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Cobalt-catalysed Stereoselective Synthesis of 2,5-trans-THF Nitrile Derivatives as a Platform for Diversification: Development and Mechanistic Studies.

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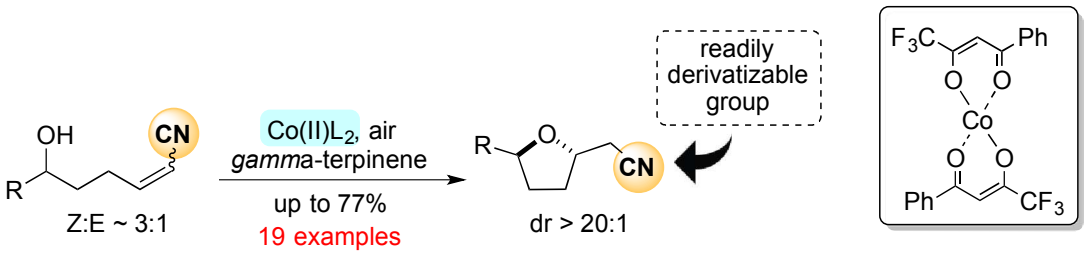
Graphical Abstract



Abstract

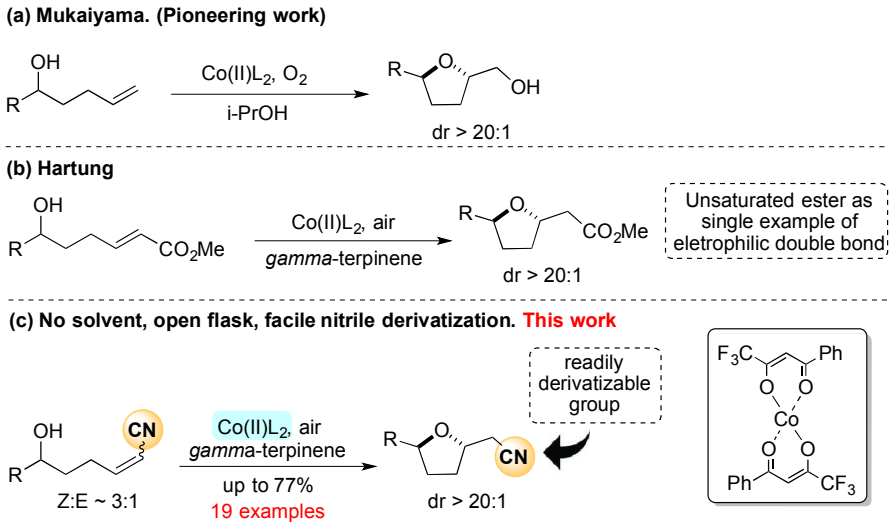
A straightforward protocol integrating a sustainable approach for synthesis of new 2,5-*trans*-THF nitrile derivatives enabling an easy diversification of its side chain scaffolds is described. The reaction tolerated different aromatic and alkyl substituents, affording the corresponding 2,5-*trans*-THFs in high diastereoselectivity. A detailed mechanistic study using DFT calculation reveals details of the ligand-exchange step, suggesting an inner-sphere *syn* attack to form the 2,5-*trans* stereochemistry as the most likely pathway, excluding the previous cation radical intermediate. The formation of a Co-C intermediate is suggested based on the homolytic cleavage to give the previously proposed free carbon radical intermediate.

Keywords: Mukaiyama oxidative cyclization, cobalt, mechanistic studies, DFT, tetrahydrofuran.

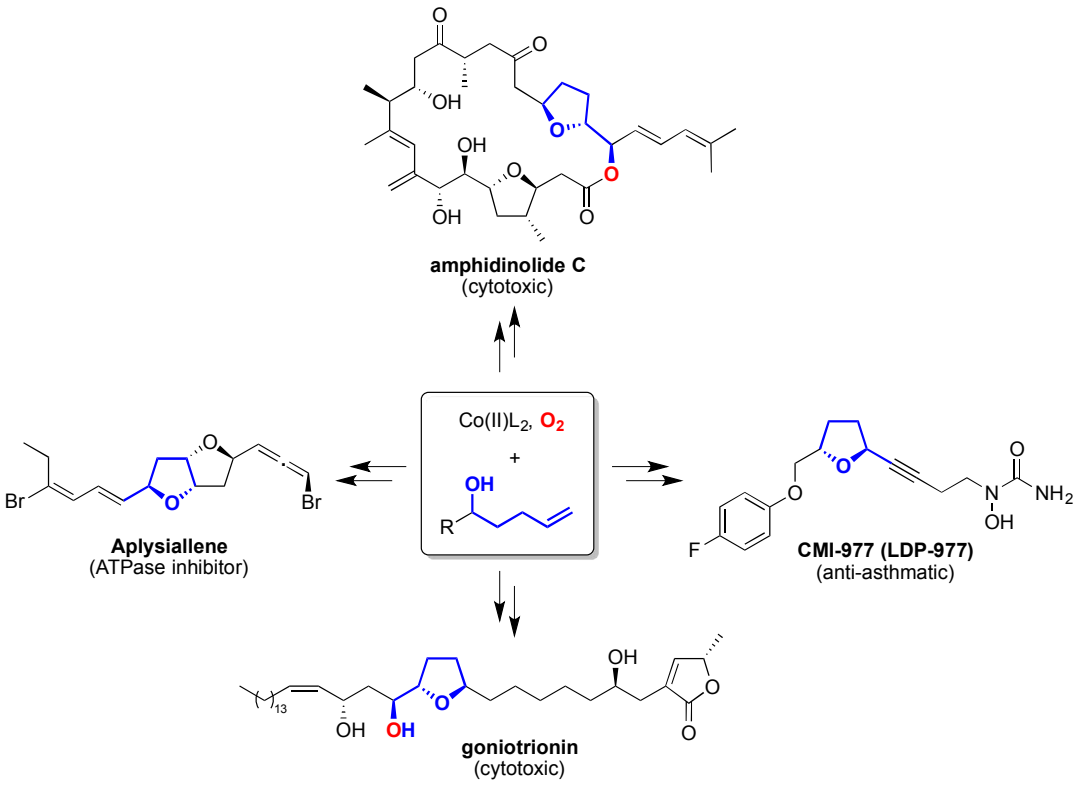
Introduction

Tetrahydrofuran (THF) is a well-known privileged skeleton frequently encountered in many biologically active natural products,[1] widely used as a synthetic building block to construct synthetic relevant heterocyclic molecules[2] and as a versatile synthetic precursor.[3] In view of their distinctive structural features, the stereoselective synthesis of chiral THFs is often attracting interest from synthetic community, and consequently several synthetic tactics have been developed.[4] In particular, tremendous efforts have been devoted to the development of new methodologies employing readily accessible bis-homoallylic alcohols to construct substituted 2,5-THF, which are encountered in many biologically active molecules and natural products.[2,3]

The pioneering work of Mukaiyama disclosed the use of a catalytic amount of Co(II) complexes for O_2 activation serving as a powerful and selective oxidant for oxidative cyclization of non-activated bis-homoallylic alcohols, offering a straightforward strategy to obtain 2,5-*trans*-THF under high levels of diastereoselectivity (Scheme 1a).[5] Some representative synthetic applications are depicted on Scheme 2.[6]



Scheme 1. Diastereoselective approaches to obtain 2,5-*trans*-THF from bis-homoallylic alcohols.



Scheme 2. Application of cobalt-catalysed cycloetherification involving non-activated bis-homoallylic alcohols under O_2.

Despite the obvious sustainable advantage of this strategy (including the abundant, low cost, cobalt metal, use of molecular oxygen as a "green" oxidant, use of "green" solvents, open reaction conditions and lack of moisture sensitivity), the generated free carbon radical intermediate[7] emerges as a flexible diversity-oriented approach to functionalize the side chain alpha-carbon position of THF rings, achieved by slight variations on reaction conditions.[8] In spite of all these characteristics, there is a lack in the application of this methodology in activated electron-deficient olefins. To date, Hartung[7a,8a] partially explored in terms of scope only a single alpha-beta-unsaturated ester, which provides excellent 2,5-*trans* diastereoselectivities under reductive termination (Scheme 1b). Subsequent application of this methodology by Wu and Forsyth in the synthesis of C15-C25 fragments of amphidinolide C3 showed this to be superior to the oxa-Michael strategy.[9] On the basis of these backgrounds,

herein, we report a protocol to integrate a sustainable approach for synthesis of new 2,5-*trans*-THF nitrile derivatives enabling an easy diversification of 2,5-THF side chain scaffold (Scheme 1c). The nitrile functional group offers easy access to a vast array of amine, tetrazole, carbonyl, imidate and other motifs.[10]

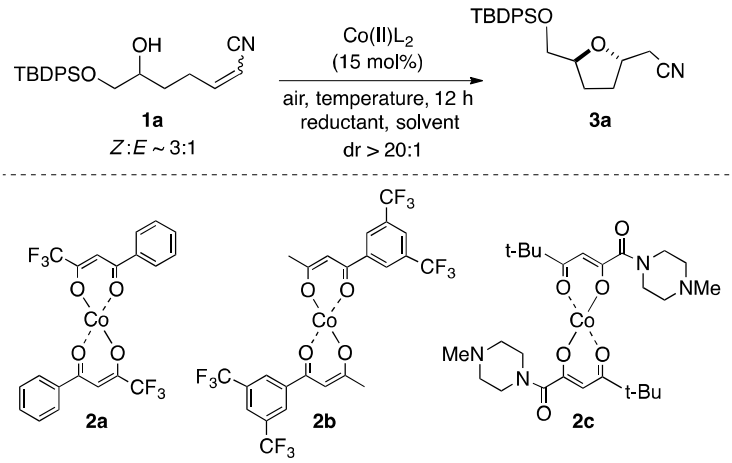
Results and Discussion

We commenced our investigations with alkenol **1a** as the standard substrate by examining various experimental conditions. On the basis of previous studies on oxidative cyclization reaction under reductive termination,[2a,7b,8] in this initial screening we choose 1,4-cyclohexadiene (1,4-CHD) as a reducing agent (Table 1). In addition, from these studies it was well-established that the stereochemical information of the olefinic π-bond is lost in the course of reaction due to the assumed radical path, although the 2,5-*trans* selectivity is retained, enabling us to use a mixture of *Z*:*E* alkenols (**1a**). The initial exploration was carried out by reacting **1a** in the presence of 1,4-CHD (20 equiv.), **2a** (15 mol%) as cobalt catalyst, toluene as reaction medium, open flask conditions (atmospheric air), and under reflux (Table 1, entry 1). The oxidative cyclization reaction afforded the 2,5-*trans*-THF **3a** in low yield (34%) but in high diastereoselectivity (dr > 20:1). Encouraged by this promising result, the reaction was performed in higher concentration by removing the toluene, and the desired product **3a** was obtained in 60% yield (entry 2). To improve the reaction efficiency further, different cobalt ligands with diverse electron-demands were subsequently examined (**2b-c**), but they all provide disappointing results (entries 3-4). Therefore, **2a** was chosen as the catalyst for additional optimization of the reaction conditions.

A reducing agent survey revealed that the source of radical hydrogen has a substantial impact on the conversion efficiency (Table 1, entries 5-8). While the 1-methyl-1,4-cyclohexadiene (1-Me-1,4-CHD), tris(trimethylsilyl)silane (TTMSS), and triethylsilane (TES) failed in provide the desired compound, the *γ*-terpinene provides **3a** in 63% of yield.

Gratifyingly, the use of *gamma*-terpinene as a reductant was more appropriate because it provided the benign *p*-cymene as a byproduct.[11] Finally, no substrate consumption occurred in the absence of O_2 and reductant (entry 9) or the cobalt catalyst **2a** (entry 10).

Table 1. Optimization of the reaction conditions.[a]



entry	reductant[d]	Co(II)L_2	temperature	solvent	yield[b]
1	1,4-CHD	**2a**	reflux	toluene	34%
2	1,4-CHD	**2a**	70 ºC	–	60%
3	1,4-CHD	**2b**	70 ºC	–	30%
4	1,4-CHD	**2c**	70 ºC	–	25%
5	1-Me-1,4-CHD	**2a**	70 ºC	–	NR[c]
6	TTMSS	**2a**	70 ºC	–	NR[c]
7	TES	**2a**	70 ºC	–	NR[c]
8	γ-terpinene	**2a**	70 ºC	–	63%
9[e]	–	**2a**	70 ºC	toluene	NR[c]
10	γ-terpinene	–	70 ºC	–	NR[c]

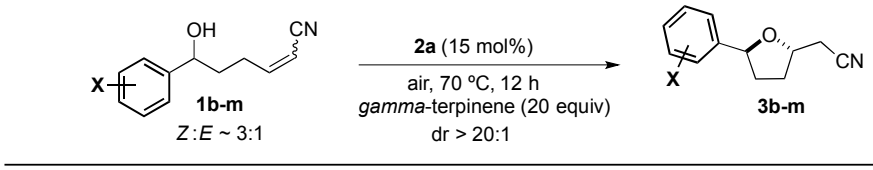
[a]The reactions were carried out in toluene (0.09 M) or without additional solvent (0.5 M), with **1a** (0.1 - 0.2 mmol) and reductant (20 equiv.) in the presence of 15 mol% of catalyst under atmospheric air at the given temperature. [b]Isolated yields after flash chromatography. [c]No reaction. [d]1,4-Cyclohexadiene (1,4-CHD), 1-methyl-1,4-cyclohexadiene (1-Me-1,4-CHD), tris(trimethylsilyl)silane (TTMSS), and triethylsilane (TES). [e]The reaction was carried out under inert atmosphere (argon) and toluene (0.5 M).

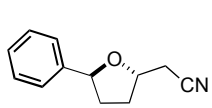
Having established optimized conditions for the oxidative cyclization of alkenol **1a** (Table 1, entry 8), we evaluated the substrate scope and generality of the transformation using different substituted alkenols. As illustrated in Table 2, a range of aromatic substituent was

tolerated. In general, the reaction smoothly afforded the corresponding 2,5-THFs in moderate to good yields (52-77%) with excellent diastereoselectivities (dr > 20:1). The electronic nature of the aromatic group (-X) only slight affected the yields, with electron-neutral (Table 1, **3b**), electron-donating (**3c-i**) and electron-withdrawing (**3j-k**) groups giving the corresponding 2,5-*trans*-THF in similar yields. Additionally, we found that *o*-Methyl (**3d**) and 3,5-di-*tert*-Butyl (**3e**) substituted derivatives also worked well, despite their steric hindrance. Unfortunately, the use of *p*-NMe_2 (**3l**), and the tertiary alcohol (**3m**) derivatives were not compatible with this protocol under the best reaction conditions.

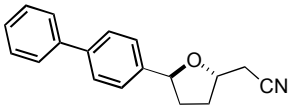
In order to further extend the scope of this protocol, aromatic chain substituents were replaced by alkyl ones. Applying our optimized reaction conditions, a series of linear alkenols exhibited comparable reactivity (Table 3, **3n-r**) and moderate to good yields (45-71%), furnishing the desirable THF in high diastereoselectivity (dr > 20:1). Gratifyingly, the protocol could be extended to include the formation of sterically hindered derivatives **3s-t** in good yields (Table 3, 69-74%, dr > 20:1). Other substrates with O-substituted derivatives, including benzyl and phenyl groups, demonstrated good reactivity (Table 3, **3u-v**, 59-64%).

Table 2: Scope of the aromatic substituents in the cobalt-catalysed oxidative cyclization reaction.

