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Synthetic Methods

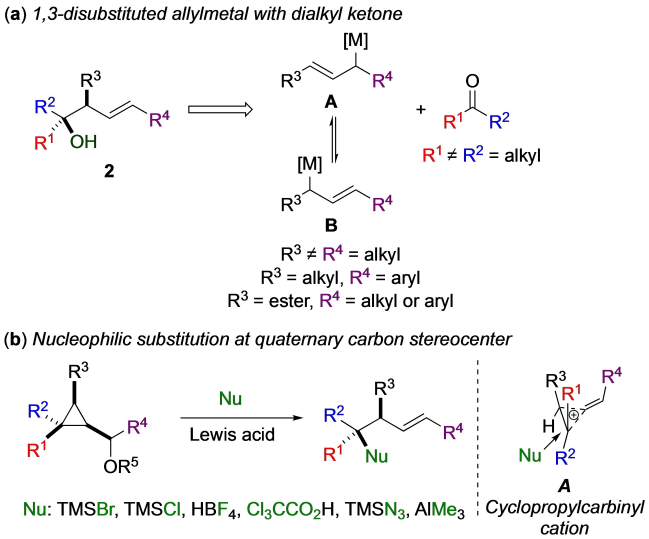
Stereoselective Construction of Tertiary Homoallyl Alcohols and Ethers by Nucleophilic Substitution at Quaternary Carbon Stereocenters

*Xu Chen[+], Kaushalendra Patel[+], and Ilan Marek**

Abstract: An efficient method for the stereoselective construction of tertiary C–O bonds via a stereoinvertive nucleophilic substitution at the quaternary carbon stereocenter of cyclopropyl carbinol derivatives using water, alcohols and phenols as nucleophiles has been developed. This substitution reaction proceeds under mild conditions and tolerates several functional groups, providing a new access to the stereoselective formation of highly congested tertiary homoallyl alcohols and ethers.

Introduction

Over the last few decades, major efforts have been invested towards the controlled construction of open-chain molecular backbones bearing sequences of stereocenters such as those found in polyketides natural products.[1] Among the several strategies that have been extensively investigated,[2] the addition of allylmetal reagents to carbonyl groups have occupied a central place.[3] The key features of this success are the level of predictability, the high diastereo- and enantioselectivity, the metals-based diversity of potential reagents, the latent functionality of the homoallyl alcohol products.[4] Despite this important accomplishment, clearly promoting this transformation to the rank of a key strategy in organic synthesis, the control of the reactivity of 1,3-disubstituted allylmetal is a significant hurdle that didn't find a definite answer (Scheme 1a). How can we favor one of the two forms of the metallotropic equilibrium when R^3 and R^4 are two similar alkyl groups (i.e., **A** versus **B** with $R^3 \neq R^4$ = alkyl)?[4b] If we combine this challenge to the additional problem of reaction on dialkyl ketone[5] as represented in Scheme 1a, then no predictable transformation exists anymore. To bring an answer to this synthetic challenge, we surmised that a different strategy that would answer all issues of predictability for the diastereo- and enantioselective preparation of **2** would be highly desirable. In this context, we have recently reported that various nucleophiles (TMSX, Cl_3CCO_2H, $TMSN_3$, HBF_4, R_3Al) were able, in the presence of a Lewis acid, to promote a selective ring-opening of polysubstituted cyclopropyl carbinols[6] (and cyclopropyl ketones)[6d] at the most substituted carbon center (Scheme 1b). Recent theoretical calculations have shown that non-classical cyclopropylcarbinyl cation **A** is a stable intermediate that undergoes a nucleophilic substitution at the most substituted quaternary carbon center in a stereoinvertive manner.[7] Using this concept for the preparation of homoallyl alcohols **2** would require the contra-intuitive addition of water (or alcohols)



Scheme 1. Problems and potential solutions for the stereoselective construction of homoallyl alcohols **2**.

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in the presence of a Lewis acid.[8] However, many reactive intermediates and catalysts are decomposed by water and more particularly Lewis acid, that have been thought to be unstable in water and therefore incompatible.

