Copper(I)-Catalyzed Synthesis of Unsymmetrical All-Carbon Bis-quaternary Centers at the Opposing α-Carbons of Cyclohexanones

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ABSTRACT: We describe a new synthetic reaction that generates all-carbon bis-quaternary centers at the opposing side of α-carbons in cyclohexanone with four different substituents in a controlled manner. Catalyzed by Cu(MeCN)4BF4 salt, this chemistry is proposed to proceed via an intermediacy of unsymmetrical O-allyl oxyallyl cations, which undergo a sequence of regioselective nucleophilic addition with substituted indoles and diastereoselective Claisen rearrangement in a single synthetic operation. The stereochemical outcome of the products features the cis diastereorelationship between the two aryl groups at the α,α′-positions.

A trend in drug discovery has progressively shifted toward the exploration of chemical structures with stereocenters. As opposed to flat aromatic compounds that tend to exhibit low solubility and bioavailability as a result of π-stacking interactions, molecules with increasing fractions of sp3-hybridized carbon atoms have been shown to offer more advantageous biophysical properties. Moreover, drug candidates that contain high counts of sp3-hybridized carbons are more likely to exhibit effective and selective binding to therapeutic proteins, including those that are difficult to target. A particular type of stereochemical systems that have gained attentions is the quaternary centers. Quaternary centers are carbon atoms that are covalently bound to four other carbon atoms at their sp3 tetrahedral vertices. Prominently featured in natural products, quaternary centers have become attractive structural motifs for drug discovery.

One limitation that has prevented broader applications of quaternary centers in drug discovery can be attributed to the challenges associated with the synthesis of these sterically congested systems. Nonetheless, there have been efforts to develop synthetic reactions that produce quaternary centers, particularly at the α-carbon of carbonyl compounds. A carbonyl system that has been scrutinized is unsymmetrical ketones that possess two similarly acidic α-hydrogens, viz. 1. The α-quaternarization of this motif could be challenging, as such a successful transformation to substituted ketones 2 would rely on judiciously designed elements to control regioselectivity. Recent methodologies that address this synthetic undertaking can be found, for instance, in the elegant work of Stoltz, who developed an extensive repertoire of transition-metal-catalyzed decarboxylative allylic alkylation reactions.

Despite these profound advancements, examples of the functionalization of simple cyclic ketones at the opposing side of α-carbons with four different substituents to produce unsymmetrical bis-quaternary centers are scarce. Conceptually, this synthetic endeavor is challenging as barriers toward regioselectivity and diastereoselectivity must be regulated to produce a single isomeric product. Without these controls, bis-quaternarization of monosubstituted cyclohexanone 1 to α,α′-bis-quaternary ketones 3 would result in multiple regioisomers along with their respective diastereomers. The difficulty and complexity to create these bis-quaternary centers are evidenced. For instance, Yamaguchi demonstrated bis-quaternization of diphenyl ketone 4 with a mixture of GaMe3, n-BuLi, and (chloroethyl)triethylsilane. This reaction produced meso ketone 5 with modest diastereoselection. Another precedent was conveyed by Stoltz, who applied a tandem enantioselective decarboxylative allylic alkylation that transformed substrate 6 to bis-quaternary ketone 7. This product was isolated in 72% yield with 4:1 dr, favoring the C2-symmetric diastereomer.

In this paper, we convey a new synthetic method to install bis-quaternary centers at the α,α′-carbons of cyclic ketones with four different substituents while managing both regioselectivity and diastereoselectivity elements, mediated by our oxyallyl cation technologies (Scheme 1). Schematically, our proposed reaction began with α-hydroxy enol ether 8 that were decorated with three different groups from simple 1,2-diketone. Ionization of this substrate would generate protected oxyallyl cation 9a. The ensuing capture of this electrophilic species by nucleophiles could be performed in a regioselective manner, thus installing the first α-quaternary center. To construct the second α-quaternary center, reaction intermediate 9b underwent in situ...
diastereoselective migration of the protecting group from the oxygen atom to the opposing α-carbon.

Our initial studies are depicted in Scheme 2. To facilitate the intended O → C migration, we envisioned the utility of the Claisen rearrangement, which would require the protection of the oxyallyl cation as an O-allyl ether. A suitable model substrate was realized in α-hydroxy O-allyl-eneol ether 10, which contained three out of the four intended substituents, i.e., methyl, phenyl, and allyl groups. This compound was easily prepared in just two simple steps from 3-phenylcyclohexane-1,2-dione upon treatment with allyl bromide and K2CO3, followed by addition of methylmagnesium bromide. The fourth substituent was incorporated by exposing substrate 10 to indole and catalytic Py·TfOH in toluene at room temperature to introduce the α-quaternary center 12 in 93% yield. This reaction was assumed to occur via unsymmetrical O-allyl oxyallyl cation intermediate 11 that was captured by indole regioselectively at the α-methyl position. To generate the second α-quaternary center, compound 12 was heated in toluene at reflux to promote the Claisen rearrangement, which produced α,α′-bis-quaternary ketone cis-13 and trans-13 as a 4.1:1 mixture of diastereomers with a combined yield of 96%. The relative stereochemistry of the major diastereomer cis-13 was confirmed by the X-ray structure, in which the phenyl and indole groups were both positioned in the axial direction.