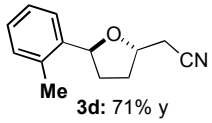




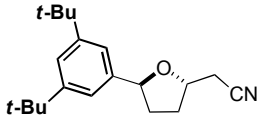
3b: 52% y



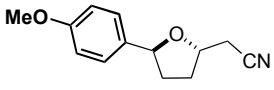
3c: 77% y



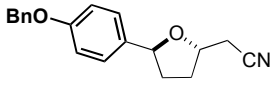
3d: 71% y



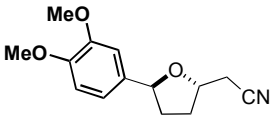
3e: 55% y



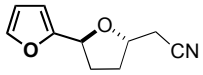
3f: 58% y



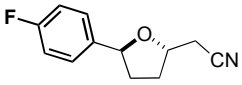
3g: 69% y



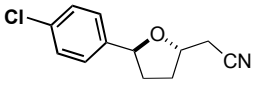
3h: 68% y



3i: 62% y

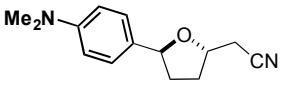


3j: 61% y

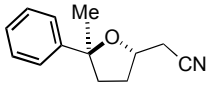


3k: 64% y

Failed Reactions

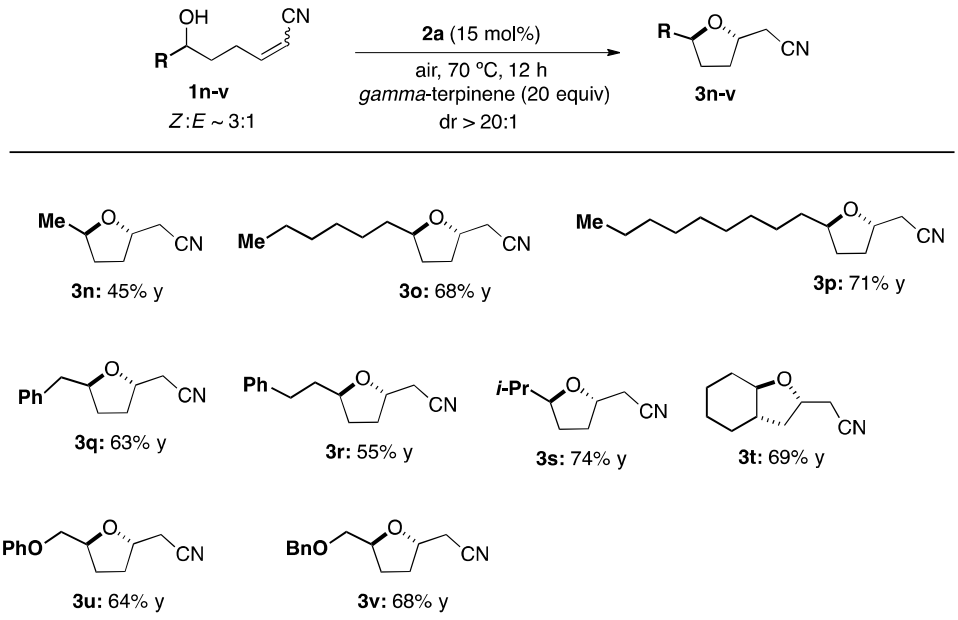


3l. 0% y

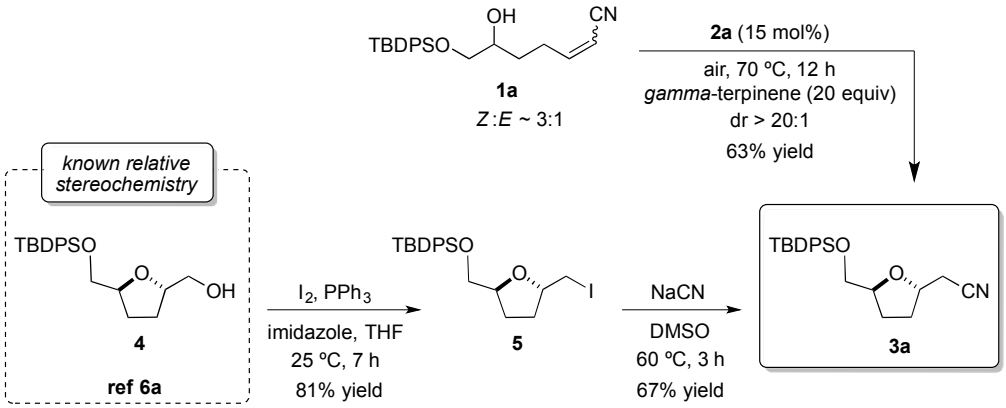


3m: 0% y

Table 3: Scope of the alkyl substituents in the cobalt-catalysed oxidative cyclization reaction.



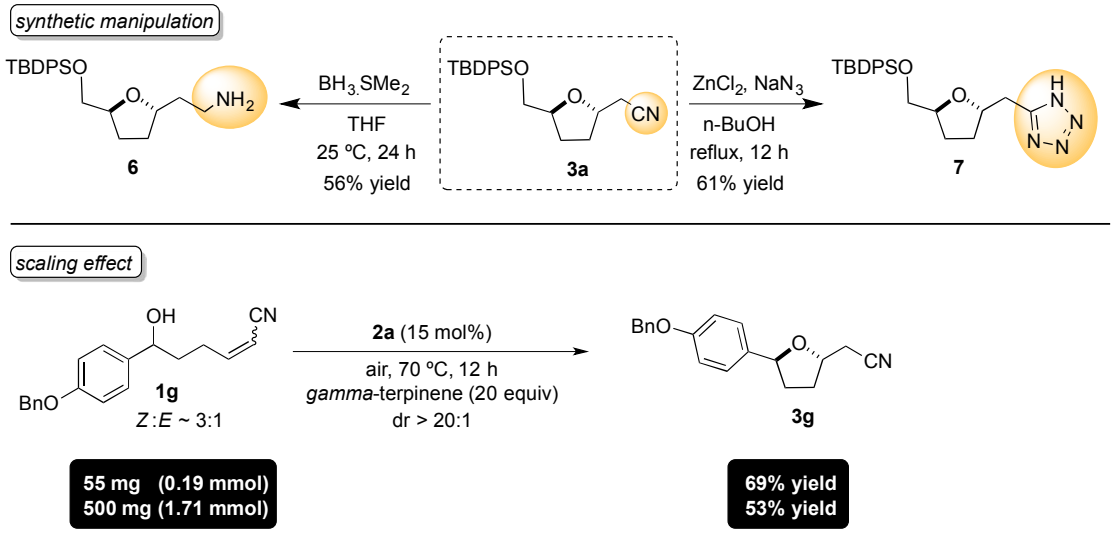
To prove the 2,5-relative configuration of tetrahydrofurans derivatives **3**, the previous known compound **4** (Scheme 3), obtained by a different synthetic route,[6a] was submitted to successive derivatizations leading to **3a**. The ^{1}H NMR and ^{13}C NMR of **3a** matched with our previous data.



Scheme 3. Proof of stereochemistry for 2,5-*trans*-THF nitrile derivatives **3**.

Therefore, we investigated the derivatization of compound **3a** to demonstrate the utility of our methodology (Scheme 4a). **3a** can be easily converted into amine **6** in 56% yield

under reduction reaction condition with $BH_3.SMe_2$. Furthermore, the tetrazole **7** can be achieved by using NaN_3 and $ZnCl_2$ in 61% yield. To demonstrate applicability (Scheme 4b), a half-gram-scale reaction of **1g** was carried out to afford **3g** in 53% yield as a single diastereoisomer (dr > 20:1). The yield remained consistent with the increase of scale.

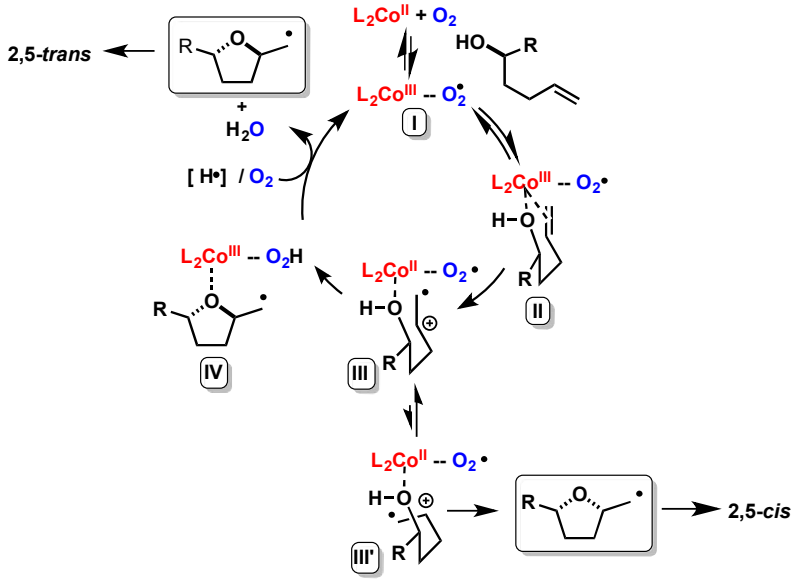


Scheme 4. (**a**) Synthetic transformations of **3a**. (**b**) Scaling effect of **1g**.

Computational Mechanistic Studies

A great progress has been made in understanding the cobalt-mediated Mukaiyama cyclization by Hartung and co-workers.[7,12] In particular, mechanistic interpretations based on kinetics experiments provide initial thoughts to understand the carbon-centered radical formation and stereoselectivity. A simple picture for these finding can be seen in Scheme 5. The proposed catalytic cycle starts after O_2 activation of Co^{II} forming a superoxo-mode doublet intermediate (**I**), which trigger an intriguing sequence of single electron transfer (SET) events. First, after ligand exchange, the lowest-energy chair-like olefin conformer in the complex **II** is converted into radical cation **III**. This conformation was proposed based on the experimentally observed diastereoselectivities. The electron uptake propensity of Co^{III} complex **I** in the SET step was associated with the strong oxidative tendency of

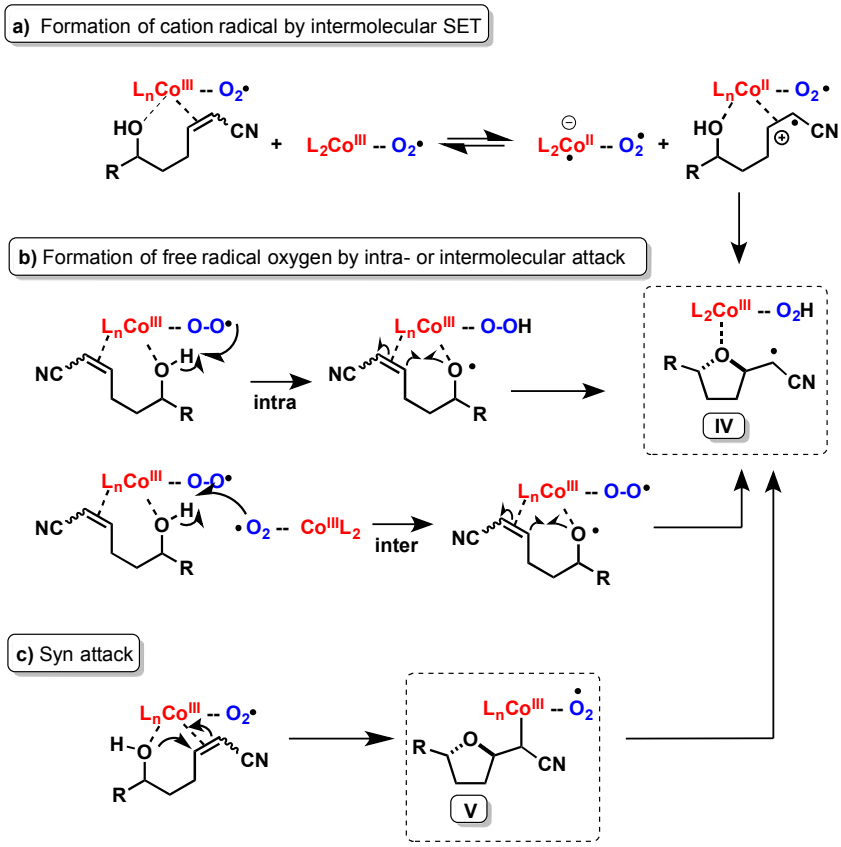
bis(trifluoroacetato)cobalt(III) complexes.[13] Finally, an oxygen attack onto the electrophilic bond creates the C-O bond and set the 2,5-*trans* stereochemistry. The reductant chosen on the present mechanism sequence is of fundamental importance because it not only regenerates the catalyst but also determines the type of radical termination of intermediate **IV** in the alkyl chain.[7]



Scheme 5. Proposed mechanism by Hartung et al. for aerobic cobalt-catalyzed tetrahydrofuran synthesis.

Despite these insights, some detailed reaction steps remain poorly understood, especially for electrophilic double bonds. In particular, considering the cobalt-mediated oxidation of π system by a SET process, it is reasonable to speculate, based on previous reports,[13,14] that an intermolecular SET may be appropriate by using a second cobalt complex (Scheme 6a). In another hypothesis, we revisited the initial mechanism proposed by Mukaiyama (Scheme 6b),[5] by the reaction of Co complex and O_2 with alkenol, forming a free radical oxygen which interacts with the coordination sphere of the cobalt complex to drive the *syn* radical cyclization attack. We speculate that the abstraction of the radical hydrogen should

occur in the complexed alkenol by intra- or intermolecular attack (Scheme 6b). In a new standpoint, and considering electrophilic olefins, a nucleophilic attack of the hydroxyl group, through an inner-sphere mechanism in a *syn* fashion on the coordinated alkene, could lead the intermediate **V**[15] producing the expected radical intermediate **IV** after homolytic cleavage (Scheme 6c). Considering these entire new hypotheses, the same reaction intermediate will produce the carbon-centered radical **IV**. A final aspect refers to the true lowest energy conformations for cobalt-alkenol complexes, which remain unknown. No detailed computational study on the mechanism of Co^{II}/Co^{III}-mediated aerobic oxidative cyclization was performed up to date. Considering the previous questions and hypothesis, we conducted a theoretical investigation using DFT and TD-DFT calculation using the Gaussian 09,[16] with the BP86[17] functional and def2-svp[18] basis set. In all calculations we add the D3 version of Grimme's dispersion with Becke-Johnson damping.[19] We include the effect of toluene on the calculations by using the IEF-PCM implicit model. To refine the electronic energy, single-point calculations were performed at BP86-D3BJ/def2-tzvp/IEF-PCM level of theory employing the BP86-D3BJ/def2-svp/IEF-PCM geometries. The Gibbs free energy was obtained from the sum of E_{ele} at BP86-D3BJ/def2-tzvp/IEF-PCM//M062X/def2-svp/IEF-PCM and thermal correction at BP86-D3BJ/def2-svp/IEF-PCM. The NBO analyses furnish the Wiberg Bond Index (WBI) at BP86-D3BJ/def2-tzvp/IEF-PCM.[20] Initially we explore the conformational behavior of cobalt-alkenol complexes. Subsequently, a detailed mechanism involving the cyclization step was done, including unsaturated-nitrile and terminal double bond. Among the mechanism evaluated, the *syn* attack (Scheme 6c) presented the most feasible Gibbs energy profile and is discussed in-deph in the main text. See SI for further details of other explored mechanisms.



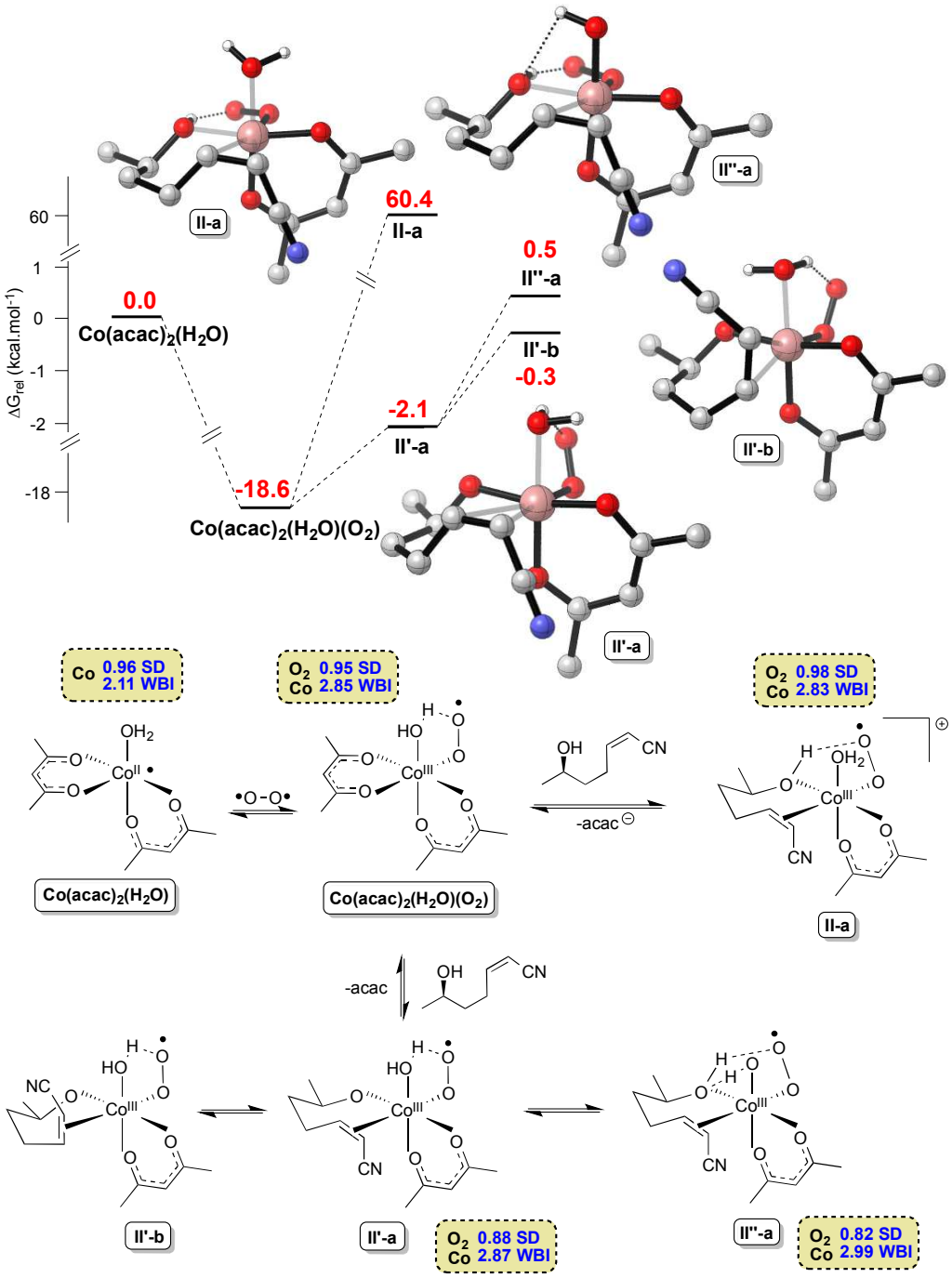
Scheme 6. Different hypotheses for the cyclization step in the aerobic cobalt-catalyzed tetrahydrofuran synthesis.