Results and Discussion

New methods for highly stereoselective construction of C–O bonds using water as oxygen source are appealing.[9] Although more and more organic transformations are nowadays smoothly performed in water,[10] we were particularly interested by the behavior of the strong Lewis acid tris(pentafluorophenyl)borane $B(C_6F_5)_3$, that is often used to promote the formation of highly active cationic catalysts for olefin polymerization in the presence of water.[11] In such case, water coordinate to $B(C_6F_5)_3$ to form a new complex[12] that becomes a strong Bronsted acid performing well for the activation of alcohols.[13] Spurred by these central features, we set out to devise a strategy to address the challenging selective preparation of these three-dimensional molecular layouts. Importantly, this would be achieved in just three catalytic steps from alkynes involving readily available reagents. All the starting materials could first be easily prepared in the first two catalytic steps (Rh and Cu) as described in Scheme 2.[6a,14] It should be noted that cyclopropenyl esters could easily be prepared enantiomerically enriched by using dirhodium tris(diphenyltriflylimidazolidinone)(acetate).[15] All details could be found in the Supporting Information.

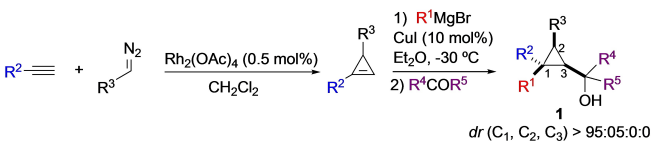
A particular attribute of our strategy is that the cyclopropyl carbinol moiety **1**, formed as a single diastereomer at C_1, C_2 and C_3 (Scheme 2), is made to serve as temporal auxiliary to subsequently promote high levels of stereochemical control. It should be noted that the stereochemistry at the carbinol center has no effect on the final stereochemical outcome of the transformation.[6]

Accordingly, when the model substrate **1a** (R^1 = Me, R^2 = Bu, R^3 = CO_2Et, R^4 = Ph, R^5 = H) was treated with 2 equivalents of H_2O in the presence of 10 mol % of $B(C_6F_5)_3$ in CH_3NO_2 as solvent (0.1 M) at room temperature for 12 h, the desired product **2a** was smoothly obtained in 78 % yield with an excellent diastereomeric ratio (*dr* > 95:05). It is important to note that the nucleophilic substitution occurs exclusively at the quaternary carbon stereocenter, and the selectivity is rationalized by the formation of the cyclopropyl carbinyl cation intermediate **A** as previously discussed in Scheme 1.[7]

