Regioselective Markovnikov hydrodifluoroalkylation of alkenes using difluoroenoxyisilanes

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Alkene hydrodifluoroalkylation is a fruitful strategy for synthesizing difluoromethylated compounds that are interesting for developing new medicinal agents, agrochemicals, and advanced materials. Whereas the anti-Markovnikov hydrodifluoroalkylation to linear-type products is developed, employing radical-based processes, the Markovnikov synthesis of branched adducts remains unexplored. Herein, we describe acid-catalyzed processes involving carbocation intermediates as a promising strategy to secure the Markovnikov regioslectivity. Accordingly, the Markovnikov hydrodifluoroalkylation of mono-, di-, tri-, and tetrasubstituted alkenes using difluoroenoxyisilanes, catalyzed by Mg(ClO₄)₂·6H₂O, is achieved. This allows the diversity-oriented synthesis of α,α-difluoroketones with a quaternary or tertiary carbon at the β-position that are otherwise difficult to access. The method is applied to the modification of natural products and drug derivatives. The resulting α,α-difluorinated ketones could be converted to the corresponding α,α-difluorinated esters or alcohols, or organofluorine compounds featuring a CF₂Ho rC F₂CF₂Ph moiety. Mechanistic studies support that Mg(ClO₄)₂·6H₂O functions as a hidden Brønsted acid catalyst.
Organofluorine compounds featuring a fluoroalkyl group have found widespread application in pharmaceutical, agrochemical, and material science because a fluorine moiety often brings about beneficial effects on the physical, chemical, and pharmaceutical properties of organic compounds. While a trifluoromethyl group is typically used to modulate the properties of molecules, increasing attention is being paid to the selective incorporation of a difluoromethyl group (CF₂-H) or a difluoromethylenyl fragment because of the capacity of CF₂-H as a lipophilic H-bond donor and the isosteric relationship between the CF₂ moiety and ethereal oxygen. In particular, with the advent of difluoromethylated drugs such as pantoprazole, efatrornithine, and gemcitabine, efficient methods for selective difluoralkylation are very much in demand in the field of drug discovery and development. Therefore, it is of current interest to develop the diversity-oriented synthesis of difluoroalkyl-containing molecules from readily accessible starting materials in an operationally simple manner.

In this context, hydrodifluoralkylation of alkenes is an important strategy due to the abundance and diversity of alkenes as carbon feedstocks in organic synthesis. In parallel to the advances made in hydrotrifluoromethylation and hydroperfluoralkylation of simple alkenes, much progress has also been made in hydrodifluoralkylation. A number of elegant protocols with anti-Markovnikov regioselectivity have been developed using different sources of CF₂, thereby allowing the facile synthesis of linear-type difluoralkylated adducts. Notable examples hereof include the following. Qing et al. used a bromodifluoromethylphosphonium salt to realize a visible-light-induced hydrodifluoromethylation of terminal alkenes. Jui described the hydrodifluoralkylation of alkenes using difluorobenzenyl radicals produced in situ via the C-F cleavage of ArCF₃. Most recently, Gouneur et al. accomplished an economic protocol using inexpensive difluoroacetic acid as the difluoromethyl reagent, under the action of 3 equiv. PhI(OAc)₂ and visible light.

Despite significant advances, Markovnikov hydrodifluoralkylation of alkenes remains a largely unsolved challenge. Currently, all the known protocols afford linear adducts with anti-Markovnikov regioselectivity. This is because these protocols rely on radical processes that involve the formation of more stable radicals after the addition of in situ-generated difluoroalkyl radicals to alkenes (Fig. 1a). However, Markovnikov hydrodifluoralkylation would yield branched adducts with a chemical space shape distinct from linear products.

In view of the intimate relationship between the properties of organic molecules and their shape, branched adducts are therefore of significant interest to the scientific community. If 1,1-di-, tri-, and tetrasubstituted alkenes are used, Markovnikov regioselectivity will allow the construction of difluoromethylated quaternary carbons. Because the selective incorporation of quaternary carbons to enhance conformational restriction has been recognized as an effective strategy to improve the properties of bioactive compounds, it seems only logical that molecules bearing a difluoromethylated quaternary carbon are interesting targets for medicinal research. With these considerations in mind, it was postulated highly desirable to develop the Markovnikov hydrodifluoralkylation of alkenes. However, such research requires several challenges to be overcome, including control of the regioselectivity as yet, unattainable by any known radical strategy—and the increased steric hindrance in the C-C bond-forming step between a more substituted alkene carbon and the fluorinated reagents.