1. Conformational search of complex I

We considered the $Co(acac)_2(H_2O)$ (acac = acetylacetonate) as the reactive complex in order to reduce the computational costs associated with the complicated conformational behavior of non-symmetric ligands. It was evaluated only octahedral monomer complexes, despite the possibility of the oxo-dimer for Co^{III} or more intricate arrangement of atoms as previously disclosed in solid state by X-ray structures.[21] We set the doublet spin state as electronic ground state for **$Co(acac)_2(H_2O)$** and **$Co(acac)_2(H_2O)(O_2)$** according to the previous experimental and theoretical calculation reports.[12]

To understand the role of diastereoselectivity by the cobalt complex, it was obtained an accurate description of conformational space of complex **II** varying the conformation of

alkenol (Scheme 7). In addition, both the *cis*- and *trans*-isomers (relative to the H_2O and O_2 position), and both double-bond faces of complexation generating the complexes **II**, including the possibility of hydroxyl proton abstraction from the alkenol (**II'**) or water (**II''**) after ligand exchange (see in SI all searched conformations for **II** and **II'**) were explored. According to our computational results, in both cases, the *cis*-isomers in chair-like conformations adopted the lowest energy and the most relevant structures are presented in Scheme 7. The molecular oxygen uptake by the **$Co(acac)_2(H_2O)$** catalyst decreased the energy gap by -18.6 kcal.mol^{-1}, spreading out spin density (SD) - obtained from the Mulliken population analysis - from cobalt (0.96 in **$Co(acac)_2(H_2O)$**) to complexed O_2 (0.95 in **$Co(acac)_2(H_2O)(O_2)$**), as described previously.[12] The increase in Wiberg bond index (WBI) (from 2.11 to 2.85) also indicates the superoxo-character of **$Co(acac)_2(H_2O)(O_2)$** complex.



Scheme 7. Ligand exchange in **Co(acac)$_2$(H$_2$O)(O$_2$)**, and lowest energy conformation of intermediates **II**, **II'** and **II''**. In blue: SD = spin density. WBI = Wiberg bond index.

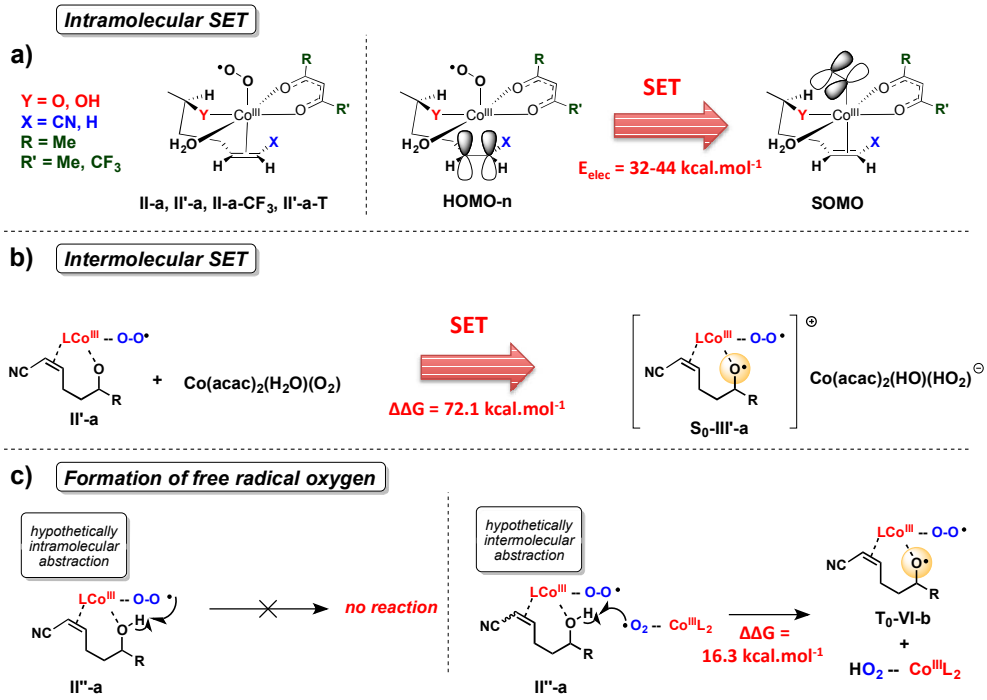
From the energetic profile, it is very unlikely to form the cationic complex **IIa**, due to the unfavorable endergonic equilibrium (energy difference of 79.0 kcal.mol^{-1}) after ligand

exchange involving the alkenol and extrusion of **acac**$^-$. The formation of lowest energy chair-like complex **II'a** (-2.1 kcal.mol^{-1}), which leads to the THF 2,5-*trans* diastereoisomer, proceeds by the hydroxyl proton abstraction of alkenol by anionic **acac**. This endergonic process involves 16.5 kcal.mol^{-1}. A less favorable equilibration involving an intramolecular proton transfer in **II'a** produces the less stable complex **II''a** (0.5 kcal.mol^{-1}). The isomeric boat-like complex **II'b**, which keeps its double-bond in axial position, and which is responsible for the formation of 2,5-*cis* diastereoisomer, is 1.8 kcal.mol^{-1} higher in energy than **II'a**. Finally, correlating the ligand exchange and proton abstraction with the SD and WBI parameters of **II-a**, **II'-a**, and **II''-a**, any substantial changes were observed.

2. Studies of single electron transfer (SET) and free radical oxygen pathways for superoxo-Co^{III} complexes.

The intramolecular SET mechanism involving the formation of intermediate **III** (Scheme 5) was explored for **II-a**, **II'-a**, **II-a-CF$_3$**, and **II'-a-T** using time-dependent density functional theory (TD-DFT) calculations as described by Wei, Niu and coworkers (Scheme 8a).[14] The evaluation of transition energies involving the olefin π–orbitals from ground state to the excited state – HOMO-n and SOMO orbitals, respectively - range from 32-44 kcal.mol^{-1}. These high intramolecular SET energies suggest an unfavorable intramolecular pathway for both systems – double bond with and without CN group. The proposed intermolecular SET transition process involving two cobalt complexes, as depicted in the Scheme 8b, involves a extremely high Gibbs free energy difference of 72.1 kcal.mol^{-1} for the cation broken-symmetry singlet **S$_0$-III'-a** complex. Finally, the investigation for the cyclization step by hydrogen abstraction and formation of free oxygen radical intermediate were equally unfavorable (Scheme 8c). By the intramolecular path, the proposed intermediate is not a minimum structure on the potential energy surface, while the intermolecular attack involves

an endergonic equilibrium, with energy differences of 16.3 kcal.mol^{-1} for the triplet complex **T_0-VI-b**.

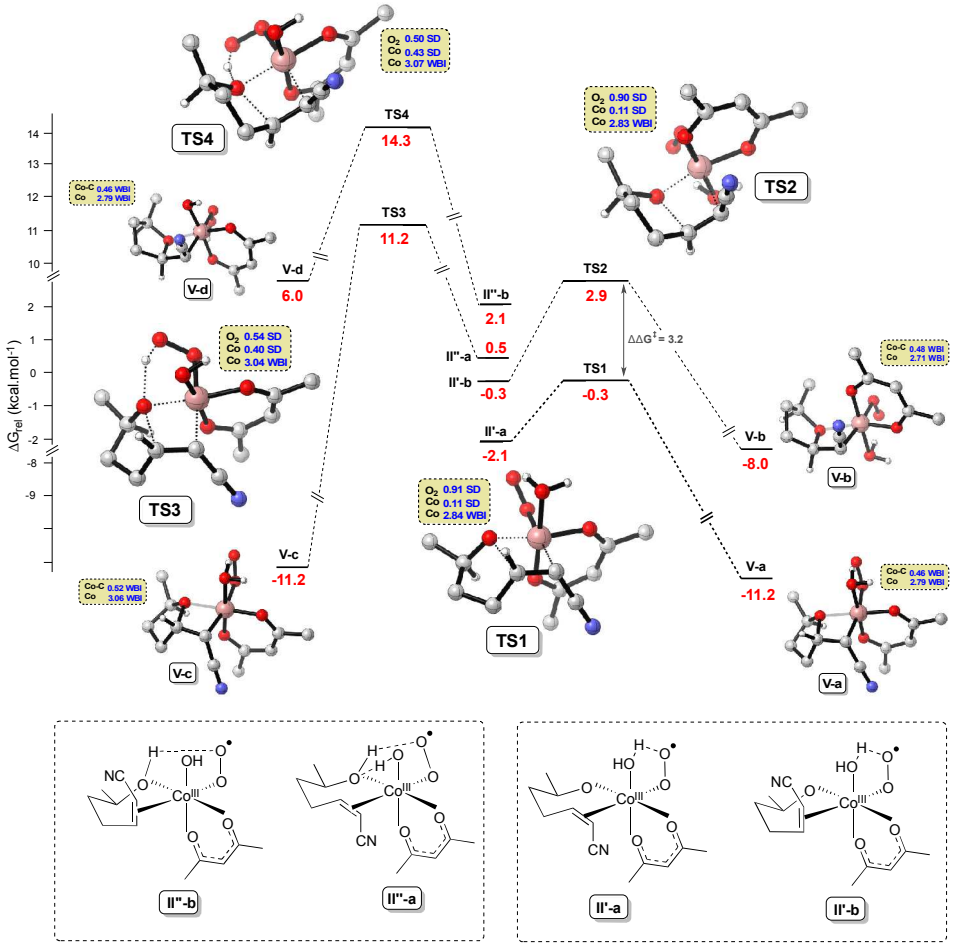


Scheme 8. (**a**) Olefin π orbital transition energy for **II-a**, **II'-a**, **II-a-CF$_3$**, and **II'-a-T**. (**b**) Suggested intermolecular SET. (**c**) Formation of free radical oxygen by intra or intermolecular attack.

3. Studies of cyclization pathways for superoxo-Co^{III}.

The investigation of the potential energy surface for the cyclization step was conducted as depicted on the Scheme 9. The *syn* attack pathway (hypothesis **c** on scheme 6) starting from **II'-a** provides the lowest activation free energy, and was determined to be only 1.8 kcal.mol^{-1} for **TS1**. This pathway forms the experimentally *trans* stereochemistry, and the formation of **V-a** intermediate involves an exergonic process by 9.1 kcal.mol^{-1} through a non-reversible step. The opposite *cis*-stereochemistry would be obtained through **TS2**, starting from **II'-b**, and was found to be 3.2 kcal.mol^{-1}, and similarly, lead to the **V-b** intermediate through a non-reversible step and releasing 7.7 kcal.mol^{-1} of energy. Supposing that **II'-a** and

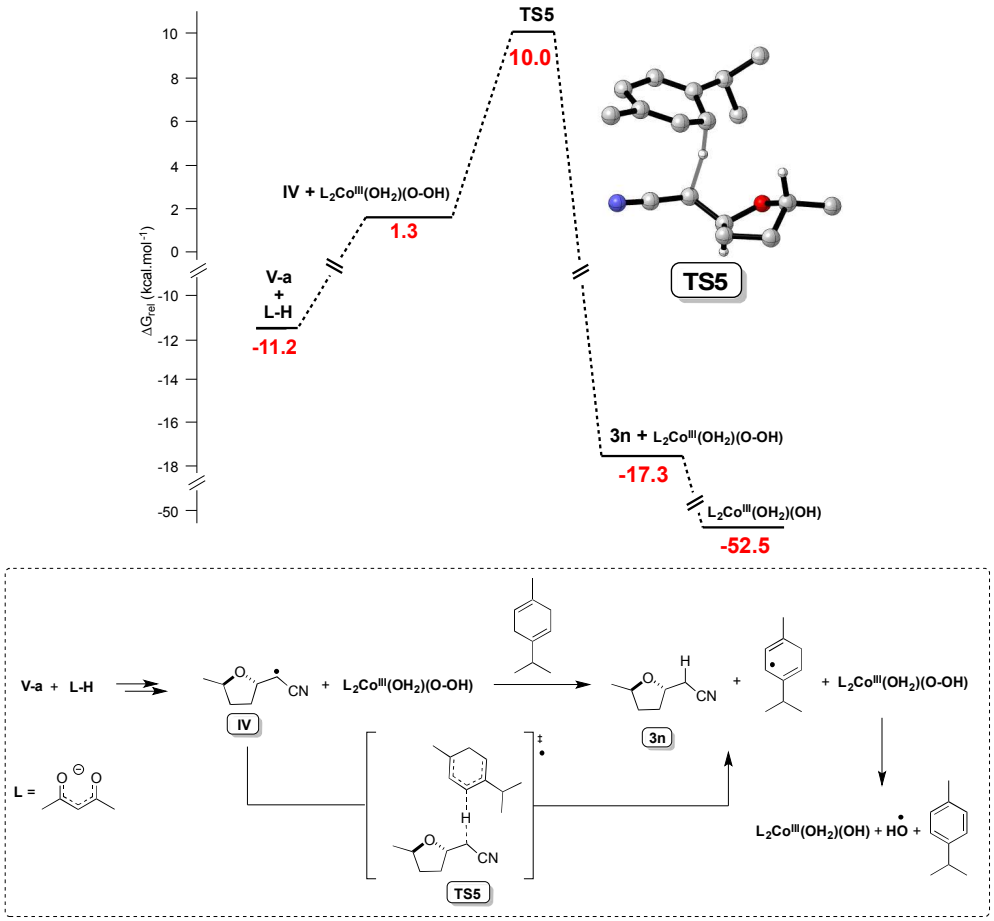
II'-b can quickly interconvert, the Curtin-Hammett principle can be assumed, being the energetic difference between **TS1** and **TS2** ($\Delta\Delta G^{\ddagger}$ = 3.2 kcal.mol^{-1}) responsible for the control of diastereoselectivity, providing a theoretical diastereoisomeric ratio of 99.3:0.7 for *trans* stereochemistry at 70 ºC, in excellent agreement with the experimental result (dr > 20:1). **TS1** corresponds to the diastereoselectivity- and rate-determining cyclization step. The analysis of the oxidation state of cobalt on **TS1** and **TS2**, by the WBI (2.84 and 2.83 for **TS1** and **TS2**, respectively) indicates a Co^{III} character for both cases (Scheme 9).



Scheme 9: Cyclization pathways for superoxo-Co^{III} involving unsaturated nitrile derivatives. Energy barrier represented in parentesis.

The intermediates **II''-a** and **II''-b** and their respective transition states – **TS3** and **TS4** in Scheme 9 – are responsible for the free radical oxygen attack (hypothesis **b** on Scheme 6), but they are in much higher energy than the lowest energy transition state **TS1**, and the intermediates **II'-a** and **II'-b**, indicating that this pathways is not favorable. In particular, we considered a concerted sequence of events involving radical formation by an intramolecular process, followed by radical cyclization. However, the mechanism proposed could be safely ruled out in the light of our theoretical calculations depicted in Scheme 9. Surprisingly, the attack of complex O_2 to the hydroxyl hydrogen in the intermediates **II''-a** and **II''-b** through **TS3** and **TS4** occurs via a heterolytic cleavage, determined by the Milliken spin density analysis. The spin densities on **TS3** and **TS4** remain centered on O_2-Co atoms (>90%), and after the proton abstraction occurs, the alkoxy attacks the double bond. Both transition states are higher in energy than **TS1** and **TS2**. A final analysis of WBI in the Scheme 9 reveals a covalent bond formation between Co-C atoms involving all calculated intermediates **Va-d**.

After homolytic cleavage and ligand exchange, we must wait for the formation of free radical carbon **IV**, together with peroxide $\mathbf{L_2Co^{III}(OH_2)(OOH)}$, as can be seen in Scheme 10. This endergonic step requires a significant input of energy (12.5 kcal.mol^{-1}), although these intermediates have similar energy to the starting materials. The formation of the product **3n** via radical abstraction of one of the hydrogens of the gamma-terpinene passes through **TS5** involving an energy barrier of 8.7 kcal.mol^{-1}. Finally, homolytic cleavage of the peroxide $\mathbf{L_2Co^{III}(OH_2)(OOH)}$, provides the cobalt intermediate $\mathbf{L_2Co^{III}(OH_2)(OH)}$ in its most stable state.

