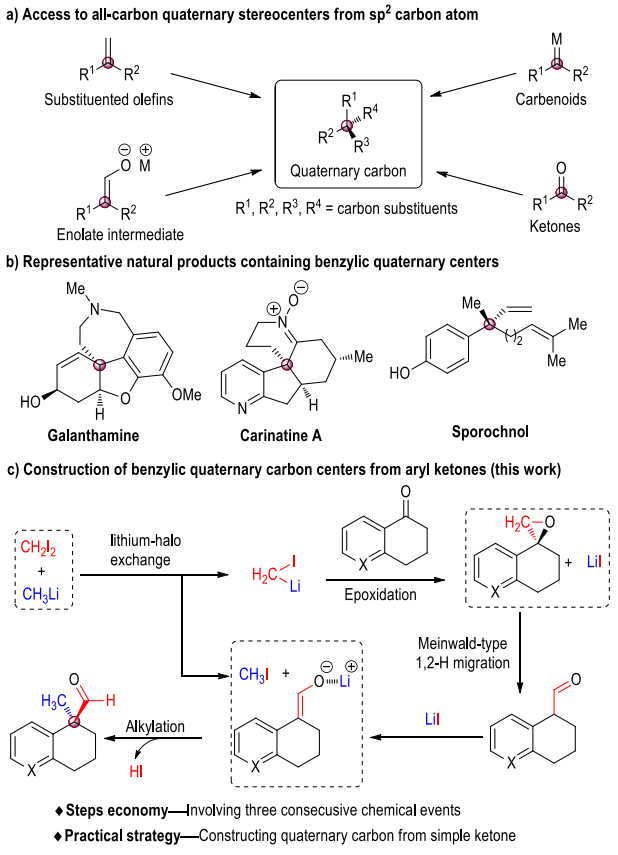
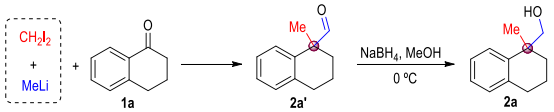


Figure 1. (a) Access to all-carbon quaternary stereocenters from sp^2 carbon atom, (b) representative natural products containing benzylic quaternary centers, and (c) strategy of all-carbon quaternary center construction used in the present study.

Table 1. Optimization of Reaction Condition[a]



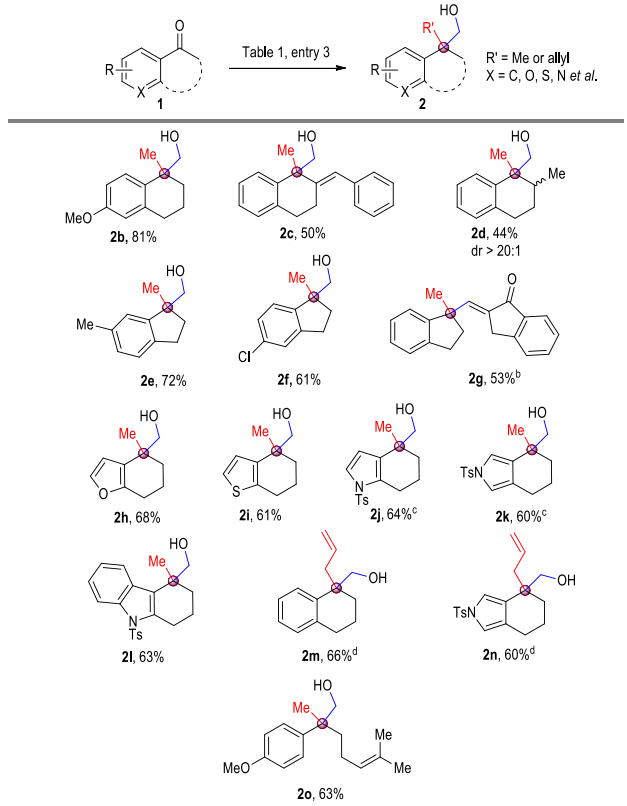
entry	CH_2I_2/MeLi (equiv)	temp (°C)	solvent	time (h)	yield (%)[b]
1	1.2/1.2	0 to rt	THF	6	20
2	1.2/1.2	−78 to rt	THF	6	31
3	2.2/2.2	−78 to rt	THF	6	75
4	2.2/2.2	−78 to rt	Et_2O	6	56
5	2.2/2.2	−78 to rt	toluene	6	40
6[c]	2.2/2.2	−78 to rt	THF	6	trace
7[d]	2.2/2.2	−78 to rt	THF	6	trace