To address these challenges, we speculated that the acid-catalyzed hydrodifluoralkylation of alkenes involving carboxylation intermediates offers a promising solution (Fig. 1b). In principle, this approach is characterized by the initial protonation of the double bond of alkenes to form the more stable carbocation according to the Markovnikov rule, followed by a C-F forming reaction with difluoromethylated nucleophiles. Such a mechanism provides the regioselectivity complementary to known anti-Markovnikov radical reactions and, beneficially, substantially expands the scope of alkenes. Current hydrodifluoralkylation reactions are largely based on monosubstituted aliphatic alkenes, with very limited examples of aryl alkenes, disubstituted alkenes, and trisubstituted alkenes being incorporated. Furthermore, to our knowledge, tetrasubstituted alkenes have never been used. In particular, aryl alkenes still present a challenge as a substrate class for radical olefin hydrodifluoralkylation, due to unproductive side reactions such as overoxidation and dimerization. In contrast, processes involving carbocations

Fig. 1 State of the art and our proposed hydrodifluoralkylation of simple alkenes. a Anti-Markovnikov alkene hydrodifluoralkylation based on radical processes (well established). b Markovnikov alkene hydrodifluoralkylation (this work).
may be useful for aryl alkenes and polysubstituted alkenes because either aryl or aliphatic substituents could stabilize the carbocation intermediate, and the steric hindrance expected for the initial protonation of alkenes is much less than that for the addition of fluoroalkyl radical (Fig. 1b vs. a). This could offer a promising approach to access structurally diverse difluoroalkylated adducts from a broad scope of alkenes, including those with a difluoroalkylated quaternary carbon.

Surprisingly, despite these attractive features, acid-catalyzed olefin hydrodifluoroalkylation remains unexplored, possibly because alkyl carbocation intermediates (strong acids) are usually unstable—they are apt to undergo deprotonation, substitution, and various side reactions with olefins, such as alkylation, dimerization, and oligomerization.44–47

Therefore, we speculate that the key to reaction development is balancing the acid strength and the activity of the difluoro reagent, allowing the rate of carbocation generation to match the C–C bond-forming reaction. To minimize side reactions, the acid catalyst should be able to produce the carbocation from alkenes under mild conditions, and the difluoroalkylated nucleophile should react with the in situ-generated carbocation, once produced, at least at a substantially faster rate than the occurrence of side reactions.

Here, we report the use of Mg(ClO₄)₂·6H₂O as an effective hidden Bronsted acid to achieve the Markovnikov hydrodifluoroalkylation of mono-, di-, tri-, and tetrasubstituted alkenes using difluoroalkoxysilanes, affording valuable α-difluoromethylated ketones that were rarely prepared via olefin hydrodifluoroalkylation.35 (Fig. 1b).

Results
Optimization of the reaction conditions. Easily available difluoroalkoxysilane 2 has been established as a versatile difluoro reagent48 to introduce an α,α-difluorinated ketone moiety that can undergo various diversifying reactions. However, its application in alkene hydrodifluoroalkylation remains unexplored. With our efforts in selective difluoroalkylation40, we have developed a variety of functionalization reactions of 2, including catalyst-free-on-water aldol reaction52, olefination using diazo reagents53, and Michael addition to tetrasubstituted electron-deficient alkenes.54 These studies brought the following to our attention: difluoroalkoxysilanes 2 are often more reactive than their nonfluorinated analogs50, which are with high nucleophilicity comparable to allylstannanes58; furthermore, to some extent, they are compatible with water52 and the reaction conditions that include superacids such as HOTf and HClO₄.50 This suggested to us that 2 could be a promising reagent in developing acid-catalyzed Markovnikov hydrodifluoroalkylation, affording structurally diverse α-branched α,α-difluorinated ketones as fluorinated synthons, as well as interesting targets for medicinal researches59.

Accordingly, we tried the reaction of 1,1-disubstituted α-ethylstyrene 1a with difluoroalkoxysilane 2a at room temperature (r.t.) in the presence of 5 mol% HOTf—a superacid widely used to generate carbocations44–47 (Fig. 2a). To our delight, the reaction finished within 5 h to afford branched adduct 3a in 36% yield. We further examined several other typical difluoroagents previously used for alkene hydrodifluoroalkylation, including difluoroacetic acid, bromodifluoromethylphosphonium bromide, and trimethylsilyl (TMS)-based difluorinated esters or sulfones. In these cases, no target products were detected, under the same conditions mentioned above, besides an olefin dimerization product (determined by gas chromatography–mass spectrometry analysis).