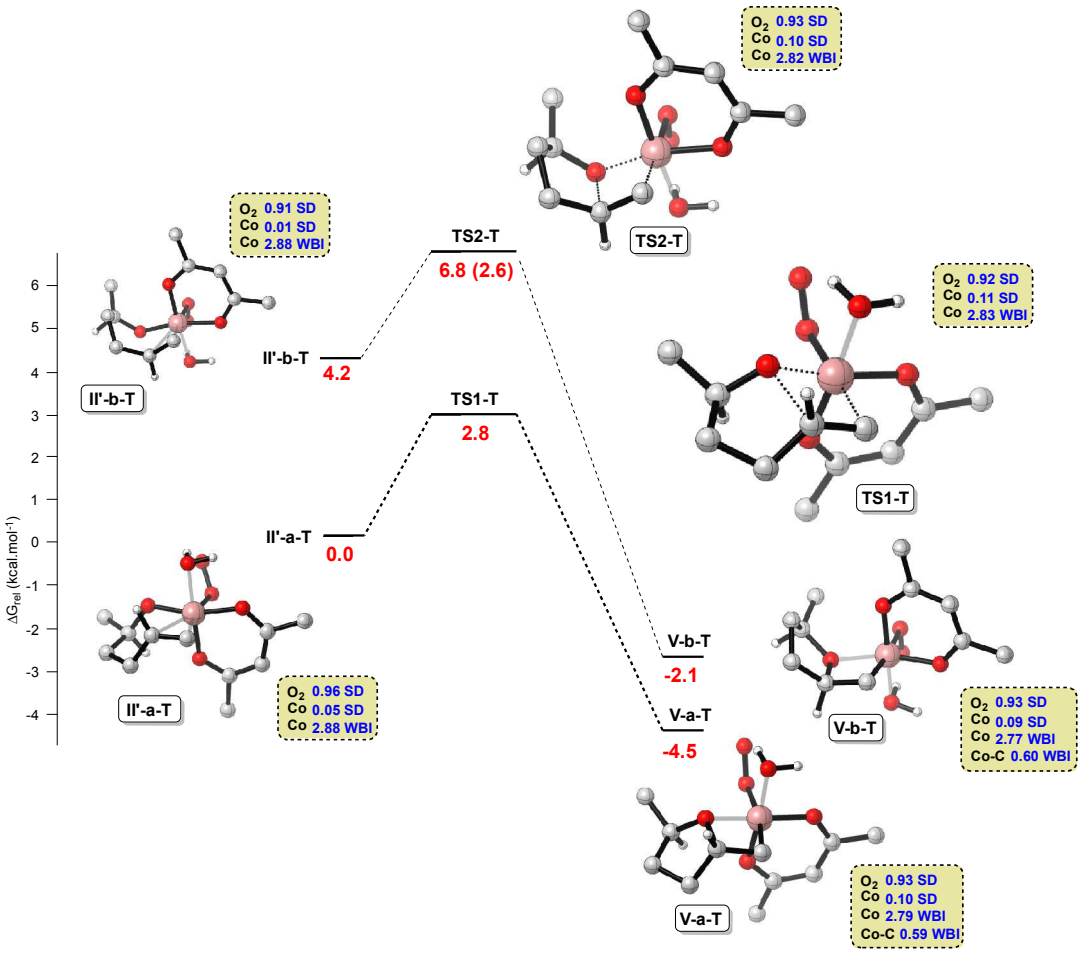


Scheme 10: (a) Formation of free carbon radical intermediate **IV**, and final product **3n.**

Assuming the energetic span model[22] and rate-determining state concept,[23] we analyze the potential energy diagrams (Schemes 7, 9, and 10), and **Co(acac)$_2$(OH$_2$)(OH)** can be considered as the TOF-determining intermediate (TDI) and the resting state catalyst. The transition state **TS5** is the TOF-determining transition state (TDTS). However, these considerations must be taken with caution, since we do not calculate all the elementary steps involved in the ligand exchange and catalyst regeneration, being both process not fully understood.

We extended this mechanistic study including the cyclization step of non-activated terminal double bond olefins starting from the lowest energy structures from Scheme 9. Our intention was to evaluate how much an unactivated olefin could change the energy barriers

via a inner-sphere *syn* attack. We find a remarkable energetic and structural similarity between the terminal and nitrile substituted olefins. As can be seen in the Scheme 11, the obtained results point out to a non-radical cyclization step pathway and the experimentally *trans* stereochemistry would be obtained through **TS1-T** starting from **II'-a-T** exhibiting only 2.8 kcal.mol^{-1} of free activation energy. The competitive **TS2-T** provides the *cis*-configuration and is higher in energy (6.8 kcal.mol^{-1}) than **TS1-T**. The energetic difference between **TS1-T** and **TS2-T** ($\Delta\Delta G^{\ddagger} = 4.0$ kcal.mol^{-1}) is responsible for the control of diastereoselectivity, providing a theoretical diastereoisomeric ratio of 99.7:0.3 for *trans* stereochemistry at 70 ºC, in perfect agreement with experimental results from the literature. The oxidation state of cobalt and WBI also indicate a Co^{III} character for all intermediates and transition states. A covalent bond character between Co-C atoms was also observed by the WBI analysis. These results, along with the studies of single electron transfer (SET) that contemplated unsubstituted olefins, give evidence that in these systems a *syn* addition mechanism could also be acting in the cyclization step.

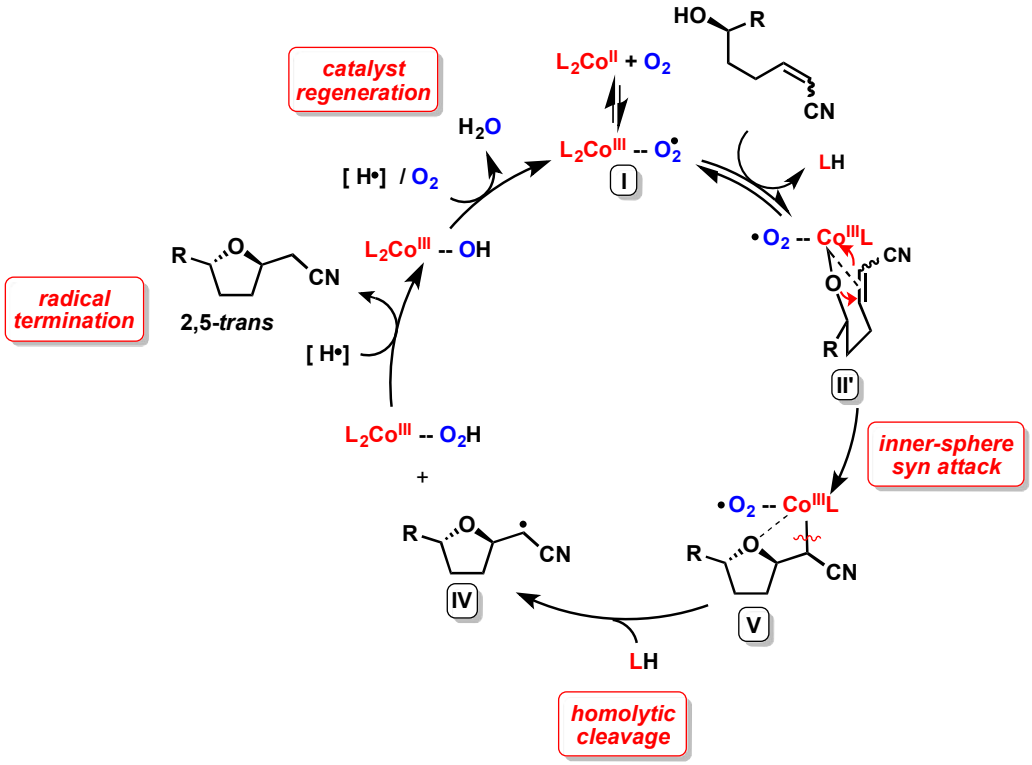


Scheme 11: Cyclization pathways for superoxo-Co^{III} involving non-activated terminal olefins.

According to the theoretical calculations, and precedent reports, a modified reaction mechanism is proposed in Scheme 12 for Mukaiyama radical cyclization of nitrile derivatives. The major modification of the previous mechanism involves the formation of intermediate **II'** after ligand-exchange, followed by an inner-sphere *syn* attack of oxygen, forming the *trans*-stereochemistry. Despite some evidence found during this work, it is not clear whether this conclusion is really general for other Mukaiyama radical cyclization variations.

From our calculations, we could hypothesize that the probable resting state catalyst **L$_2$Co^{III}OH** and the transition state involved in the radical termination and formation of the

product are the turnover determining-states. The energy differences between the transition states forming 2,5-*anti*-**V** and 2,5-*syn*-**V** drive the stereochemical preference. Finally, the intermediate **V** is suggested to participate in the catalytic cycle,[5,15] which after a homolytic cleavage forms the free carbon radical intermediate **IV,** and follow the previously proposed radical termination step and cobalt regeneration.



Scheme 12. Proposed modified mechanism for aerobic cobalt-catalyzed tetrahydrofuran synthesis of nitrile derivatives.

Conclusions

In summary, we report a protocol integrating a sustainable approach for synthesis of new 2,5-*trans*-THF nitrile derivatives enabling an easy diversification of 2,5-THF side chain scaffolds. The reaction tolerated different aromatic and alkyl substituents, affording the corresponding 2,5-*trans*-THFs in high selectivity. A detailed mechanistic study using DFT

calculation investigates the conformational behavior of reactive intermediates, and afforded insights into cyclization step, including the unsaturated-nitrile and terminal double bond. The major highlights include details of ligand-exchange step, and an inner-sphere *syn* attack to form the 2,5-*trans* stereochemistry, excluding the previously cation radical intermediate. It was suggested that the formation of Co-C intermediate **V** which can be easily decomposed by a homolytic cleavage forms the previously proposed free carbon radical intermediate **IV**. More detailed studies to support our theoretical conclusions are in progress and will be disclosed in due course.

EXPERIMENTAL SECTION

Commercial grade reagents and solvents were purchased and used without further purification; when necessary, they were purified as recommended.[24] Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium/benzophenone. Dichloromethane (CH_2Cl_2) was distilled from CaH_2. Flash column chromatography was carried out using silica gel 60 (230-400 mesh). Analytical thin layer chromatography (TLC) was performed using silica gel aluminum sheets. The TLC plates were visualized with UV light, and stained with phosphomolybdic acid, vanillin, or $KMnO_4$ solution, followed by heating. The ^1H and ^{13}C NMR spectra were recorded at 400MHz for ^1H and at 100 MHz for ^{13}C, respectively. The chemical shifts (δ) for ^1H and ^{13}C are reported in ppm using tetramethylsilane (TMS) as an internal standard for ^1H NMR spectra, and using the solvent peak as an internal standard ($CDCl_3$ at 77.0 ppm) for ^{13}C NMR spectra. Coupling constants (*J*) are given in hertz. The following abbreviations are used to indicate the multiplicity: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; b = broad; quint = quintet; sext = sextet; dd = doublet of doublets; dt = doublet of triplets; dq = doublet of quartets; tt = triplet of triplets; ddt = doublet of doublet of triplets; ddq = doublet of doublet of quartets; dddd = doublet of doublet of

doublet of doublets. The signals from the minor isomers, when not superimposed with the major isomer, are listed in brackets. For the infrared spectra, wavelengths of maximum absorbance (max) are quoted in wavenumbers (cm^{-1}). High-resolution mass spectra (HRMS) were recorded using electrospray ionization (ESI) (Hybrid linear ion trap–orbitrap FT-MS and QqTOF/MS – Microtof – QII models). For details of theoretical calculations and citation of the programs, please see the SI.

Preparation of catalysts 2a-c: The catalysts **2a**,[25] **2b**,[2c] and **2c**[26] were prepared according to the literature.

General procedure for preparation of alkenols 8a-v: The alkenols **8a-v** were prepared following the **Method A** or **B**, starting from an aldehyde or epoxide, respectively.

Method A: Freshly prepared 3-butenylmagnesium bromide solution (2 equiv, 0.5 M in THF) was added to a flame-dried flask under an Ar atmosphere at 0 °C, and a solution of **aldehyde** (15 mmol) in anhydrous THF (20 mL) was added dropwise while stirring the reaction vigorously. After 10 min at −20 °C and 1 h at r.t., a saturated aqueous solution of ammonium chloride (10 mL) and H_2O (5 mL) were added. The suspension was warmed to r.t., and the reaction mixture was extracted with EtOAc (2 × 10 mL). The combined organic phases were dried (Na_2SO_4) and filtered, and the solvent was removed in vacuum. Purification by flash column chromatography using EtOAc/hexane (2:8) as the eluent gave the secondary alcohol **8**.

Method B: Freshly prepared allyl magnesium bromide solution (3 equiv, 0.5 M in Et_2O) was added to a flame-dried flask under an Ar atmosphere at 0 °C, and a solution of **epoxide** (15 mmol) in anhydrous THF (20 mL) was added dropwise while stirring the reaction vigorously. After 10 min at −20 °C and 1 h at r.t., a saturated aqueous solution of ammonium chloride (10 mL) and H_2O (5 mL) were added. The suspension was warmed to r.t., and the reaction mixture was extracted with EtOAc (2 × 10 mL). The combined organic phases were dried

(Na_2SO_4) and filtered, and the solvent was removed in vacuum. Purification by flash column chromatography using EtOAc/hexane (2:8) as eluent gave the secondary alcohol **8**.

8a:[6a] Synthesized according to the literature.

8b:[27] Synthesized according to **Method A** furnishing the known compound in 63% (12.3 mmol, 1.99 g) isolated yield as light yellow oil; R_f 0.71 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37-7.32 (m, 3H), 7.28 (m, 2H), 5.83 (ddt, *J* = 17.1, 10.2, 6.6 Hz, 1H), 5.03 (dq, *J* = 17.1, 1.7 Hz, 1H), 5.00-4.95 (m, 1H), 4.70 (dd, *J* = 7.9, 5.5 Hz, 1H), 2.15 (m, 2H), 1.97-1.75 (m, 3H).

8c:[28] Synthesized according to **Method A** furnishing the known compound in 77% (6.29 mmol, 1.50 g) isolated yield as a white solid; R_f 0.60 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59-7.52 (m, 4H), 7.44-7.29 (m, 5H), 5.94-5.84 (ddt, *J* = 17.1, 10.4, 6.7 Hz, 1H), 5.04 (dq, *J* = 1.6, 10.4 Hz, 1H), 5.00-4.96 (m, 1H), 4.69 (dd, *J* = 5.3, 7.6 Hz, 1H), 2.23-2.05 (m, 3H), 1.96-1.76 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.6, 140.7, 140.4, 138.1, 128.7, 127.2, 127.1, 127.0, 126.3, 115.0, 73.7, 38.0, 30.0.

8d:[29] Synthesized according to **Method A** furnishing the known compound in 74% (8.85 mmol, 1.56 g) isolated yield as a pale yellow oil; R_f 0.42 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) 7.43 (d, *J* = 8.0 Hz, 1H), 7.23-7.07 (m, 3H), 5.83 (ddt, *J* = 17.4, 10.4, 6.7 Hz, 1H); 5.08-5.00 (m, 1H), 5.00-4.95 (m, 1H), 4.9 (dd, *J* = 7.5, 4.7 Hz, 1H), 2.29 (s, 3H), 2.27-2.08 (m, 2H), 2.03 (bs, 1H), 1.86-1.69 (m, 2H).

8e: Synthesized according to **Method A** furnishing the new compound in 69% (4.12 mmol, 1.13 g) isolated yield as a white solid; R_f 0.59 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 (t, *J* = 1.8 Hz, 1H). 7.19 (d, *J* = 1.8 Hz, 2H), 5.87 (ddt, *J* = 17.2, 10.3, 6.5 Hz, 1H), 5.05 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.01-4.96 (m, 1H), 4.68 (dd, *J* = 7.9, 5.3 Hz, 1H), 2.29-2.08 (m, 2H), 1.97-1.85 (m, 2H), 1.84-1.73 (m, 1H), 1.33 (s, 18H); **^{13}C NMR** (101

MHz, $CDCl_3$) δ 150.9, 143.9, 138.4, 121.6, 120.0, 114.8, 74.7, 38.1, 34.9, 31.5, 30.3. **HRMS**: calculated for $C_{19}H_{30}NaO$ $(M+Na)^+$ 297.2189; found 297.2189.

8f:[30] Synthesized according to **Method A** furnishing the known compound in 70% (6.97 mmol, 1.34 g) isolated yield as a yellow oil; R_f 0.59 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 5.83 (ddt, J = 17.0, 10.2, 6.5 Hz, 1H), 5.05-4.99 (m, 1H), 4.99-4.94 (m, 1H), 4.66-4.60 (m, 1H), 3.78 (s, 3H), 2.25-2.01 (m, 3H), 1.96-1.71 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 30.0, 37.9, 55.5, 73.5, 113.7, 114.7, 127.1, 136.8, 138.2, 158.9.