Attempts to improve diastereoselectivity in the Claisen rearrangement was then carried out by screening various Lewis acid catalysts that could hypothetically serve either as an oxyphilic activator or as a π-complex activator to compound 12. As shown in entries 1–3, BF3·OEt2, AgOTf, and Cu(OTf)2 caused decomposition. The effects of counter-anion were evaluated through the use of copper salts, such as CuCl2, CuSO4, Cu(acac)2, and Cu(NO3)2·6H2O (entries 4–7). Only a marginal improvement was noted. Nonetheless, we observed a remarkable enhancement in diastereoselectivity with either Cu(BF4)2·6H2O or Cu(MeCN)4BF4 catalysts. In fact, these reactions produced α,α′-bis-quaternary ketone cis-13 as a single diastereomer. To affirm that copper(I) and (II) species were responsible to drive the diastereocontrol, we evaluated NaBF4, AgBF4, and Ni(BF4)2·6H2O. Such catalysts did not yield consequential induction (entries 10–12). From the fundamental viewpoint, these screening results showcased a new mode of reactivity to dictate diastereoselectivity in the Claisen rearrangement involving simple cyclohexanone systems, in which the stereocontrol elements were provided by a catalyst and an α-quaternary center.

We envisioned that the Lewis acidity of copper(I) and (II) tetrafluoroborate could be also exploited to ionize α-hydroxy O-allylenol ether 10 to unsymmetrical O-allyl oxyallyl cation 11. Upon regioselective nucleophilic capture by indole, the Claisen reaction mixture.

**Scheme 1. Synthesis of Bis-Quaternary Centers at the α-Positions of Ketones**

**Scheme 2. Proof-of-Concept and Reaction Optimization**
The rearrangement of the emerging α-quaternary center 12 could be induced in situ by the same catalyst at an elevated reaction temperature to produce α,α′-bis-quaternary ketone cis-13 in a single synthetic protocol. Indeed, we were able to achieve this cascade transformation using catalytic Cu(MeCN)₄BF₄ salt in dichloroethane, from which product cis-13 was isolated in 94% yield as a single diastereomer. Detailed reaction optimization is discussed in the Supporting Information.

With the optimized conditions in hand, we evaluated the scope of reactions, starting with substituted indoles (Scheme 3). In these examples, our reactions produced the corresponding α,α′-bis-quaternary ketone products with >20:1 dr. Commencing with electron-rich 5-methoxy-, 6-benzyloxy-, 5-p-methoxyphenyl (PMP)-, and 5-hydroxy-substituted indoles, ketones 14a−14d were generated in 42−88% yields. Halogen-containing indoles were found to be compatible. For example, the use of 5-iodo-, 7-bromo-, and 5,6-dichloro-substituted indoles produced the respective ketones 14e−14g in good yields. Electron-deficient methyl-5-carboxylate indole and protected N-methylindole could be also employed to furnish ketones 14h and 14i in 58% and 73% yields, respectively.

The nature of the aromatic substituent at the α-carbon was then examined using a series of α-hydroxy O-allylenol ether substrates 15. While methoxyphenyl at the para- and meta-positions produced ketones 16a and 16b in 89% and 88% yields, respectively, a substantial erosion in yield of product 16c was noted with the ortho-counterpart. Other electron-donating substituents, such as benzodioxane and thiophenolate ether, produced the respective ketones 16d and 16e in excellent yields. Interestingly, substrate bearing a dimethylaminophenyl group failed to react, leading only to a recovery of the starting material. We surveyed halogen and electron-withdrawing groups, such as p-chlorophenyl, m-fluoro-p-methoxyphenyl, and p-trifluoromethylphenyl. These afforded products 16g−16i in good yields. Heteroaromatic substituents, such as N-methyl carbazole, benzothiophene, and 3-methylthiophene, were well tolerated to provide ketones 16j−16l in 69−95% yields.

The substituent effects in the O-allyl moiety were also examined using substrates 17. In this study, methyl, n-hexyl, and benzyl groups were introduced at the internal C2 position, which furnished α,α′-bis-quaternary ketones 18a to 18c in excellent yields.