Because extensive olefin dimerization occurred, we next tried optimizing the acid catalysts in an effort to improve the yield—this emerged as being crucial (Fig. 2b). Ordinary strong Brønsted acids such as p-TsOH and CF₂CO₂H failed to give the desired product 3a; only H₂SO₄ afforded 3a in 15% yield. Another common superacid, HClO₄, used as a 70% aqueous solution, improved the yield of 3a to 55%, but the reaction time was longer. This indicated that a small amount of water could be tolerated. Because the reaction was performed in air, a trace amount of water should be present, which might bind to a Lewis acid to give a conjugate acid to then generate a carbocation from the alkene44–47,60. We therefore next examined the performance of Lewis acids.

Of the metal triflates we screened, Fe(OTf)₃, Sc(OTf)₃, Ph₃P–AuOTf, and Ga(OTf)₃ could mediate this reaction. Ga (OTf)₃ proved to be the best; 3a was obtained in 75% yield after 3 h. However, the highly hygroscopic nature of triflates made it difficult to reproduce the result. We therefore turned our attention to using the easier-to-handle metal perchlorate hydrates. After intensive optimization, Mg(ClO₄)₂·6H₂O was identified as the catalyst of choice; it afforded 3a in a reproducible 82% yield, which was further improved to 92% if using 10 mol% catalyst. For details of optimization of conditions, see the Supplementary Information.

Scope with respect to different alkenes. With the optimized condition in hand, the scope of this Markovnikov hydrodifluoroalkylation was determined (Fig. 3). First, the synthesis of α,α-gem-difluoro-β-arylation ketones 3a–3aj from 1,1-disubstituted alkene 1 were examined. Styrenes with either an α-alkyl or α-aryl group all worked well to afford products 3a–e in 62–97% yields. 2-Aryl-1-butene with different α-substituents afforded the products 3f–r in 20–98% yields. Exo-cyclo 1,1-disubstituted alkenes afforded the corresponding ketones 3s–u in 78–99% yields. The structure of 3s was confirmed by the X-ray diffraction analysis of its hydrazine derivative 3s′ (see the Supplementary Information for details). Alkenes with various α-positioned aliphatic groups were also viable substrates; they afforded products 3v–3ac in 28–83% yields. Notably, functionalized 1,1-disubstituted alkenes bearing a ketone, alkyl, ester, cyano, halogen atom, or ether group all afforded the target adducts 3ad–3aj in 70–95% yields.

Remarkably, the scope of this hydrodifluoroalkylation could be extended to polysubstituted alkenes. Trisubstituted styrenes, with aryl or alkyl substituents, reacted with difluoroalkoxysilane 2a to afford the desired adducts 5a–d in 66–92% yields. Trisubstituted endocyclic olefins also afforded products 5e and 5f in 84% and
In all, 3 mol% Mg(ClO₄)₂·6H₂O, 3 equiv. the Supplementary Information. Reaction conditions: alkenes (0.3 mmol), 4 NATURE COMMUNICATIONS | https://doi.org/10.1038/s41467-020-19387-4 | www.nature.com/naturecommunications

![Chemical structures and reactions](image)

**Fig. 3 Scope of the Markovnikov hydrodifluoroalkylation with respect to different alkenes.** The structure of each numbered alkene is shown in the Supplementary Information. Reaction conditions: alkenes (0.3 mmol), 2a (0.45 mmol), Mg(ClO₄)₂·6H₂O (10 mol%), and CICH₂CH₂Cl (3 mL), in air at room temperature. *n* in all, 3 mol% Mg(ClO₄)₂·6H₂O, 3 equiv. 2a. *At* 50 °C. *n* in all, 5 mol% Mg(ClO₄)₂·6H₂O, 3 equiv. 2a. *In* all, 1 mol% Mg(ClO₄)₂·6H₂O, 3 equiv. 2a. *(E)-N-(1,4-diphenylbut-3-en-2-yl)-4-methyl benzenesulfonamide 9d was used. *(E)-((1,3-diphenylallyl)oxy) trimethylsilane 9e was used.*
79% yield, respectively. Besides aryl-substituted olefins, trialkyl-substituted alkenes were also viable substrates, affording the desired products 5g-j in reasonable yields. Notably, tetrasubstituted olefin 6, never before used for hydrofluoroalkylation, worked well with 2a to afford the target adducts 5k-n in 44–74% yields.