8g: Synthesized according to **Method A** furnishing the new compound in 53% (5.29 mmol, 1.42 g) isolated yield as a white solid; R_f 0.61 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45-7.28 (m, 5H), 7.25 (d, J = 8.5 Hz, 2H), 6.95 (d, J = 8.5 Hz, 2H), 5.82 (ddt, J = 17.2, 10.2, 6.5 Hz, 1H), 5.05 (s, 2H), 5.03 (dq, J = 17.2, 1.7 Hz, 1H), 4.99-4.95 (m, 1H), 4.62 (dd, J = 7.2, 6.1 Hz, 1H), 2.19-2.00 (m, 2H), 1.93-1.83 (m, 2H), 1.81-1.71 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.2, 138.2, 137.0, 136.9, 128.6, 127.9, 127.4, 127.1, 114.9, 114.7, 73.6, 70.0, 37.9, 30.1. **HRMS**: calculated for $C_{18}H_{20}NaO_2$ $(M+Na)^+$ 291.1356; found 291.1356.

8h: Synthesized according to **Method A** furnishing the new compound in 51% (4.59 mmol, 1.02 g) isolated yield as a yellow oil; R_f 0.54 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.87 (d, J = 1.7 Hz, 1H), 6.82 (dd, J = 8.3, 1.7 Hz, 1H), 6.80 (d, J = 8.3 Hz, 1H), 5.82 (ddt, J = 17.2, 10.3, 6.7 Hz, 1H), 5.02 (dq, J = 17.2, 1.6 Hz, 1H), 4.99-4.94 (m, 1H), 4.59 (dd, J = 7.5, 5.8 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 2.45 (bs, 1H), 2.19-2.01 (m, 2H), 1.93-1.81 (m, 1H), 1.80-1.69 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.8, 148.1, 138.1, 137.2, 118.0, 114.7, 110.7, 108.8, 73.6, 55.7, 55.6, 37.8, 30.0. **HRMS**: calculated for $C_{13}H_{18}NaO_3$ $(M+Na)^+$ 245.1148; found 245.1148.

8i:[31] Synthesized according to **Method A** furnishing the known compound in 61% (9.13 mmol, 1.39 g) isolated yield as a yellow oil; R_f 0.71 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38-7.34 (m, 1H), 7.32 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.23 (d, *J* = 3.2 Hz, 1H), 5.83 (ddt, *J* = 17.1, 10.3, 6.6 Hz, 1H), 5.05 (dq, *J* = 10.1, 1.6 Hz, 1H), 5.01-4.96 (m, 1H), 4.69 (t, *J* = 6.8 Hz, 1H), 2.24-1.98 (m, 3H), 1.94 (q, *J* = 7.1 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.6, 141.9, 137.8, 115.1, 110.1, 105.9, 67.2, 34.5, 29.7.

8j:[28] Synthesized according to **Method A** furnishing the known compound in 71% (7.10 mmol, 1.28 g) isolated yield as yellow oil; R_f 0.69 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32–7.26 (m, 2H), 7.04–6.99 (m, 2H), 5.82 (ddt, *J* = 17.1, 10.2, 6.5 Hz, 1H), 5.03 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.00–4.96 (m, 1H), 4.70-4.64 (m, 1H), 2.17–1.98 (m, 3H), 1.93–1.70 (m, 2H).

8k:[32] Synthesized according to **Method A** furnishing the known compound in 71% (7.06 mmol, 1.39 g) isolated yield as a pale yellow oil; R_f 0.62 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34-7.22 (m, 4H), 5.90-5.74 (m, 1H), 5.09-4.94 (m, 2H), 4.72-4.62 (m, 1H), 2.21-2.03 (m, 2H), 2.02-1.68 (m, 3H).

8l:[33] Synthesized according to **Method A** furnishing the known compound in 50% (4.31 mmol, 885 mg) isolated yield as a green oil; R_f 0.76 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.9 Hz, 2H), 6.70 (d, *J* = 8.9 Hz, 2H), 5.82 (ddt, *J* = 17.1, 10.3, 6.4 Hz, 1H), 5.01 (dq, *J* = 17.1, 1.8 Hz, 1H) 4.97-4.92 (m, 1H), 4.57-4.52 (m, 1H), 2.91 (s, 6H), 2.18-1.93 (m, 3H), 1.94-1.83 (m, 1H), 1.80-1.69 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.1, 138.4, 132.5, 126.9, 114.6, 112.5, 73.7, 40.6, 37.6, 30.2.

8m:[32] Synthesized according to **Method A** furnishing the known compound in 57% (6.81 mmol, 1.20 g) isolated yield as a colorless oil; R_f 0.52 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44-7.39 (m, 2H), 7.36-7.29 (m, 2H), 7.25-7.19 (m, 1H), 8.83-5.72 (m, 1H), 4.98-4.92 (m, 1H), 4.92-4.88 (m, 1H), 2.09-1.97 (m, 2H), 1.96-1.84 (m, 3H),

1.55 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.6, 138.7, 128.1, 126.5, 124.7, 114.5, 74.6, 43.0, 30.2, 28.4.

8n:[34] Synthesized according to **Method B** furnishing the known compound in 59% (4.71 mmol, 472 mg) isolated yield as a colorless oil; R_f 0.57 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.83 (ddq, J = 17.1, 10.2, 6.3 Hz, 1H), 5.04 (dq, J = 17.1, 1.7 Hz, 1H), 4.99-4.95 (m, 1H), 3.82 (sext, J = 6.2 Hz, 1H), 2.24-2.07 (m, 2H), 1.71 (bs, 1H), 1.62-1.49 (m, 2H), 1.20 (d, J = 6.4 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.5, 114.7, 67.6, 38.2, 30.1, 23.4.

8o:[32] Synthesized according to **Method A** furnishing the known compound in 67% (8.04 mmol, 1.37 g) isolated yield as a colorless oil; R_f 0.67 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.91-5.77 (m, 1H), 5.08-5.00 (m, 1H), 4.99-4.91 (m, 1H), 3.65-3.54 (m, 1H), 2.27-2.05 (m, 2H), 1.76-1.20 (m, 12H), 0.89 (t, J = 6.9 Hz, 3H).

8p:[35] Synthesized according to **Method A** furnishing the known compound in 73% (13.8 mmol, 2.94 g) isolated yield as a yellow oil; R_f 0.64 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.84 (ddt, J = 17.1, 10.3, 6.9 HZ, 1H), 5.05 (dq, J = 17.1, 1.7 Hz, 1H), 4.96 (ddt, J = 10.3, 1.7, 1.2 Hz, 1H), 3.65-3.57 (m, 1H), 2.25-2.07 (m, 2H), 1.64-1.36 (m, 5H), 1.36-1.18 (m, 13H), 0.88 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.6, 114.7, 71.5, 37.5, 36.5, 31.9, 30.1, 29.66, 29.60, 29.55, 29.3, 25.6, 22.7, 14.1.

8q:[36] Synthesized according to **Method A** furnishing the known compound in 64% (8.00 mmol, 1.41 g) isolated yield; R_f 0.59 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32-7.26 (m, 2H), 7.24-7.17 (m, 3H), 5.82 (ddt, J = 17.1, 10.2, 6.7 Hz, 1H), 5.07-5.00 (m, 1H), 4.99-4.94 (m, 1H), 3.80 (tt, J = 8.1, 4.6 Hz, 1H), 2.80 (dd, J = 13.6, 4.6 Hz, 1H), 2.64 (dd, J = 13.6, 8.1 Hz, 1H), 2.30-2.09 (m, 2H), 1.70 (bs, 1H), 1.66-1.61 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.5, 138.4, 129.5, 128.5, 126.4, 114.8, 77.0, 44.0, 35.8, 30.0.

8r:[32] Synthesized according to **Method A** furnishing the known compound in 61% (0.72 mmol, 137 mg) isolated yield; R_f 0.61 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30-7.23 (m, 2H), 7.21-7.15 (m, 3H), 5.81 (ddt, *J* = 17.0, 10.3, 6.6 Hz, 1H), 5.03 (dq, *J* = 17.0, 1.6 HZ, 1H), 4.96 (ddt, *J* = 10.3, 1.9, 1.3 Hz, 1H), 3.63 (tt, *J* = 7.7, 4.7 Hz, 1H), 2.83-2.71 (m, 1H), 2.70-2.56 (m, 1H), 2.25-2.07 (m, 2H), 1.84-1.67 (m, 3H), 1.64-1.49 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.1, 138.4, 128.3, 125.7, 114.7, 70.8, 39.0, 36.5, 32.0, 30.0.

8s:[37] Synthesized according to **Method A** furnishing the known compound in 78% (7.78 mmol, 998 mg) isolated yield as a colorless oil; R_f 54 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.85 (ddt, *J* = 17.0, 10.3, 6.8 Hz, 1H), 5.05 (dq, *J* = 17.0, 1.6 Hz, 1H), 4.97 (ddt, *J* = 10.3, 1.9, 1.0 Hz, 1H), 3.42-3.34 (m, 1H), 2.31-2.19 (m, 1H), 2.17-2.06 (m, 1H), 1.72-1.62 (m, 1H), 1.60-1.41 (m, 2H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.91 (d, *J* = 6.9 Hz, 3H).

8t:[38] Synthesized according to **Method B** furnishing the known compound in 74% (10.3 mmol, 1.45 g) isolated yield as a colorless oil; R_f 0.71 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.93-5.72 (m, 1H), 5.12-4.95 (m, 2H), 3.30-3.15 (m, 1H), 2.57-2.41 (m, 2H), 2.01-1.88 (m, 2H), 1.83-1.67 (m, 2H), 1.66-1.57 (m, 1H), 1.39-1.07 (m, 4H), 0.99-0.87 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.3, 115.7, 74.2, 44.7, 37.1, 35.4, 30.1, 25.3, 24.8.

8u:[39] Synthesized according to **Method B** furnishing the known compound in 68% (9.90 mmol, 1.92 g) isolated yield as a green oil; R_f 0.65 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.22-7.16 (m, 2H), 6.90-6.84 (m, 1H), 6.84-6.79 (m, 2H), 5.75 (ddt, *J* = 17.1, 10.3, 6.6 Hz, 1H), 5.02-4.95 (m, 1H), 4.98-4.92 (m, 1H), 3.96-3.91 (m, 1H), 3.88 (dd, *J* = 9.2, 3.1 Hz, 1H), 3.75 (dd, *J* = 9.2, 7.4 Hz, 1H), 2.26-2.05 (m, 3H), 1.67-1.52 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.5, 138.0, 129.5, 121.1, 115.1, 114.5, 71.9, 69.6, 32.1, 29.6.

8v:[40] Synthesized according to **Method B** furnishing the known compound in 67% (0.81 mmol, 167 mg) isolated yield as light yellow oil; R_f 0.59 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38-7.29 (m, 5H), 5.81 (ddt, *J* = 17.1, 10.2, 6.5 Hz, 1H), 5.03 (dq, *J* = 17.1, 1.6 Hz, 1H), 4.98-4.94 (m, 1H), 4.55 (s, 2H), 3.86-3.78 (m, 1H), 3.50 (dd, *J* = 9.4, 3.9 Hz, 1H), 3.34 (dd, *J* = 7.6, 9.3 Hz, 1H), 2.42 (bs, 1H), 2.27-2.06 (m, 2H), 1.62-1.50 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.2, 137.9, 128.4, 127.8, 127.7, 114.8, 74.5, 73.3, 69.8, 32.2, 29.7.

General procedure for preparation of alkenols 1a-v: Following a slight modified experimental procedure of the literature.[41]

In a pre-dried round-bottom flask, acrylonitrile (2 equiv) was added to a solution of alkenol (0.50 mmol) in DCM (15 mL) at room temperature. To this solution was added **HG-II (**Hoveyda-Grubbs-II**)** (5 mol%) in one portion and the round-bottom flask was fitted with a pre-dried reflux condenser. This reaction mixture was then heated to reflux for 12 h. The reaction was allowed to return to room temperature and ethyl vinyl ether (50 equiv) and DMSO (50 equiv) were then added to the reaction mixture. The solution was then agitated for additional 1 h in air. After removal of the volatiles under reduced pressure, the crude was immediately purified by silica gel flash column chromatography (EtOAc/hexanes, 2:8) and the alkenol **1** was obtained as an inseparable mixture of Z/E (major/minor, respectively) isomer.

1a: Synthesized according to the general procedure furnishing the new compound in 63% (0.18 mmol, 67 mg) isolated yield (*Z*:*E* 3:1) as a colorless oil; R_f 0.38 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.68-7.62 (m, 4H), 7.48-7.37 (m, 6H), [6.69 (dt, *J* = 16.3, 7.1 Hz, 1H)], 6.49 (dt, *J* = 11.0, 7.6Hz, 1H), 5.33-5.26 (m, 1H), 3.77-3.69 (m, 1H), 3.65 (dd, *J* = 10.1, 3.5 Hz, 1H), [3.64 (dd, *J* = 9.9, 3.5 Hz, 1H)], 3.50 (dd, *J* = 10.1, 7.3 Hz, 1H), [3.48 (dd, *J* = 10.1, 7.1 Hz, 1H)], 2.61-2.45 (m, 2H), 1.63 (bs, 1H), 1.62-1.42 (m, 2H), 1.07 (s,

9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ [155.3], 154.6, 135.5, 132.9, 129.9, 127.8, [117.4], 115.9, [100.1], 99.7, 71.1, [70.8], 67.7, 31.2, [30.6], [29.4], 28.2, 26.8, 19.2. **HRMS**: calculated for $C_{23}H_{29}NNaO_2Si$ $(M+Na)^+$ 402.1860; found 402.1858.

1b: Synthesized according to the general procedure furnishing the new compound in 54% (0.33 mmol, 62 mg) isolated yield (*Z*:*E* 2.6:1) as a light yellow oil; R_f 0.39 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40-7.27 (m, 5H), [6.73 (dt, *J* = 16.3, 6.9 Hz, 1H)], 6.50 (dt, *J* = 10.9, 7.6 Hz, 1H), [5.33 (dt, *J* = 16.3, 1.7 Hz, 1H)], 5.31 (dt, *J* = 10.9, 1.3 Hz, 1H), 4.72 (dd, *J* = 7.7, 5.5 Hz, 1H), 2.64-2.45 (m, 2H), [2.41-2.24 (m, 2H)], 2.03-1.79 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ [155.3], 154.5, 143.9, 128.7, [128.0], 127.9, 125.8, 116.0, [113.1], [100.1], 99.8, 73.8, [73.5], 37.3, [36.6], [29.6], 28.5. **HRMS**: calculated for $C_{12}H_{13}NNaO$ $(M+Na)^+$ 210.0889; found 210.0890.

1c: Synthesized according to the general procedure furnishing the new compound in 63% (0.26 mmol, 69 mg) isolated yield (*Z*:*E* 3:1) as a yellow oil; R_f 0.35 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59-7.53 (m, 4H), 7.46-7.31 (m, 5H), [6.72 (dt, *J* = 16.3, 7.0 Hz, 1H)], 6.49 (dt, *J* = 10.9, 7.6 Hz, 1H), [5.32 (dt, *J* = 16.3, 1.5 Hz, 1H), 5.29 (dt, *J* = 10.9, 1.3 Hz, 1H), 4.73 (dd, *J* = 8.0, 5.3 Hz, 1H), [4.70 (dd, *J* = 7.7, 5.3 Hz, 1H)], 2.64-2.46 (m, 2H), [2.41-2.22 (m, 2H)], 2.26 (bs, 1H), 2.02-1.80 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ [155.3], 154.5, 142.9, [142.8], [140.8], 140.7, 140.6, [140.5], 128.7, [127.4], 127.3, 127.0, 126.2, [117.4], 115.9, [100.0], 99.7, 73.3, [73.1], 37.2, [36.5], [29.6], 28.4. **HRMS**: calculated for $C_{18}H_{17}NNaO$ $(M+Na)^+$ 286.1202; found 286.1200. IR (neat) 3426, 2924, 2220, 1618, 1485, 1072, 1007, 843, 765, 734, 698.

1d: Synthesized according to the general procedure furnishing the new compound in 59% (0.33 mmol, 67 mg) isolated yield (*Z*:*E* 2.8:1) as a colorless oil; R_f 0.33 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48-7.41 (m, 1H), 7.24-7.10 (m, 3H), [6.73 (dt, *J* = 16.4, 6.9 Hz, 1H)], 6.52 (dt, *J* = 10.9, 7.7 Hz, 1H), [5.32 (dt, *J* = 16.4, 1.3 Hz, 1H)], 5.31 (dt, *J*

= 10.9, 1.4 Hz, 1H), 4.94 (dd, *J* = 8.3, 4.5 Hz, 1H), [4.92 (dd, *J* = 7.9, 4.8 Hz, 1H)], 2.64-2.53 (m, 2H), [2.43-2.33 (m, 2H)], 2.32 (s, 3H), [2.31 (s, 3H)], 2.03 (bs, 1H), 1.93-1.75 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ [155.4], 154.6, 142.1, [141.9], 134.2, [130.5], 130.5, [127.5], 127.4, 126.4, 125.0, [117.4], 115.9, [100.0], 99.7, 69.9, [69.6], 36.1, [35.3], [29.7], 28.6, 18.9. **HRMS**: calculated for $C_{13}H_{15}NNaO$ $(M+Na)^+$ 224.1046; found 224.1046. IR (neat) 3447, 3136, 2220, 1624, 1402, 1140, 1098, 914, 760.