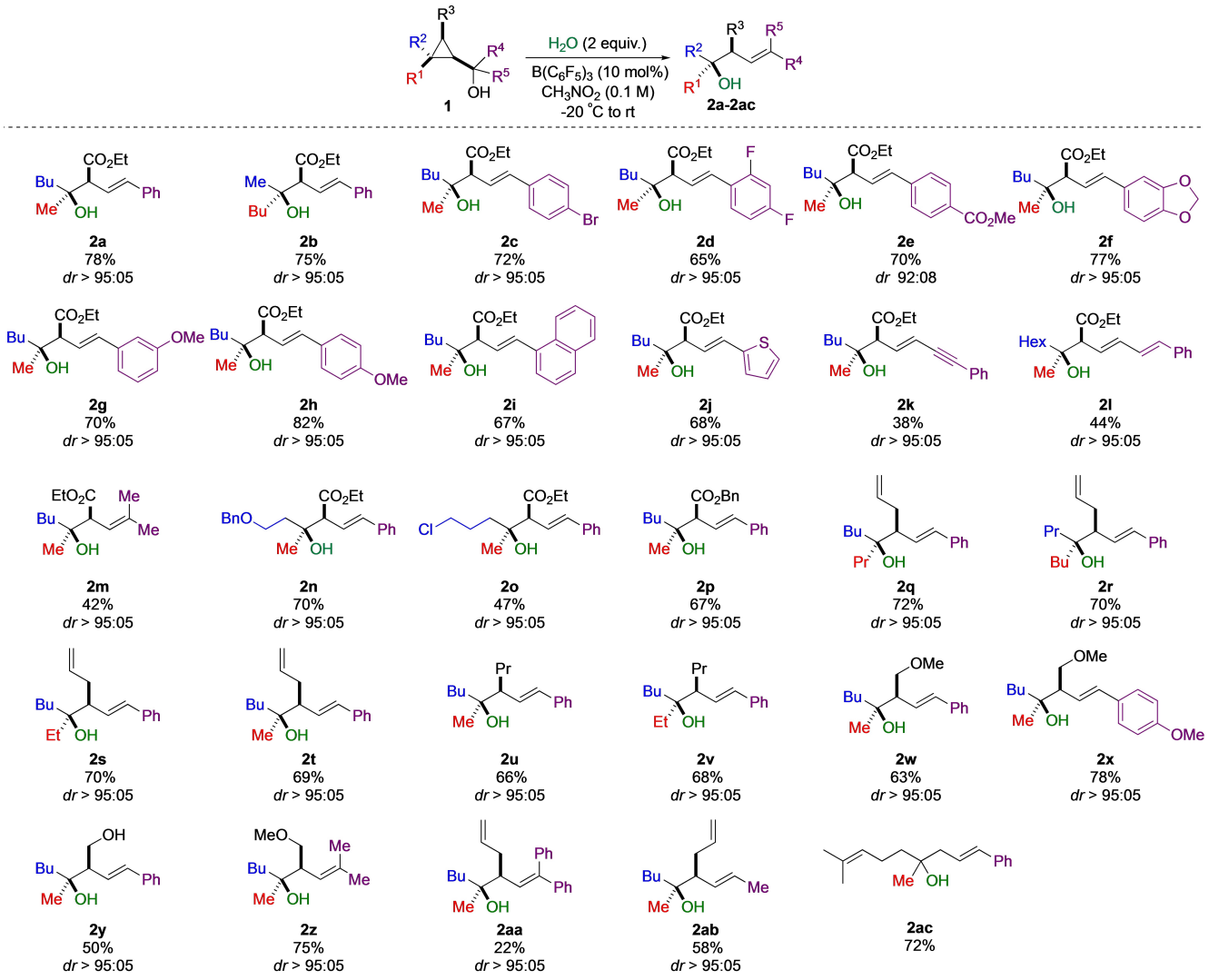
The opposite diastereomer **2b** could be easily prepared by permuting the nature of the two substituents at the quaternary carbon stereocenter (originally from the alkyne and the Grignard reagent) with an excellent diastereomeric ratio (*dr* > 95:05). The relative configurations were established by comparison with authentic samples and the reaction proceed in all cases with a pure inversion of configuration at the quaternary carbon stereocenter.[6,7] Various substituents of either electron-donating or electron-withdrawing groups on the aryl group could equally participate in the reaction and provide **2c**–**2i** in good yields and excellent diastereoselectivities. Cyclopropyl carbinol **1j** bearing electron-rich thiophene also underwent an efficient and selective nucleophilic substitution to give **2j**. Interestingly, the nature of the substituent R^4 can be varied and the presence of an enyne, diene or alkyl groups did not alter the outcome of the transformation (Scheme 3, **2k**–**2m**). The nature of the substituents R^2 can have functionalities such as OBn or Cl (**2n** and **2o** respectively, Scheme 3) underlining that the reaction proceeds selectively at the quaternary carbon stereocenter by cleaving a C–C bond in the presence of more reactive functional groups. The nature of the substituent R^3 could be successfully varied as an allyl (**2q** to **2t**), alkyl (**2u**–**2v**), ether groups (**2w** and **2x**) and even an alcohol moiety (**2y**) could be present. It should be noted that secondary non-aromatic (**2ab**) as well as tertiary alcohol (**2z** and **2aa**) also provide the desired product although in low yield for **2aa** due to a competitive intramolecular Friedel–Crafts reaction.[16] Cyclopropyl carbinol **1ac** prepared from geraniol could also be smoothly transformed to **2ac**.

Having an easy access to stereodefined homoallyl alcohols **2**, we then considered using the same strategy to prepare their ether counterparts. Indeed, hindered dialkyl ethers are of high values in medicinal chemistry as extensive sp^3-rich fragments substitution around ether bond increases the complexity of three-dimensional structure of a molecule as well as prevents unnecessary metabolic process that can lead to rapid degradation in vivo.[17] The Williamson ether synthesis[18] and Mitsunobu reaction[19] are two powerful tools for the preparation of primary or secondary alkyl ethers. However, due to their sterically sensitive nature, these reactions usually derail when hindered nucleophiles or electrophiles are considered. Although several alternatives have appeared in the literature in the last few years,[9j,20] the preparation of stereodefined tertiary alkyl ethers still represents a challenging transformation.