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### Scheme 3. Scope of Reactions

| Substituted Indole | Aromatic Substituent | O-allyl Substituent |
|-------------------|----------------------|---------------------|
| ![Indole Structure](image1.png) | ![Aromatic Substituent](image2.png) | ![O-allyl Substituent](image3.png) |

| κ经验 | δ经验 | γ经验 |
|-------|-------|-------|
| 14a   | 14b   | 14c   |
| 88% (11 + 12 h) | 75% (41 + 16 h) | 73% (13 + 25 h) |
| 14d   | 14e   | 14f   |
| 42% (48 + 17 h) | 57% (18 + 22 h) | 48% (23 + 11 h) |

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"Isolated yield after column chromatography. "H NMR analyses of the crude mixture indicated >20:1 dr. The reaction was performed on a 1 g scale. Crude dr of compound 16c could not be determined due to the complex mixture."
satisfactory yields as a single diastereomer. The bromo variant was also tolerated by the reaction conditions to generate product 18d in 47% yield, but the Claisen rearrangement required a prolonged reaction time. We then proceeded to the phenyl group. While the creation of the α-indolyl bearing quaternary center proceeded in this case, the Claisen rearrangement to install the second α-quaternary center in product 18e unexpectedly produced complex mixtures upon heating. A similar phenomenon was also observed with an electron-withdrawing trifluoromethyl group in which the Claisen rearrangement led to decomposition instead of yielding ketone 18f.

Scheme 4 depicts a series of reactions to gather some mechanistic insights of this reaction. The copper(I) species was the active oxidation state of the catalyst. While our reactions were performed in typical benchtop settings, treatment of either substrates 10 and 12 with Cu(MeCN)₄BF₄ in an oxygen-free glovebox also furnished the corresponding product cis-13 in excellent yields as a single diastereomer. The intermolecular interaction between the copper catalyst and the Claisen rearrangement substrate appeared to be rather labile as it was affected by simple steric changes in the α-aliphatic region. When effectively bound to α-methyl substrate 10, the catalyst would provide a strong governance toward the cis stereoselectivity. Nonetheless, replacement of the α-methyl group with ethyl in α-hydroxy O-allylenol ether 19 rendered the copper-catalyzed Claisen rearrangement nondiastereoselective. The O → C allyl migration appeared to have proceeded via an intramolecular Claisen rearrangement, as opposed to the alternative transition-migration pathway. The O-hydroxy group was not essential for the noted stereoselectivity. As corroborated in α-indolyl substrate 21 and 22a produced a mixture of α,α′-bis-quaternary ketones 16a and 22b. None of the crossover products were detected in the crude reaction mixture by ¹H NMR analyses. The allyl migration itself was found to be stereospecific, as (Z)-deuterated substrate 23a generated the corresponding ketone 23b as a single diastereomer with the allyl group transpositioned at the γ-carbon.

The relative stereochemistry of the α,α′-bis-quaternary centers in many of our products were confirmed using X-ray crystallography. This analysis also revealed a peculiar conformation in which the cis aromatic groups were both placed in the axial position, thus allowing orientations of these rings within a reasonable distance for possible π-stacking interactions. While the origin of this diastereomeric outcome remained unclear, we deduced that the presence of both aryl groups was not essential for the noted stereoselectivity. As corroborated in α-indolyl substrate 24a, replacement of the phenyl substituent at the opposing side of the α-carbon with a methyl group led to the Claisen rearrangement under the catalytic conditions to produce monoaryl-substituted α,α′-bis-quaternary ketone 24b with a cis stereochemical outcome as confirmed by X-ray structure analyses. In contrast, the background thermal rearrangement furnished the product with an innate 3:7:1 diastereomeric ratio.

In conclusion, we have showcased a new method to synthesize unsymmetrical ketones bearing all-carbon bis-quaternary stereocenters at the α,α′-positions. Our chemistry converted a simple and readily accessible substrate in α-hydroxy O-allylenol ethers to highly complex, stereoechemically elaborate α,α′-bis-quaternary ketones in a single synthetic reaction. Cu(MeCN)₄BF₄ catalyst was found to be uniquely effective for this transformation. Further studies are ongoing in our laboratory. The results will be reported in due course.

ASSOCIATED CONTENT
Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c01890.

Experimental procedure and characterization data (PDF)
FAIR data, including the primary NMR FID files, for compounds cis-13, trans-13, 14a−14i, 16a−16e, 16g−16l, 18a−18d, cis-20, trans-20, 22b, 23b, and 24b (ZIP)

Scheme 4. Experiments to Gather Mechanistic Insights

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CCDC 2072233–2072242 and 2072247–2072248 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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Notes
The authors declare no competing financial interest.

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(15) (a) Subjecting an analogous 5-membered substrate to the optimized reaction conditions produced the corresponding cyclopentanone adduct in 65% yield as a 2.7:1 mixture of diastereomers, which were inseparable by column chromatography. The relative stereochemistry of the major diastereomer was not determined. See the Supporting Information. (b) The optimized reaction conditions were found to be compatible only with substituted indoles. Further studies to expand the scope of nucleophiles are ongoing.

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