1e: Synthesized according to the general procedure furnishing the new compound in 55% (0.20 mmol, 59 mg) isolated yield (*Z*:*E* 2.6:1) as a light yellow oil; R_f 0.35 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38-7.35 (m, 1H), 7.19-7.17 (m, 2H), [7.17-7.15 (m, 2H)], [6.74 (dt, *J* = 16.3, 6.9 Hz, 1H)], 6.51 (dt, *J* = 10.9, 7.8 Hz, 1H), [5.33 (dt, *J* = 16.3, 1.6 Hz, 1H)], 5.30 (dt, *J* = 10.9, 1.5 Hz, 1H), 4.70 (dd, *J* = 8.2, 4.9 Hz, 1H), [4.66 (dd, *J* = 8.2, 4.8 Hz, 1H)], 2.68-2.49 (m, 2H), [2.47-2.28 (m, 2H)], 2.02-1.91 (m, 2H), 1.89-1.78 (m, 1H), 1.33 (s, 18H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ [155.5], 154.7, [151.2], 151.1, 143.23, [143.15], [122.04], 121.98, 119.9, [117.5], 115.9, [100.0], 99.6, 74.5, [74.2], 37.3, [36.7], 34.9, 31.5, [29.9], 28.8. **HRMS**: calculated for $C_{20}H_{29}NNaO$ $(M+Na)^+$ 322.2141; found 322.2144. IR (neat) 3443, 3138, 2959, 2220, 1599, 1402, 1020, 803.

1f: Synthesized according to the general procedure furnishing the new compound in 57% (0.29 mmol, 64 mg) isolated yield (*Z*:*E* 2.9:1) as a light yellow oil; R_f 0.34 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30-7.23 (m, 2H), 6.82-6.87 (m, 2H), [6.72 (dt, *J* = 16.3, 7.0 Hz, 1H)], 6.49 (dt, *J* = 10.9, 7.6 Hz, 1H), [5.32 (dt, *J* = 16.3, 1.7 Hz, 1H)], 5.30 (dt, *J* = 10.9, 1.4 Hz, 1H), 4.67 (dd, *J* = 7.7, 5.5 Hz, 1H), [4.64 (dd, *J* = 7.7, 5.4 Hz, 1H)], 3.81 (s, 3H), 2.60-2.42 (m, 2H), [2.39-2.24 (m, 2H)], 2.25-1.75 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.3, [155.3], 154.6, 136.0, 127.0, [117.4], 115.9, 114.0, [100.1], 99.7, 73.4, [73.1], 55.3, 37.2, [36.5], [29.7], 28.5. **HRMS**: calculated for $C_{13}H_{15}NNaO_2$ $(M+Na)^+$ 240.0995; found 240.0995.

1g: Synthesized according to the general procedure furnishing the new compound in 69% (0.26 mmol, 75 mg) isolated yield (*Z*:*E* 3:1) as a colorless oil; R_f 0.31 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45-7.20 (m, 7H), 6.99-6.93 (m, 2H), [6.70 (dt, *J* = 16.3, 6.9 Hz, 1H)], 6.47 (dt, *J* = 10.8, 7.6 Hz, 1H), [5.30 (dt, *J* = 16.3, 1.4 Hz, 1H)], 5.28 (dt, *J* = 10.8, 1.2 Hz, 1H), 5.05 (s, 2H), 4.64 (dd, *J* = 7.9, 5.5 Hz, 1H), [4.60 (dd, *J* = 7.9, 5.5 Hz, 1H)], 2.59-2.40 (m, 2H), [2.35-2.20 (m, 2H)], 1.99-1.47 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.4, [155.4], 154.6, 136.9, [136.8], 136.3, [136.2], 128.6, 127.9, 127.4, 127.0, [117.4], 115.9, 114.9, [100.0], 99.7, 73.3, [73.0], 70.0, 37.1, [36.5], [29.7], 28.5. **HRMS**: calculated for $C_{19}H_{19}NNaO_2$ $(M+Na)^+$ 316.1308; found 316.1309. IR (neat) 2922, 2220, 1609, 1508, 1456, 1240, 1024, 831, 739, 696.

1h: Synthesized according to the general procedure furnishing the new compound in 65% (0.29 mmol, 72 mg) isolated yield (*Z*:*E* 3:1) as a yellow oil; R_f 0.24 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.85-6.73 (m, 3H), [6.66 (dt, *J* = 16.3, 7.0 Hz, 1H)], 6.72 (dt, *J* = 10.9, 7.9 Hz, 1H), [5.26 (dt, *J* = 16.3, 1.7 Hz, 1H)], 5.23 (dt, *J* = 10.9, 1.3 Hz, 1H), 4.58 (dd, *J* = 7.8, 5.4 Hz, 1H), [4.55 (dd, *J* = 7.8, 5.3 Hz, 1H)], 3.820 (s, 3H), [3.815 (s, 3H)], [3.802 (s, 3H)], 3.799 (s, 3H), 2.55-2.35 (m, 2H), [2.29-2.16 (m, 2H)], 2.05 (bs, 1H), 1.94-1.67 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ [155.3], 154.5, [149.2], 149.1, [148.7], 148.6, 136.6, [136.5], 118.03, [117.98], [117.4], 115.9, 111.0, 108.8, [108.7], [100.0], 99.7, 73.5, [73.3], 55.9, 55.8, 37.2, [36.5], [29.7], 28.5. **HRMS**: calculated for $C_{14}H_{17}NNaO_3$ $(M+Na)^+$ 270.1101; found 270.1103. IR (neat) 2922, 2220, 1516, 1458, 1263, 1234, 1140, 1026, 764.

1i: Synthesized according to the general procedure furnishing the new compound in 53% (0.34 mmol, 61 mg) isolated yield (*Z*:*E* 2.8:1) as a yellow oil; R_f 0.27 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32-7.30 (m, 1H), [6.65 (dt, *J* = 16.3, 7.0 Hz, 1H)], 6.43 (dt, *J* = 10.9, 7.7 Hz, 1H), 6.29-6.26 (m, 1H), 6.21-6.19 (m, 1H), [6.19-6.17 (m, 1H)],

[5.28 (dt, *J* = 16.3, 1.7 Hz, 1H)], 5.25 (dt, *J* = 10.9, 1.3 Hz, 1H), 4.65 (t, *J* = 6.7 Hz, 1H), [4.62 (t, *J* = 6.8 Hz, 1H)], 2.54-2.41 (m, 2H), [2.34-2.21 (m, 2H)], 2.00-1.88 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ [155.7], 154.9, 154.1, 142.1, [117.3], 115.8, 110.3, 106.3, [106.2], [100.2], 99.9, 66.9, [66.7], 33.8, [33.2], [29.3], 28.0. **HRMS**: calculated for $C_{10}H_{11}NNaO_2$ $(M+Na)^+$ 200.0682; found 200.0691.

1j: Synthesized according to the general procedure furnishing the new compound in 51% (0.28 mmol, 57 mg) isolated yield (*Z*:*E* 3:1) as a green oil; R_f 0.33 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.28-7.21 (m, 2H), 7.00-6.93 (m, 2H), [6.65 (dt, *J* = 16.3, 7.0 Hz, 1H)], 6.42 (dt, *J* = 10.9, 7.9 Hz, 1H), [5.25 (dt, *J* = 16.3, 1.7 Hz, 1H)], 5.24 (dt, *J* = 10.9, 1.3 Hz, 1H), 4.63 (dd, *J* = 7.9, 5.3 Hz, 1H), [4.61 (dd, *J* = 7.9, 5.3 Hz, 1H)], 2.53-2.36 (m, 2H), [2.29-2.18 (m, 2H)], 2.00 (bs, 1H), 1.92-1.69 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.3 (d, *J* = 246.8 Hz), [155.1], 154.3, 139.7, 127.4 (d, *J* = 8.5 Hz), [117.3], 115.8, 115.5 (d, *J* = 21.3 Hz), [100.2], 99.9, 73.0, [72.8], 37.3, [36.7], [29.6], 28.4. **HRMS**: calculated for $C_{12}H_{12}FNNaO$ $(M+Na)^+$ 228.0795; found 228.0795. IR (neat) 3414, 2918, 2222, 1603, 1510, 1402, 1223, 1011, 837, 741.

1k: Synthesized according to the general procedure furnishing the new compound in 48% (0.24 mmol, 54 mg) isolated yield (*Z*:*E* 3:1) as a yellow oil; R_f 0.34 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35-7.31 (m, 2H), 7.31-7.27 (m, 2H), [6.73 (dt, *J* = 16.5, 7.1 Hz, 1H)], 6.50 (dt, *J* = 10.9, 7.7 Hz, 1H), [5.34 (dt, *J* = 16.5, 1.9 Hz, 1H)], 5.32 (dt, *J* = 10.9, 1.4 Hz, 1H), 4.71 (dd, *J* = 8.1, 5.1 Hz, 1H), 2.60-2.48 (m, 2H), [2.38-2.28 (m, 2H)], 2.25 (s, 1H), 2.00-1.80 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ [150.0], 154.2, 142.4, [142.2], 133.6, [128.82], 128.78, 127.12, [127.08], 115.9, [100.3], 100.0, 73.0, [72.8], 37.3, [36.6], [29.5], 28.3. **HRMS**: calculated for $C_{12}H_{12}ClNNaO$ $(M+Na)^+$ 244.0500; found 244.0499.

1l: Synthesized according to the general procedure furnishing the new compound in 47% (0.20 mmol, 46 mg) isolated yield (*Z*:*E* 3:1) as a light yellow oil; R_f 0.31 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24-7.17 (m, 2H), 6.74-6.69 (m, 2H), 6.49 (dt, *J* = 10.9, 7.7 Hz, 1H), [5.31 (dt, *J* = 16.3, 1.7 Hz, 1H)], 5.29 (dt, *J* = 10.9, 1.3 Hz, 1H), 4.60 (dd, *J* = 7.6, 5.6 Hz, 1H), [4.58 (dd, *J* = 7.7, 5.9 Hz, 1H)], [2.95 (s, 6H)], 2.95 (s, 6H), 2.60-2.40 (m, 2H), [2.38-2.20 (m, 2H)], 2.03-1.75 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ [155.7], 155.0, 150.6, 131.7, 127.0, 116.1, 112.7, [100.0], 99.7, 73.8, [73.5], 40.7, 37.2, [36.4], [30.0], 28.9. **HRMS**: calculated for $C_{14}H_{19}N_2O$ $(M+H)^+$ 231.1492; found 231.1495. IR (neat) 2934, 2249, 1516, 1458, 1265, 1236, 1138, 762.

1m: Synthesized according to the general procedure furnishing the new compound in 51% (0.29 mmol, 58 mg) isolated yield (*Z*:*E* 3.4:1) as a green oil; R_f 0.21 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46-7.32 (m, 4H), 7.28-7.22 (m, 1H); [6.63 (dt, *J* = 16.3, 7.0 Hz, 1H)], 6.40 (dt, *J* = 10.9, 7.7 Hz, 1H), [5.22 (dt, *J* = 16.3, 1.7 Hz, 1H)], 5.21 (dt, *J* = 10.9, 1.3 Hz, 1H), 2.50-2.20 (m, 2H), 1.98-1.87 (m, 2H), 1.85 (bs, 1H), 1.61 (s, 3H), [1.60 (s, 3H)]; **^{13}C NMR** (101 MHz, $CDCl_3$) δ [155.9], 155.0, 146.9, [146.7], 128.3, 126.9, 124.6, [117.5], 115.8, [99.4], 99.2, 74.2, [74.1], 42.4, [41.8], [30.6], 30.2, [28.2], 26.9. **HRMS**: calculated for $C_{13}H_{15}NNaO$ $(M+Na)^+$ 224.1046; found 224.1047.

1n: Synthesized according to the general procedure furnishing the new compound in 60% (0.96 mmol, 120 mg) isolated yield (*Z*:*E* 2.9:1) as a colorless oil; R_f 0.36 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ [6.69 (dt, *J* = 16.3, 6.9 Hz, 1H)], 6.48 (dt, *J* = 10.9, 7.6 Hz, 1H), [5.30 (dt, *J* = 16.3, 1.7 Hz, 1H)], 5.27 (dt, *J* = 10.9, 1.3 Hz, 1H), 3.81-3.68 (m, 2H), [2.36-2.21 (m, 2H)], 2.18 (bs, 1H), 1.58-1.47 (m, 2H), 1.16 (d, *J* = 6.2 Hz, 3H), [1.14 (d, *J* = 6.2 Hz, 3H)]; **^{13}C NMR** (101 MHz, $CDCl_3$) δ [155.8], 155.0, [117.4], 115.9, [99.7], 99.4, 67.0, [66.8], 37.1, [36.6], [29.5], 28.3, [23.5], 23.4. **HRMS**: calculated for $C_7H_{11}NNaO$ $(M+Na)^+$ 148.0733; found 148.0736. IR (neat) 2930, 2224, 1373, 1082, 1038, 970, 903.

1o: Synthesized according to the general procedure furnishing the new compound in 57% (0.30 mmol, 58 mg) isolated yield (*Z*:*E* 3:1) as a colorless oil; R_f 0.34 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ [6.76 (dt, *J* = 16.3, 7.0 Hz, 1H)], 6.54 (dt, *J* = 10.9, 7.9 Hz, 1H), [5.36 (dt, *J* = 16.3, 1.7 Hz, 1H)], 5.33 (dt, *J* = 10.9, 1.3 Hz, 1H), 3.67-3.55 (m, 1H), 2.64-2.48 (m, 2H), [2.48-2.27 (m, 2H)], 1.68-1.51 (m, 2H), 1.51-1.39 (m, 3H), 1.37-1.22 (m, 8H), 0.89 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ [155.8], 155.0, [117.5], 116.0, [99.9], 99.6, 71.1, [70.9], [37.7], 37.5, 35.6, [35.0], 31.7, [29.7], 29.2, 28.3, 25.5, 22.5, 14.0. **HRMS**: calculated for $C_{12}H_{21}NNaO$ $(M+Na)^+$ 218.1515; found 218.1517. IR (neat) 3393, 2926, 2222, 1622, 1456, 1069, 741.

1p: Synthesized according to the general procedure furnishing the new compound in 54% (0.25 mmol, 60 mg) isolated yield (*Z*:*E* 2.9:1) as a colorless oil; R_f 0.29 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ [6.76 (dt, *J* = 16.4, 7.0 Hz, 1H)], 6.54 (dt, *J* = 10.8, 7.7 Hz, 1H), [5.36 (dt, *J* = 16.4, 1.7 Hz, 1H)], 5.32 (dt, *J* = 10.8, 1.3 Hz), 3.67-3.57 (m, 1H), 2.61-2.50 (m, 2H), [2.47-2.23 (m, 2H)], 1.67-1.51 (m, 2H), 1.49-1.38 (m, 3H), 1.35-1.20 (m, 14H), 0.88 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ [155.7], 155.0, [99.9], 99.6, 71.1, [71.0], [37.7], 37.6, 35.6, [35.0], 31.9, 29.7, 29.6, 29.5, 29.3, 28.4, 25.6, 22.7, 14.1. **HRMS**: calculated for $C_{15}H_{27}NNaO$ $(M+Na)^+$ 260.1985; found 260.1985. IR (neat) 3447, 2924, 2222, 1622, 1458, 1088, 741.

1q: Synthesized according to the general procedure furnishing the new compound in 58% (0.33 mmol, 66 mg) isolated yield (*Z*:*E* 2.9:1) as a colorless oil; R_f 0.38 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36-7.29 (m, 2H), 7.28-7.24 (m, 1H), 7.23-7.17 (m, 2H), [6.74 (dt, *J* = 16.3, 7.0 Hz, 1H)], 6.53 (dt, *J* = 10.9, 7.9 Hz, 1H), [5.35 (dt, *J* = 16.3, 1.7 Hz, 1H)], 5.32 (dt, *J* = 10.9, 1.3 Hz, 1H), 3.88-3.76 (m, 1H), 2.85 (dd, *J* = 13.5, 4.3 Hz, 1H), [2.81 (dd, *J* = 13.5, 4.3 Hz, 1H)], 2.68 (dd, *J* = 13.5, 8.4 Hz, 1H), [2.67 (dd, *J* = 13.5, 8.4 Hz, 1H)], 2.64-2.53 (m, 2H), [2.51-2.28 (m, 2H)], 1.76-1.57 (m, 3H); **^{13}C NMR** (101 MHz,

$CDCl_3$) δ [155.5], 154.8, 137.9, 129.4, [129.3], [128.74], 128.69, [126.8], 126.7, [117.5], 116.0, [100.0], 99.7, 71.8, [71.5], [44.3], 44.1, 34.9, [34.4], [29.7], 28.4. **HRMS**: calculated for $C_{13}H_{15}NNaO$ $(M+Na)^+$ 224.1046; found 224.1048. IR (neat) 3435, 2926, 2220, 1603, 1495, 1454, 1248, 1082, 746, 700.