We were therefore wondering whether other weak or bulky nucleophiles such as alcohols and phenols could be used, which would provide a new access to stereodefined tertiary alkyl ethers (Scheme 4). When the same experimental conditions were used on a model substrate **1ad** (R^1 = Me, R^2 = Bu, R^3 = CH_2OMe, R^4 = Ph, R^5 = H, R^6 = Me) using 2 equivalents of MeOH in the presence of 10 mol % of $B(C_6F_5)_3$ in CH_3NO_2 as solvent at room temperature, only moderate yields were observed. However, and to our delight, when the reaction was performed in DCM at 0 °C in the presence of 2.5 mol % of $FeCl_3$ and slowly warm to room temperature, the corresponding tertiary ether **3a** was obtained in 79 % yield with an excellent diastereomeric ratio (*dr* > 95:05). The opposite diastereomer **3b** could be equally

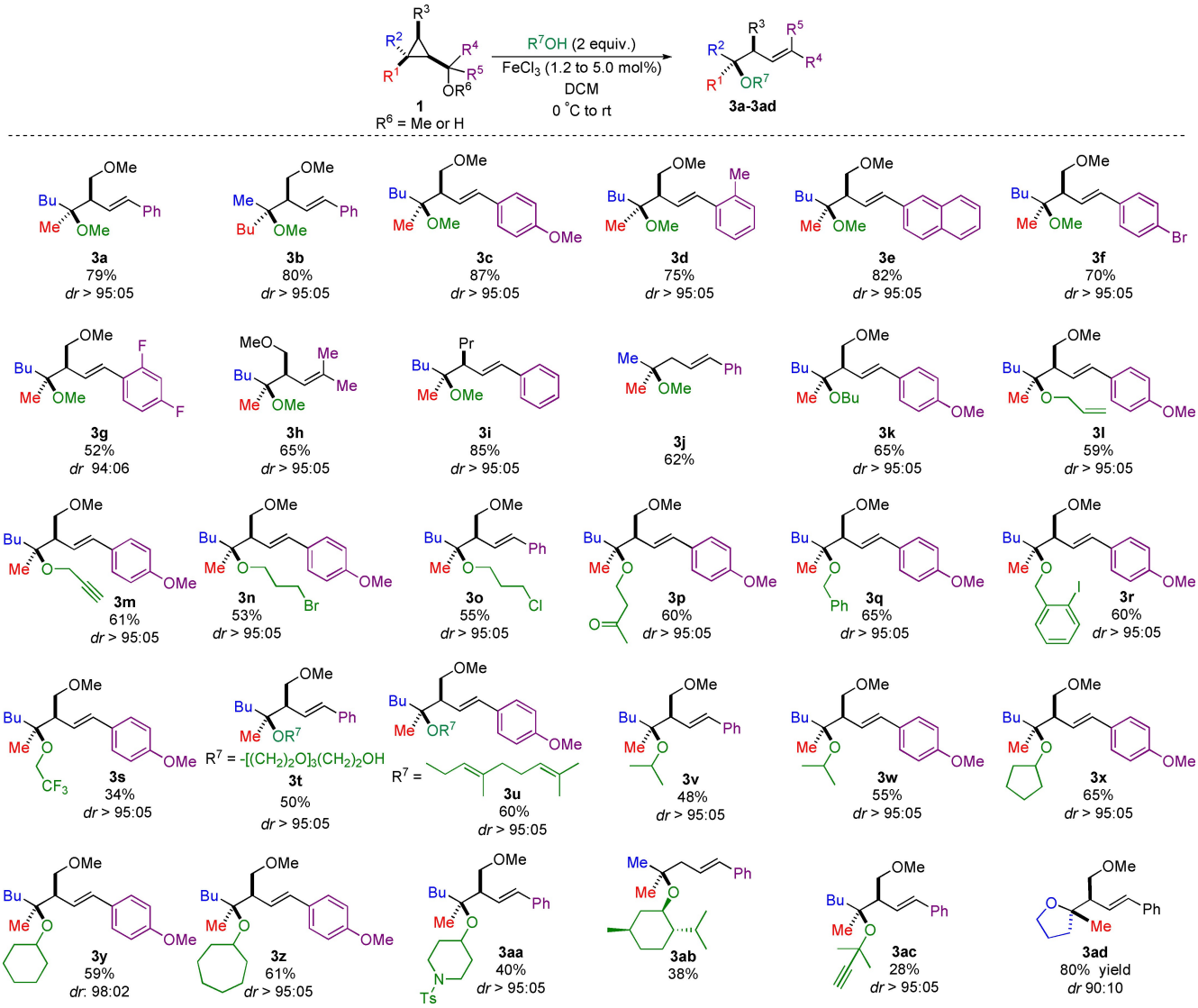


Scheme 2. General strategy for the preparation of starting materials.



Scheme 3. $B(C_6F_5)_3$-catalyzed nucleophilic substitution of cyclopropyl carbinols derivatives **1** with water. Yields for isolated products after purification by flash chromatography on silica gel and diastereomeric ratios were determined by NMR.