[a]Unless otherwise noted, the reactions of ketone **1a** (0.20 mmol) and CH_2I_2 (2.2 equiv) were performed in 4 mL THF, MeLi (2.2 equiv) was added at the indicated temperature and warmed up to rt stirred for 6 h under Ar. The aldehyde **2a′** was obtained by flash column chromatography. Then the aldehyde **2a′** was reduced with $NaBH_4$ (1.0 equiv) in MeOH (2 mL) at 0 °C for 10 min. [b]Isolated yields. [c]$CeCl_3$ (1.0 equiv) was added. [d]CH_2Br_2 instead of CH_2I_2.

of CH_2I_2/MeLi to 2.2 equiv (entry 3). Solvent screening indicated that THF is the best solvent (entries 4 and 5), and no further yield increase was achieved. Notably, aldehyde formation was severely suppressed in the presence of $CeCl_3$ (entry 6), and the use of CH_2Br_2 instead of CH_2I_2 afforded a complex mixture containing only trace amount of the desired product (entry 7).

With the optimized conditions in hand, we investigated the substrate scope of the above transformation (Table 2),

Table 2. Substrate Scope[a]



[a]Unless otherwise noted, all reactions were performed with ketone (0.20 mmol), CH_2I_2 (2.2 equiv) in THF (4 mL), MeLi (2.2 equiv) was added at −78 °C and warmed up to rt stirred for 6 h under Ar. The aldehyde was obtained by flash column chromatography. Then the aldehyde was reduced with $NaBH_4$ (1.0 equiv) in MeOH (2 mL) at 0 °C for 10 min. Yields of the isolated product. [b]No reduction progress. [c]$ClCH_2I$ was used instead of CH_2I_2. [d]Allyl bromide (3.0 equiv) was added.

revealing that the highest yield of the desired product (**2b**) was obtained for 6-methoxytetralone (**1b**). For selectivity investigation, α,β-unsaturated naphthalenone (**1c**) was reacted under the standard reaction conditions to furnish an allylic quaternary carbon center with excellent chemoselectivity and in acceptable yield. Similarly, α-methyl tetralone (**1d**) afforded the desired product with high diastereoselectivity (dr >20:1) and in moderate yield. In addition, indanones were also compatible with the standard conditions; e.g., species bearing electron-donating (methyl group, **1e**) and electron-withdrawing (chloro group, **1f**) substituents were converted into the desired products in high yields. Intriguingly, non-substituted indanone **1g** yielded an aldol condensation product **2g**, rather than desired aldehyde product. **2g** was formed in situ between aldehyde product **1g′** and substrate **1g**. This condensation reaction could not be suppressed by variation of reaction conditions, in which case unidentified mixtures and decreased yields were observed.

To increase the synthetic utility of the developed strategy, we applied it to heteroaromatic ketones (**1h**−**1l**) with furan,

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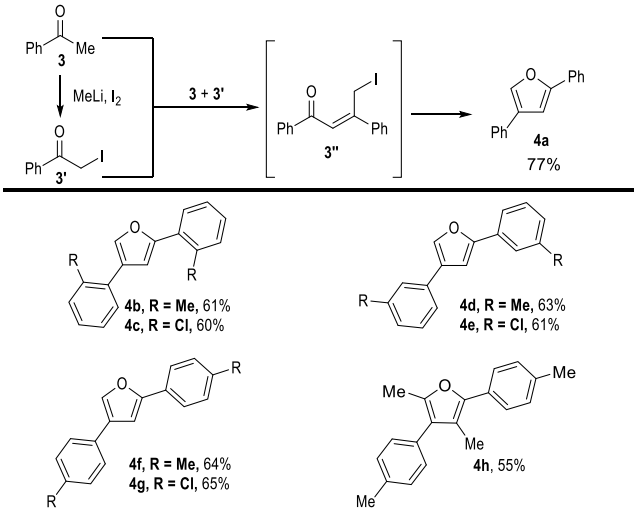
thiophene, pyrrole, and indole moieties, obtaining the corresponding quaternary carbon centers in satisfactory yields (**2h**–**2l**).

As the above cascade reaction was well suited for the construction of methyl-substituted quaternary carbons, we decided to examine the effects of additional electrophiles to enhance product diversity and practicability. In particular, allyl bromide was used as an electrophile to form multifunctional quaternary carbon units. When 3.0 equiv of allyl bromide were added to the reaction system, products **2m** and **2n** containing allyl-substituted quaternary carbons were obtained in 66% and 60% yield, respectively, which indicated that allyl bromide could be trapped by the enolate intermediate.