1r: Synthesized according to the general procedure furnishing the new compound in 53% (0.30 mmol, 65 mg) isolated yield (*Z*:*E* 3.3:1) as a colorless oil; R_f 0.21 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32-7.26 (m, 2H), 7.23-7.17 (m, 3H), [6.73 (dt, *J* = 16.3, 7.0 Hz, 1H)], 6.51 (dt, *J* = 10.9, 7.9 Hz, 1H), [5.32 (dt, *J* = 16.3, 1.7 Hz, 1H)], 5.31 (dt, *J* = 10.9, 1.3 Hz, 1H), 3.70-3.58 (m, 1H), 2.85-2.73 (m, 1H), 2.74-2.62 (m, 1H), 2.61-2.47 (m, 2H), [2.45-2.24 (m, 2H)], 1.87-1.72 (m, 2H), 1.71-1.54 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ [155.5], 154.7, 141.6, [141.5], 128.5, 128.4, [126.03], 125.95, [117.5], 116.0, [100.0], 99.8, 70.4, [70.3], [39.2], 39.0, 35.7, [35.2], 32.0, [29.6], 28.3. **HRMS**: calculated for $C_{14}H_{17}NNaO$ $(M+Na)^+$ 238.1202; found 238.1200. IR (neat) 3138, 2220, 1402, 1009, 912, 744, 700.

1s: Synthesized according to the general procedure furnishing the new compound in 71% (0.55 mmol, 84 mg) isolated yield (*Z*:*E* 3.3:1) as a colorless oil; R_f 0.39 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ [6.77 (dt, *J* = 16.3, 7.0 Hz, 1H)], 6.56 (dt, *J* = 10.9, 7.9 Hz, 1H), [5.40-5.33 (m, 1H)], 5.36-5.29 (m, 1H), 3.43-3.30 (m, 1H), 2.67-2.48 (m, 2H), [2.50-2.24 (m, 2H)], 1.80-1.48 (m, 4H), 0.93 (d, *J* = 6.8 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ [156.0], 155.2, [117.5], 116.00, [99.8], 99.4, 75.8, [75.6], [33.8], 33.7, 32.4, [31.8], [30.0], 28.7, 18.6, [18.6], 17.1. **HRMS**: calculated for $C_9H_{15}NNaO$ $(M+Na)^+$ 176.1046; found 176.1045.

1t: Synthesized according to the general procedure furnishing the new compound in 55% (0.39 mmol, 64 mg) isolated yield (*Z*:*E* 2:1) as a green oil; R_f 0.27 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ [6.76 (ddd, *J* = 16.3, 8.5, 6.7 Hz, 1H)], 6.58 (ddd, *J* =

10.9, 9.0, 6.7 Hz, 1H), 5.36 (m, 1H), [5.35 (m, 1H)], 3.28 (td, *J* = 9.9, 4.4 Hz, 1H), [3.22 (td, *J* = 10.2, 4.7 Hz, 1H)], 2.81 (dddd, *J* = 8.1, 6.3, 4.3, 1.4 Hz, 1H), [2.68 (dddd, *J* = 8.4, 6.2, 4.0, 1.7 Hz, 1H)], 2.40 (dt, *J* = 14.4, 8.6 Hz, 1H), [2.17-2.08 (m, 1H)], 2.00-1.92 (m, 1H), 1.84-1.59 (m, 4H), [1.59-1.35 (m, 2H)], 1.32-1.11 (m, 3H), [1.11-0.89 (m, 2H)]; **^{13}C NMR** (101 MHz, $CDCl_3$) δ [155.1], 154.4, [117.5], 116.3, [100.7], 100.2, 74.1, [74.0], 44.8, [44.5], [36.7], [36.1], 36.0, 35.3, 30.5, [30.4], 25.3, 24.8. **HRMS**: calculated for $C_{10}H_{15}NNaO$ $(M+Na)^+$ 188.1046; found 188.1047. IR (neat) 3445, 2930, 2222, 1618, 1449, 1061, 1036, 741.

1u: Synthesized according to the general procedure furnishing the new compound in 59% (0.30 mmol, 66 mg) isolated yield (*Z*:*E* 3.7:1) as a green oil; R_f 0.41 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34-7.24 (m, 2H), 7.02-6.95 (m, 1H), 6.94-6.88 (m, 2H), [6.78 (dt, *J* = 16.3, 7.0 Hz, 1H), 6.57 (dt, *J* = 10.9, 7.7 Hz, 1H), [5.40 (dt, *J* = 16.3, 1.7 Hz, 1H)], 5.36 (dt, *J* = 10.9, 1.3 Hz, 1H), 4.08-3.99 (m, 1H), 3.99 (dd, *J* = 9.0, 3.0 Hz, 1H), [3.97 (dd, *J* = 9.0, 3.0 Hz, 1H)], 3.86 (dd, *J* = 9.0, 7.2 Hz, 1H), 2.65 (dddd, *J* = 10.6, 7.3, 2.8, 1.3 Hz, 1H), [2.56-2.44 (m, 2H)], 2.44-2.34 (m, 1H), 1.81-1.69 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.4, [155.1], 154.3, 129.6, 121.3, [117.8], 115.9, 114.6, [100.4], 100.1, 71.7, 69.3, [69.1], 31.5, [30.9], [29.4], 28.1. **HRMS**: calculated for $C_{13}H_{15}NNaO_2$ $(M+Na)^+$ 240.0995; found 240.0992. IR (neat) 3470, 2936, 2222, 1599, 1238, 756, 692.

1v: Synthesized according to the general procedure furnishing the new compound in 57% (0.27 mmol, 63 mg) isolated yield (*Z*:*E* 3.5:1) as a colorless oil; R_f 0.31 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41-7.27 (m, 5H), [6.72 (dt, *J* = 16.3, 7.0 Hz, 1H), 6.52 (dt, *J* = 10.9, 7.7 Hz, 1H), [5.34 (dt, *J* = 16.3, 1.7 Hz, 1H)], 5.31 (dt, *J* = 10.9, 1.3 Hz, 1H), 4.55 (s, 2H), [4.54 (s, 2H)], 3.87-3.74 (m, 1H), 3.50 (dd, *J* = 9.4, 3.2 Hz, 1H), [3.48 (dd, *J* = 9.4, 3.2 Hz, 1H)], 3.35 (dd, *J* = 9.4, 7.5 Hz, 1H), [3.33 (dd, *J* = 9.4, 7.5 Hz, 1H)], 2.60-2.44 (m, 3H), [2.46-2.25 (m, 2H)], 1.67-1.52 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ

[155.3], 154.6, 137.7, 128.5, [127.9], 127.8, 127.7, [117.4], 115.9, [100.1], 99.8, 74.1, 73.4, 69.5, [69.3], 31.5, [30.9.], [29.4], 28.2. **HRMS**: calculated for $C_{14}H_{17}NNaO_2$ $(M+Na)^+$ 254.1151; found 254.1150. IR (neat) 3447, 2922, 2220, 1456, 1124, 1092, 741, 698.

General procedure for preparation of 2,5-*trans*-THFs 3: A solution of the alkenol **1** (0.20 mmol), reductant (according to the Table 1) (20 equiv), and cobalt(II) catalyst (15 mol%) was stirred for 12 h at 70°C in conventional laboratory atmosphere. The reaction mixture was cooled (25 °C) and volatiles were evaporated and the product purified by silica gel flash chromatography (EtOAc/hexanes, 2:8) to give **3** as the single diastereoisomer (dr > 20:1).

3a: Synthesized according to the general procedure furnishing the new compound in 63% (0.065 mmol, 25 mg) isolated yield as a colorless oil; R_f 0.40 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72-7.63 (m, 4H), 7.46-7.34 (m, 6H), 4.28-4.20 (m, 2H), 3.69 (dd, *J* = 10.8, 4.4 Hz, 1H), 3.62 (dd, *J* = 10.8, 4.2 Hz, 1H), 2.59 (dd, *J* = 16.6, 5.8 Hz, 1H), 2.53 (dd, *J* = 16.6, 5.1 Hz, 1H), 2.26-2.16 (m, 1H), 2.15-2.05 (m, 1H), 2.02-1.90 (m, 1H), 1.82-1.70 (m, 1H), 1.06 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.6, 133.4, 129.7, 127.7, 117.5, 80.2, 74.5, 66.1, 31.5, 27.6, 26.8, 24.2, 19.2. **HRMS**: calculated for $C_{23}H_{29}NNaO_2Si$ $(M+Na)^+$ 402.1860; found 402.1858. IR (neat) 2930, 2857, 2251, 1472, 1427, 1113, 1080, 824, 743, 704, 613.

3b: Synthesized according to the general procedure furnishing the new compound in 52% (0.13 mmol, 25 mg) isolated yield as a light yellow oil; R_f 0.43 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38-7.22 (m, 5H), 5.14 (dd, *J* = 7.8, 5.4 Hz, 1H), 4.52-4.44 (m, 1H), 2.73 (dd, *J* = 16.8, 5.0 Hz, 1H), 2.65 (dd, *J* = 16.8, 4.5 Hz, 1H), 2.52-2.43 (m, 1H), 2.36-2.25 (m, 1H), 2.01-1.89 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 133.6, 128.6, 127.7, 125.6, 117.6, 81.7, 74.8, 35.2, 31.9, 24.6. **HRMS**: calculated for $C_{12}H_{13}NNaO$ $(M+Na)^+$ 210.0889; found 210.0891. IR (neat) 2924, 2220, 1686, 1449, 1263, 1204, 1061, 750, 702.

3c: Synthesized according to the general procedure furnishing the new compound in 77% (0.14 mmol, 38 mg) isolated yield as a yellow oil; R_f 0.48 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.63-7.29 (m, 9H), 5.18 (t, J = 7.2 Hz, 1H), 4.49 (q, J = 5.2 Hz, 1H), 2.73 (dd, J = 16.6, 5.9 Hz, 1H), 2.64 (dd, J = 16.6, 4.1 Hz, 1H), 2.55-2.42 (m, 1H), 2.38-2.27 (m, 1H), 2.05-1.89 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.2, 140.8, 140.5, 128.7, 127.23, 127.15, 127.0, 126.0, 117.6, 81.3, 74.6, 34.9, 31.7, 24.4. **HRMS**: calculated for $C_{18}H_{17}NNaO$ $(M+Na)^+$ 286.1202; found 286.1204. IR (neat) 2922, 2249, 1458, 1375, 1063, 764, 698.

3d: Synthesized according to the general procedure furnishing the new compound in 71% (0.15 mmol, 31 mg) isolated yield as a colorless oil; R_f 0.55 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41-7.36 (m, 1H), 7.23-7.11 (m, 3H), 5.32 (dd, J = 8.2, 6.4 Hz, 1H), 4.56-4.48 (m, 1H), 2.71 (dd, J = 16.7, 5.9 Hz, 1H), 2.64 (dd, J = 16.7, 4.7 Hz, 1H), 2.55-2.45 (m, 1H), 2.37-2.27 (m, 1H), 2.31 (s, 3H), 2.01-1.91 (m, 1H), 1.88-1.77 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.4, 134.3, 130.4, 127.2, 126.1, 124.3, 118.3, 78.9, 74.6, 33.4, 31.7, 24.5, 19.2. **HRMS**: calculated for $C_{13}H_{15}NNaO$ $(M+Na)^+$ 224.1046; found 224.1045. IR (neat) 2930, 2249, 1458, 1062, 754.

3e: Synthesized according to the general procedure furnishing the new compound in 55% (0.090 mmol, 27 mg) isolated yield pale yellow oil; R_f 0.49 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 (t, J = 1.8 Hz, 1H), 5.11 (dd, J = 7.7, 5.9 Hz, 1H), 4.53-4.46 (m, 1H), 2.72 (dd, J = 16.6, 5.9 Hz, 1H), 2.65 (dd, J = 16.6, 4.6 Hz, 1H), 2.50-2.40 (m, 1H), 2.37-2.30 (m, 1H), 2.05-1.91 (m, 2H), 1.32 (s, 18H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.8, 141.0, 121.8, 115.3, 119.9, 82.3, 74.5, 35.0, 34.9, 31.9, 31.5, 24.5. **HRMS**: calculated for $C_{20}H_{29}NNaO$ $(M+Na)^+$ 322.2141; found 322.2144.

3f: Synthesized according to the general procedure furnishing the new compound in 58% (0.12 mmol, 27 mg) isolated yield pale oil; R_f 0.46 (20% ethyl acetate in hexane). **^{1}H NMR**

(400 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.7 Hz, 1H), 6.80 (d, *J* = 8.7 Hz, 1H), 5.00 (t, *J* = 7.3 Hz, 1H), 4.41-4.31 (m, 1H), 3.73 (s, 3H), 2.61-2.41 (m, 2H), 2.39-2.31 (m, 1H), 2.27-2.17 (m, 1H), 1.93-1.78 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 134.1, 130.3, 126.9, 115.9, 113.9, 81.3, 74.3, 55.29, 34.9, 31.8, 24.8. **HRMS**: calculated for $C_{13}H_{15}NNaO_2$ $(M+Na)^+$ 240.0995; found 240.0996. IR (neat) 2922, 2220, 1676, 1601, 1248, 1175, 1061, 1032, 831.

3g: Synthesized according to the general procedure furnishing the new compound in 69% (0.13 mmol, 38 mg) isolated yield as a colorless oil; R_f 0.57 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44-7.29 (m, 5H), 7.25-7.21 (m, 2H), 6.97-6.92 (m, 2H), 5.08-5.03 (m, 1H), 5.06 (s, 2H), 4.48-4.38 (m, 1H), 2.63 (dd, *J* = 16.8, 6.0 Hz, 1H), 2.55 (dd, *J* = 16.8, 4.5 Hz, 1H), 2.46-2.35 (m, 1H), 2.35-2.25 (m, 1H), 1.99-1.86 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.3, 137.0, 134.4, 128.6, 127.9, 127.4, 126.9, 117.5, 114.8, 81.3, 74.4, 70.0, 34.9, 31.8, 24.6. **HRMS**: calculated for $C_{19}H_{19}NNaO_2$ $(M+Na)^+$ 316.1308; found 316.1305.

3h: Synthesized according to the general procedure furnishing the new compound in 65% (0.13 mmol, 32 mg) isolated yield as a yellow oil; R_f 0.53 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.87-6.81 (m, 3H), 5.08 (dd, *J* = 8.4, 6.2 Hz, 1H), 4.51-4.43 (m, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 2.71 (dd, *J* = 16.8, 5.8 Hz, 1H), 2.63 (dd, *J* = 16.8, 4.6 Hz, 1H), 2.47-2.38 (m, 1H), 2.36-2.28 (m, 1H), 2.02-1.90 (m 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.2, 148.6, 134.7, 118.3, 118.0, 111.2, 109.1, 81.6, 74.6, 56.1, 56.0, 35.1, 32.0, 24.7. **HRMS**: calculated for $C_{14}H_{17}NNaO_3$ $(M+Na)^+$ 270.1100; found 270.1098.

3i: Synthesized according to the general procedure furnishing the new compound in 62% (0.17 mmol, 30 mg) isolated yield as a deep yellow oil; R_f 0.51 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.32 (dd, *J* = 3.1, 1.8 Hz, 1H), 6.28-6.27 (m, 1H), 5.15 (t, *J* = 6.9 Hz, 1H), 4.41-4.33 (m, 1H), 4.33 (dd, *J* = 16.8, 6.0 Hz, 1H), 2.62 (dd, *J* = 16.8, 4.5 Hz, 1H), 2.42-2.21 (m, 3H), 1.98-1.87 (m, 1H); **^{13}C NMR** (101

MHz, $CDCl_3$) δ 154.0, 142.6, 117.2, 110.2, 107.3, 74.7, 74.1, 31.4, 30.4, 24.1. **HRMS**: calculated for $C_{10}H_{11}NNaO_2$ $(M+Na)^+$ 200.0682; found 200.0681.

3j: Synthesized according to the general procedure furnishing the new compound in 61% (0.15 mmol, 30 mg) isolated yield as a green oil; R_f 0.40 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32-7.23 (m, 2H), 7.07-6.99 (m, 2H), 5.10 (t, J = 7.3 Hz, 1H), 4.45 (quint, J = 6.3 Hz, 1H), 2.64 (dd, J = 16.5, 5.8 Hz, 1H), 2.55 (dd, J = 16.5, 4.5 Hz, 1H), 2.49-2.40 (m, 1H), 2.35-2.24 (m, 1H), 1.99-1.84 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.2 (d, J = 252.0 Hz), 137.9, 127.2 (d, J = 8.1 Hz), 118.5, 115.3 (d, J = 20.2 Hz), 80.9, 74.5, 35.1, 31.7, 24.7. **HRMS**: calculated for $C_{12}H_{12}FNNaO$ $(M+Na)^+$ 228.0795; found 228.0796. IR (neat) 2928, 2251, 1607, 1510, 1225, 1063, 835.