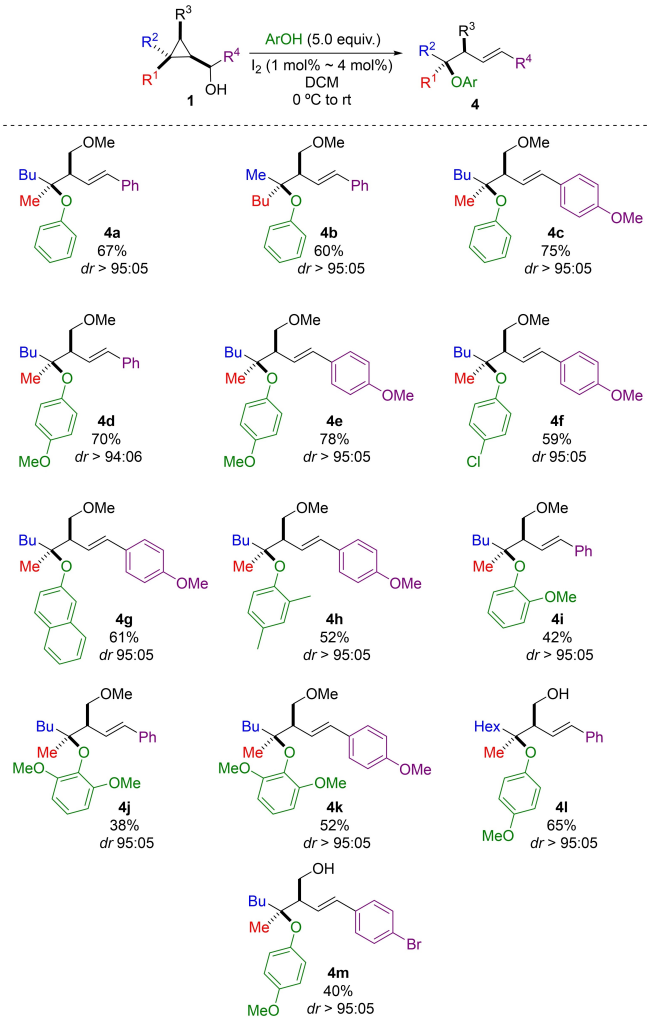
prepared via permutation of two substituents at the quaternary carbon stereocenter. Using methanol as nucleophile, various cyclopropyl ethers with electron-donating and -withdrawing groups were transformed into the corresponding tertiary alkyl ethers (**3c–3g**) in good yields with excellent diastereoselectivities ($dr > 95:05$). For the addition of MeOH, protected alcohols were used ($R^6 = Me$) whereas for all other addition reactions of alcohols, the parent cyclopropyl carbinols ($R^6 = H$) were used. Tertiary alcohol could also be transformed to ether **3h** with similar selectivities. It should be noted that $R^3 = CH_2OMe$ is not mandatary as **1al** ($R^3 = n$Pr) and **1am** ($R^3 = H$) were smoothly converted to **3i** and **3j**, respectively. The exclusive formation of tertiary ether **3j** from **1am** without formation of other constitutional isomer indicates that the nucleophile reacts at the most substituted carbon center, namely at the quaternary carbon center, still suggest the preferred pathway on the center possessing the highest positive character of the non-classical cyclopropylcarbinyl cation. Then, we explored the scope of alcohols in the stereoselective construction of tertiary C–O bond using cyclopropyl carbinols **1w, 1x** and **1am** as reaction partners. Thanks to the mild reaction conditions, a variety of functional groups were tolerated. The synthetically versatile terminal alkene (**3l**) and alkyne (**3m**) functional groups could be easily incorporated by using allylic and propargyl alcohols respectively as nucleophiles. Alkyl bromide (**3n**), chloride (**3o**) and ketone (**3p**), which might be eroded by basic or transition metal-catalyzed reaction conditions, were compatible in this reaction. 2-Iodobenzyl alcohol could be converted to ether **3r** in high yield. It is worth mentioning that the very poor nucleophile trifluoroethanol could also be transformed to fluorinated ether **3s** although in low yields but excellent selectivity. Monoprotected PEG ether **3t**, usually difficult to access, can be easily prepared just by changing the catalyst from $FeCl_3$ to I_2. Next, the more challenging sterically hindered secondary and tertiary alcohols were investigated (**3v–3ac**). Secondary alcohols were found to be competent coupling partners.