Finally, acyclic aromatic ketones were investigated to further expand the substrate scope. Ketone **1o** bearing a tethered alkene substituent afforded an acyclic quaternary carbon-containing product (**2o**) in 63% yield. However, when acetophenone (**3**) was employed, 2,4-diphenylfuran (**4a**)[14] was isolated in 41% yield instead of the expected quaternary carbon product (Table 3). This unexpected result was ascribed

Table 3. Syntheses of Furans from Acetophenones[a,b]



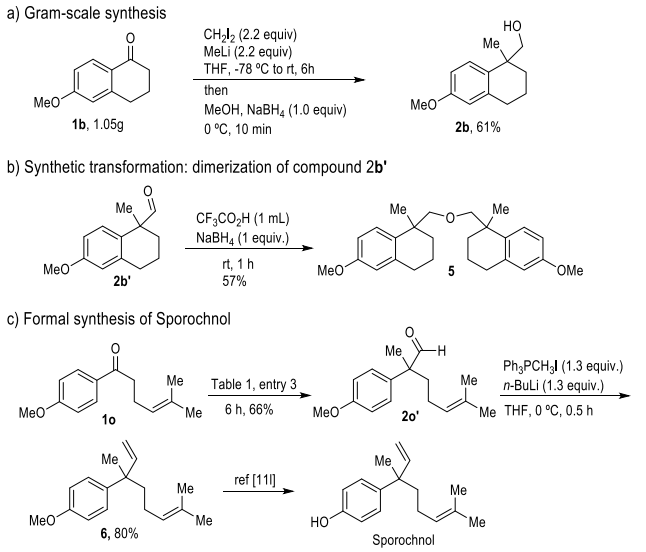
[a]Reaction condition: **3** (0.20 mmol), MeLi (4.4 equiv), I_2 (1.1 equiv) in THF (4 mL), Ar, 0 °C, 4 h. [b]Yields of isolated product.

to the formation of α-iodo-acetophenone (**3′**)[15] in the presence of I_2 generated from LiI under oxidative conditions. The aldol condensation of **3** and **3′** afforded chalcone derivative **3′′**, and subsequent annulation furnished the furan product.[14b]

Syntheses of furans from simple ketones through a series of chemical transformations especially condensation of acetophenone and haloacetophenone remain rare.[14c] Therefore, we decided to increase the yield of furans obtained under our conditions. After a brief optimization of reaction conditions (4.4 equiv MeLi, 1.1 equiv I_2, THF, 0 °C, 4 h), the yield of **4a** was increased to 77%. Substrates with aryl moieties bearing both electron-donating and electron-withdrawing groups readily participated in this transformation, affording the desired products (**4b**–**4g**) in good yields with no significant differences (Table 3). *para*-Methyl phenylacetone is also suitable for this reaction, with a slightly decreased yield (55%). This transformation was concluded to be an effective strategy for the synthesis of 2,4-diaryl furans.

To demonstrate the practical utility of the developed method, a gram-scale reaction was performed, leading to the formation of **2b** with 61% yield (Scheme 1a). Also, it was

Scheme 1. Synthetic Transformation and Application



applied to the synthesis of structurally interesting molecules and bioactive natural products. Notably, **2b′** (obtained from **1b** in 84% yield) was converted into symmetric ether **5** via reduction with $NaBH_4$ in CF_3CO_2H (Scheme 1b). Next, our method was applied to the synthesis of (±)-sporochnol.[12] Under standard conditions, aldehyde **2o′** was generated from **1o**, CH_2I_2, and MeLi in 66% yield, and the following Wittig methylation of **2o′** gave terminal alkene **6** in 80% yield, which completed the formal synthesis of (±)-sporochnol (Scheme 1c).

In summary, the transformation of aromatic ketones into benzylic all-carbon quaternary stereocenters has been achieved via three consecutive chemical events in one pot, and this strategy is of high practicability for the synthesis of natural products and pharmaceuticals. In particular, the developed method was employed in the formal synthesis of sporochnol and the selective synthesis of furans from acetophenones. Thus, we anticipate that our methods will be widely used in the synthetic community. Further use of this strategy is in progress, and the results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02204.

Experimental procedure, characterization data and spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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