3k: Synthesized according to the general procedure furnishing the new compound in 64% (0.081 mmol, 18 mg) isolated yield as a light yellow oil; R_f 0.45 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33-7.29 (m, 2H), 7.27-7.22 (m, 2H), 5.11 (dd, J = 8.2, 6.4 Hz, 1H), 4.50-4.43 (m, 1H), 2.71 (dd, J = 16.7, 5.7 Hz, 1H), 2.62 (dd, J = 16.7, 4.7 Hz, 1H), 2.51-2.42 (m, 1H), 2.35-2.26 (m, 1H), 2.01-1.83 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.8, 133.2, 128.6, 126.8, 117.5, 80.8, 74.7, 35.1, 31.7, 24.5. **HRMS**: calculated for $C_{12}H_{12}ClNNaO$ $(M+Na)^+$ 244.0500; found 244.0497.

3n: Synthesized according to the general procedure furnishing the new compound in 45% (0.15 mmol, 19 mg) isolated yield as a colorless oil; R_f 0.52 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.31-4.18 (m, 2H), 2.59 (dd, J = 16.5, 5.7 Hz, 1H), 2.53 (dd, J = 16.5, 4.9 Hz, 1H), 2.26-2.10 (m, 2H), 1.85-1.74 (m, 1H), 1.61-1.50 (m, 1H), 1.23 (d, J = 6.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 117.8, 76.1, 73.6, 33.7, 31.7, 24.4, 20.9. **HRMS**: calculated for $C_7H_{11}NNaO$ $(M+Na)^+$ 148.0733; found 148.0736. IR (neat) 2930, 2249, 1719, 1456, 1379, 1292, 1190, 1084, 702.

3o: Synthesized according to the general procedure furnishing the new compound in 68% (0.17 mmol, 33 mg) isolated yield as a colorless oil; R_f 0.41 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.26-4.18 (m, 1H), 4.10-4.02 (m, 1H), 2.58 (dd, *J* = 16.7, 5.7 Hz, 1H), 2.52 (dd, *J* = 16.7, 4.7 Hz, 1H), 2.24-2.07 (m, 2H), 1.83-1.71 (m, 1H), 1.63-1.51 (m, 1H), 1.47-1.34 (m, 2H), 1.34-1.23 (m, 8H), 0.88 (t, *J* = 6.9 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 118.4, 80.3, 73.5, 35.6, 31.8, 31.7, 31.5, 29.3, 26.0, 24.4, 22.5, 14.0. **HRMS**: calculated for $C_{12}H_{21}NNaO$ $(M+Na)^+$ 218.1515; found 218.1515. IR (neat) 2928, 2251, 1466, 1377, 1069.

3p: Synthesized according to the general procedure furnishing the new compound in 71% (0.21 mmol, 49 mg) isolated yield as a colorless oil; R_f 0.49 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.26-4.18 (m, 1H), 4.10-4.02 (m, 1H), 2.57 (dd, *J* = 16.7, 6.0 Hz, 1H), 2.52 (dd, *J* = 16.7, 4.7 Hz, 1H), 2.24-2.07 (m, 2H), 1.83-1.71 (m, 1H), 1.64-1.52 (m, 2H), 1.47-1.36 (m, 2H), 1.35-1.22 (m, 14H), 0.88 (t, *J* = 6.8 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 118.3, 80.3, 73.5, 35.7, 31.9, 31.8, 31.5, 29.63, 29.55, 29.51, 29.3, 26.0, 24.4, 22.6, 14.1. **HRMS**: calculated for $C_{15}H_{27}NNaO$ $(M+Na)^+$ 260.1985; found 260.1985. IR (neat) 2926, 2251, 1717, 1460, 1071, 887, 721.

3q: Synthesized according to the general procedure furnishing the new compound in 63% (0.12 mmol, 25 mg) isolated yield as a colorless oil; R_f 0.51 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31-7.27 (m, 2H), 7.24-7.19 (m, 3H), 4.40-4.32 (m, 1H), 4.29-4.22 (m, 1H), 2.93 (dd, *J* = 13.6, 6.0 Hz, 1H), 2.74 (dd, *J* = 13.6, 6.8 Hz, 1H), 2.59 (dd, *J* = 16.7, 5.9 Hz, 1H), 2.53 (dd, *J* = 16.7, 4.7 Hz, 1H), 2.20-2.11 (m, 1H), 2.09-2.00 (m, 1H), 1.81-1.63 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.1, 129.3, 128.4, 126.4, 117.5, 80.7, 74.0, 41.7, 31.4, 31.2, 24.3. **HRMS**: calculated for $C_{13}H_{15}NNaO$ $(M+Na)^+$ 224.1046; found 224.1043. IR (neat) 2928, 2249, 1719, 1452, 1070, 702.

3r: Synthesized according to the general procedure furnishing the new compound in 55% (0.098 mmol, 21 mg) isolated yield as a colorless oil; R_f 0.51 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31-7.22 (m, 2H), 7.22-7.15 (m, 3H), 4.30-4.22 (m, 1H), 4.13-4.04 (m, 1H), 2.79-2.62 (m, 2H), 2.59 (dd, *J* = 16.5, 6.2 Hz, 1H), 2.54 (dd, *J* = 16.5, 5.0 Hz, 1H), 2.25-2.07 (m, 2H), 1.94-1.83 (m, 1H), 1.82-1.71 (m, 2H), 1.66-1.54 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.8, 128.4, 125.8, 117.6, 79.4, 73.7, 37.3, 32.4, 31.8, 31.5, 24.3. **HRMS**: calculated for $C_{14}H_{17}NNaO$ $(M+Na)^+$ 238.1202; found 238.1202. IR (neat) 2928, 2249, 1495, 1454, 1063, 700.

3s: Synthesized according to the general procedure furnishing the new compound in 74% (0.29 mmol, 44 mg) isolated yield as a colorless oil; R_f 0.57 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.21-4.11 (m, 1H), 3.79-3.71 (m, 1H), 2.52 (dd, *J* = 16.7, 5.7 Hz, 1H), 2.46 (dd, *J* = 16.7, 4.7 Hz, 1H), 2.21-2.11 (m, 1H), 2.08-1.98 (m, 1H), 1.79-1.56 (m, 3H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.86 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 118.5, 85.5, 73.8, 33.0, 31.8, 29.3, 24.5, 19.1, 18.1. **HRMS**: calculated for $C_9H_{15}NNaO$ $(M+Na)^+$ 176.1046; found 176.1045.

3t: Synthesized according to the general procedure furnishing the new compound in 69% (0.23 mmol, 38 mg) isolated yield as a colorless oil; R_f 0.41 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.33-4.24 (m, 1H), 3.35-3.27 (m, 1H), 2.66 (dd, *J* = 16.6, 6.0 Hz, 1H), 2.57 (dd, *J* = 16.6, 4.8 Hz, 1H), 2.28-2.22 (m, 1H), 2.14-2.08 (m, 1H), 1.98-1.92 (m, 1H), 1.85-1.80 (m, 1H), 1.76-1.70 (m, 1H), 1.55-1.46 (m, 2H), 1.34-1.24 (m, 2H), 1.22-1.13 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 117.8, 83.5, 73.2, 46.2, 37.2, 31.1, 28.6, 25.5, 24.8, 24.1. **HRMS**: calculated for $C_{10}H_{15}NNaO$ $(M+Na)^+$ 188.1046; found 188.1047. IR (neat) 2931, 2247, 1418, 1061, 1005.

3u: Synthesized according to the general procedure furnishing the new compound in 64% (0.14 mmol, 31 mg) isolated yield as a green oil; R_f 0.41 (20% ethyl acetate in hexane). **^{1}H**

NMR (400 MHz, $CDCl_3$) δ 7.33-7.26 (m, 2H), 6.98-6.87 (m, 3H), 4.53-4.47 (m, 1H), 4.37-4.30 (m, 1H), 3.99 (dd, *J* = 9.9, 4.3 Hz, 1H), 3.96 (dd, *J* = 9.9, 5.1 Hz, 1H), 2.66 (dd, *J* = 16.7, 5.9 Hz, 1H), 2.60 (dd, *J* = 16.7, 4.9 Hz, 1H), 2.34-2.20 (m, 2H), 2.02-1.82 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.7, 129.4, 121.0, 117.3, 114.6, 78.1, 74.6, 70.1, 31.3, 28.2, 24.1. **HRMS**: calculated for $C_{13}H_{15}NNaO_2$ $(M+Na)^+$ 240.0995; found 240.0996.

3v: Synthesized according to the general procedure furnishing the new compound in 68% (0.14 mmol, 33 mg) isolated yield as a colorless oil; R_f 0.54 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37-7.30 (m, 5H), 4.59 (d, *J* = 12.2 Hz, 1H), 4.55 (d, *J* = 12.2 Hz, 1H), 4.36-4.30 (m, 1H), 4.30-4.23 (m, 1H), 3.50 (dd, *J* = 10.1, 3.9 Hz, 1H), 3.45 (dd, *J* = 10.1, 5.5 Hz, 1H), 2.62 (dd, *J* = 16.7, 5.9 Hz, 1H), 2.57 (dd, *J* = 16.7, 4.7 Hz, 1H), 2.27-2.16 (m, 1H), 2.16-2.05 (m, 1H), 1.86-1.73 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.1, 128.5, 128.4, 127.6, 117.4, 78.9, 74.4, 73.4, 72.4, 31.3, 28.2, 24.1. **HRMS**: calculated for $C_{14}H_{17}NNaO_2$ $(M+Na)^+$ 254.1152; found 254.1149. IR (neat) 2926, 2249, 1719, 1452, 1078, 740, 700.

Stereochemistry determination: preparation of compounds 4, 5 and 3a:

4:[6a] Synthesized according to the literature.

5:[42] PPh_3 (1.5 equiv, 982 mg, 3.75 mmol), imidazole (3 equiv, 503 mg, 7.4 mmol), and I_2 (1.5 equiv, 938 mg, 3.75 mmol) were added to a solution of alcohol **4** (900 mg, 2.43 mmol) in THF (22 mL) at 0 ºC and the reaction mixture was allowed to warm to room temperature. After 2 h, an additional quantity of PPh_3 (1.5 equiv, 982 mg, 3.75 mmol), imidazole (3 equiv, 503 mg, 7.4 mmol), and I_2 (1.5 equiv, 938 mg, 3.75 mmol) were added to the reaction mixture. After an additional 1 h, the reaction mixture was diluted with Et_2O (40 mL) and poured into saturated $Na_2S_2O_3$ solution (22 mL), and the reaction mixture was extracted with Et_2O (30 mL x 3). The organic extracts were dried over Na_2SO_4, filtered, and concentrated. Purification of the residue by flash column chromatography (EtOAc/hexanes, 2:8) to give **5**

(944 mg, 1.97 mmol) in 81% yield as a yellow oil and a single diastereoisomer. R_f 0.80 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71-7.64 (m, 4H), 7.45-7.35 (m, 6H), 4.23 (tt, *J* = 6.8, 4.5 Hz, 1H) 4.13-4.06 (m, 1H), 3.66 (dd, *J* = 10.7, 4.5 Hz, 1H), 3.63 (dd, *J* = 10.7, 4.5 Hz), 3.25 (dd, *J* = 9.9, 4.9 Hz, 1H), 3.22 (dd, *J* = 9.9, 6.8 Hz, 1H), 2.23-2.13 (m, 1H), 2.11-2.02 (m, 1H), 1.98-1.87 (m, 1H), 1.73-1.63 (m, 1H), 1.05 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.6, 133.5, 129.6, 127.6, 80.3, 78.8, 66.2, 32.3, 28.0, 26.8, 19.2, 10.7. **HRMS**: calculated for $C_{22}H_{29}INaO_2Si$ $(M+Na)^+$ 503.0874; found 503.0875.

3a:[2f] Under a nitrogen atmosphere, NaCN (1.5 equiv, 145 mg, 2.97 mmol) was added to a solution of **5** (944 mg, 1.98 mmol) in DMSO (5 mL) at r.t.. The reaction mixture was stirred at 60 °C for 1 h. The reaction was quenched with saturated aqueous NH_4Cl (15 mL). The mixture was extracted with AcOEt (3 x 20 mL). The organic layer was washed with water (3 x 5 mL), then brine (5 mL), dried over Na_2SO_4, and evaporated in vacuo. Purification of the residue by flash column chromatography (EtOAc/hexanes, 2:8) gave **3a** (502 mg, 1.33 mmol) in 67% yield as a colorless oil and a single diastereoisomer. R_f 0.40 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72-7.63 (m, 4H), 7.46-7.34 (m, 6H), 4.28-4.20 (m, 2H), 3.69 (dd, *J* = 10.8, 4.4 Hz, 1H), 3.62 (dd, *J* = 10.8, 4.2 Hz, 1H), 2.59 (dd, *J* = 16.6, 5.8 Hz, 1H), 2.53 (dd, *J* = 16.6, 5.1 Hz, 1H), 2.26-2.16 (m, 1H), 2.15-2.05 (m, 1H), 2.02-1.90 (m, 1H), 1.82-1.70 (m, 1H), 1.06 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.6, 133.4, 129.7, 127.7, 117.5, 80.2, 74.5, 66.1, 31.4, 27.6, 26.8, 24.1, 19.2.

6:[43] To a solution of **3a** (52 mg, 0.137 mmol) in anhydrous THF (1.5 mL) under argon was added dropwise borane dimethyl sulfide complex (0.064 mL, 0.685 mmol, 5 equiv) using a syringe. The reaction mixture was stirred at room temperature during 24 h. Methanol was added slowly at 0 °C until no further bubbling or reaction was observed, followed by addition of a small quantity of silica gel. The residual heterogeneous mixture was stirred during 1 h at r.t.. The solvent was removed under reduced pressure and the residue purified by flash

column chromatography (EtOAc/hexanes, 2:8) to give **6** (29 mg, 0.077 mmol) in 56% yield as a colorless oil. R_f 0.43 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.69-7.64 (m, 4H), 7.45-7.37 (m, 6H), 4.19-4.12 (m, 1H), 4.09-4.00 (m, 1H), 3.66 (dd, J = 10.7, 4.1 Hz, 1H), 3.60 (dd, J = 10.7, 4.8 Hz, 1H), 3.03-2.85 (m, 2H), 2.10-1.93 (m, 2H), 1.87-1.48 (m, 6H), 1.06 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.6, 133.4, 129.7, 127.7, 80.2, 79.8, 66.2, 48.1, 33.3, 32.5, 27.3, 26.8, 19.2. **HRMS**: calculated for $C_{23}H_{34}NO_2Si$ $(M+H)^+$ 384.2353; found 384.2353.

7: NaN_3 (10.0 mg, 0.158 mmol) and $ZnCl_2$ (17.0 mg, 0.131 mmol) were added to a solution of the nitrile **3a** (50.0 mg, 0.131 mmol) in *n*-BuOH (2.5 mL). The reaction mixture was stirred at 100 °C for 2.5 h. When the starting material had been consumed (monitored by TLC), the solvent was evaporated under reduced pressure. Next, 5% NaOH (1 mL) was added and the mixture was stirred for 5 min, the suspension was filtered, and the solid washed with 5% NaOH (1 mL). The pH of the filtrate was adjusted to 1.0 with concentrated HCl, followed by extraction with EtOAc (3 × 10 mL). The solvent was removed under reduced pressure and the residue purified by flash column chromatography (EtOAc/hexanes, 2:8) to give **7** (34 mg, 0.080 mmol) in 61% yield as a yellow solid. R_f 0.38 (20% ethyl acetate in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.98 (bs, 1H), 7.68-7.62 (m, 4H), 7.43-7.33 (m, 6H), 4.26-4.17 (m, 2H), 3.70 (dd, J = 11.0, 3.9 Hz, 1H), 3.63 (dd, J = 11.0, 5.5 Hz, 1H), 3.33 (dd, J = 15.6, 3.2 Hz, 1H), 3.00 (dd, J = 15.6, 8.4 Hz, 1H), 2.20-2.11 (m, 1H), 2.03-1.93 (m, 1H), 1.88-1.77 (m, 1H), 1.65-1.51 (m, 1H), 1.05 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.5, 134.8, 133.1, 129.8, 127.8, 80.1, 76.2, 66.3, 31.5, 29.4, 27.6, 26.8, 19.2. **HRMS**: calculated for $C_{23}H_{30}N_4NaO_2Si^+(M+Na)^+$ 445.2030; found 445.2030.

Supporting Information. ^{1}H, and ^{13}C NMR of all new compounds. Cartesian coordinates, absolute energy, and frequencies for all calculated structures. IRC for all transition states. This material is available free of charge via the Internet at http://pubs.acs.org.

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