Scheme 4. $FeCl_3$-catalyzed preparation of stereodefined homoallyl ethers **3**. Yields of isolated products after purification by flash chromatography on silica gel and diastereomeric ratios were determined by NMR.

Both acyclic (**3v** and **3w**) and cyclic alcohols of various ring sizes (**3x–z**) participate in the reaction. Alcohol containing basic piperidine ring could also give ether **3aa**. L-Menthol as a naturally occurring chiral secondary alcohol could be tolerated (**3ab**). Interestingly, sterically demanding tertiary alcohols could also participate in the reaction to deliver the hindered bis-tert-alkyl ethers **3ac** with an excellent diastereoselectivity albeit with a low yield due to the presence of significant amount of alkene resulting from a competitive elimination reaction. It should be noted that *t*BuOH doesn't provide the expected product. Interestingly, this methodology could be extended to the synthesis of cyclic ether via an intramolecular nucleophilic substitution reaction as **3ad** was formed in 80 % yield with a 90:10 diastereomeric ratio.

A different type of ethers, namely aryl-alkyl ethers, are also common synthetic intermediates and are present in numerous natural products.[19,21] S_NAr (nucleophilic aromatic substitution) reactions[22] and transition-metal-catalyzed methodologies[23] have shown some success for the preparation of tertiary alkyl-aryl ethers, but the scope is often limited to highly activated aryl halides. Albeit some nice examples were reported,[22,24] the development of a new approach to stereodefined and sterically hindered tertiary alkyl-aryl ethers is still appealing. Encouraged by the successful realization of etherification reactions with aliphatic alcohols, we considered using phenols as nucleophiles. However, the key to success for this transformation was to replace the Lewis acid catalyst $FeCl_3$ for the addition of phenol as the latter form a complex with the former (called ferric chloride test).[25] Molecular iodine, a mild and low toxic Lewis acid, has attracted our attention for its good performance in the activation of alcohols.[26] To our delight, when **1w** was treated with phenol and 2 mol % of I_2 in DCM at room temperature, the corresponding tertiary-aryl ether **4a** was obtained in 67 % yield with a diastereoselectivity higher than 95:05 (Scheme 5).



Scheme 5. Iodine-catalyzed nucleophilic substitution of cyclopropyl carbinols with phenols. Yields of isolated products after purification by flash chromatography on silica gel and diastereomeric ratios were determined by NMR.

The opposite diastereomer **4b** could equally be prepared with similar selectivity and yield. Phenols containing electron-withdrawing and -donating groups on the *para*-position can be both converted to the aryl-alkyl ethers **4c**–**4g** in good yields with excellent diastereoselectivities. Generally, cyclopropanes possessing an electron-rich R^4 substituent lead to higher yields of the corresponding ether products (**4c** vs **4a**, **4e** vs **4d**, **4k** vs **4j**) underlining the easiest formation of the initial cyclopropylcarbinyl species. *Ortho*-methyl and -methoxy substituted phenols both can participate in the reaction to give the corresponding ethers **4h** and **4i** in moderated yields. Much to our delight, the extremely sterically hindered and electron-rich 2,6-dimethoxy-substituted aryl ethers **4j** and **4k** could be obtained in moderate yields with excellent diastereoselectivities (Scheme 5). It is also important to point out that tertiary alkyl-aryl ethers **4l** and **4m** containing a primary alcohol moiety could be smoothly prepared by preferentially breaking a carbon-carbon bond and reaction at the quaternary carbon center with a pure inversion of configuration. These results show that stereodefined polysubstituted homoallyl alcohols and ethers can now easily be prepared by using an alternative strategy using cyclopropyl carbinol as a central platform in only three catalytic steps from commercially available alkynes.

Conclusion

In conclusion, we have developed an efficient method for the stereoselective construction of tertiary C–O bonds via a highly regio- and stereo-selective nucleophilic substitution at congested quaternary carbon stereocenter of cyclopropyl carbinol derivatives using water, alcohols and phenols as nucleophiles. This transformation proceeds under very mild reaction conditions, displays remarkable substrate scope and occurs with a complete inversion of the stereochemical configuration at the quaternary carbon stereocenter, offering a new avenue to access otherwise synthetically challenging hindered stereodefined polysubstituted tertiary homoallyl alcohols and ethers with high stereopurity.

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Conflict of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: Allylic Compounds · Cyclopropanes · Nucleophilic Substitution · Stereoinvertion · Synthetic Methods

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