Aside from the diversity-oriented construction of difluoroalkylated quaternary carbons, this method is workable for the synthesis of a,a-difluoroalkyl ketone 8 with a tertiary carbon from mono- and 1,2-disubstituted alkenes 7 and 9. Monosubstituted alkene 7, cis-1,2-disubstituted olefins such as indene, dihydronapthalene, and 6,7-dihydro-5H-benzocycloheptene all readily afforded the corresponding adducts 8a-i in 34–83% yields. Interestingly, N-Ts allyl amine 9d or O-TMS-protected allyl alcohol 9e, with a trans-1,2-disubstituted alkene, afforded difluoroalkylated ketones 8j and 8k in 91% and 93% yield, respectively, possibly via an S_N1 reaction pathway. The structure of 8k was further confirmed by X-ray crystallographic analysis.

These results strongly support our hypothesis that can secure for Markovnikov regioselectivity complementary to radical processes. Furthermore, it promisingly incorporates the use of a broad range of alkenes, including mono-, di-, tri-, and tetrasubstituted ones, with good functional group compatibility. Noticeably, various aryl alkenes, which are problematic substrates for radical processes, afforded the desired branched adducts in generally good-to-excellent yields.

Scope of fluorinated silyl enol ethers. Next, various difluoroenoxyisilanes 2 were examined. Those that have methyl, methoxy, or chloro groups as substituents on the aliphatic ring reacted with alkene 1j to provide products 10a-c in 72–80% yields (Fig. 4). Difluoroenoxyisilanes 2e-h bearing a 2-naphthyl, thiophen, 5-methylfuryl, or alkenyl group were also competent substrates, affording products 10d–g in 71–87% yields. However, reactions with the aliphatic difluoroenoxyisilanes 2i, j failed. Notably, such acid catalysis was also workable for Markovnikov hydromono fluoridealkylation. Here, both acyclic and cyclic monofluorinated silyl enol ethers, as were viable substrates, as exemplified by the synthesis of monofluoroalkylated ketones 10h–j in good yields, albeit with low diastereoselectivity (d.r.).

Fluorine substitution plays a key role in this olefin hydroalkylation; both the a,a-dichlorinated silyl enol ether 2n and the nonfluorinated analog 2o failed to produce any desired products, under the same conditions (Fig. 4). This observation is in accordance with our previous observations in the aldol and olefination reactions. The failure of nonfluorinated silyl enol ether 2o was not because it was hydrolyzed in a faster rate than difluoroenoxyisilane 2a under the standard condition (for details, see the Supplementary Information). It took 12 h for 2o to be fully hydrolyzed, but no desired product could be detected by GC–MS analysis of the reaction mixture. However, at present, the origin of such dramatic fluorine effects is unclear.

Late-stage functionalization. The high functional group tolerance of this acid-mediated hydrodifluoroalkylation reaction offers a promising strategy for modifying olefinic derivatives of natural products, drugs, and carbohydrates. As shown in Fig. 5, treatment of a natural product flavononid analog with 2a under the optimized conditions afforded the difluoroalkylated flavonoid derivative 11 in 42% yield. The hydrodifluoroalkylation of several drug olefinic derivatives from estrone, fenofibrate, and fenbufen delivered the corresponding difluoro analogs 12–14 in 64–77% yields. Furthermore, the difluoroketone moiety could be smoothly introduced into the camphorsultam scaffold and a carbohydrate to afford 15 (51% yield) and 16 (77% yield) via this hydrodifluoroalkylation.

Gram-scale synthesis and synthetic utility. To showcase the synthetic application of this methodology further, a Gram-scale

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**Fig. 4 Scope of silyl enol ether 2 and the fluorine effect.** Reaction conditions: alkene 1j (0.3 mmol), 2 (0.45 mmol), Mg(ClO4)2·6H2O (10 mol%), and CICH2CH2Cl (3 mL) in air at room temperature.
The development of pharmaceutical agents, we initially evaluated
importance of diversity-oriented synthesis of anticancer drug development, and once again, lay stress on the
(cytotoxic effects ranged from 4.22 to 58.25 µM, 
and 1.5 equiv), r.t. 

The reaction catalyzed by 10 mol% HClO4 (aq. 70%) proceeded at a much faster rate than that catalyzed by Mg(ClO4)2·6H2O, but occurred, even when the reaction time was extended to 20 h.

On the other hand, the model reaction proceeded smoothly in the presence of 10 or 20 mol% HClO4 (aq. 70%), affording product 3a in 67% or 71% yield, respectively, within 1 h (Fig. 7a). The reaction catalyzed by 10 mol% HClO4 (aq. 70%) proceeded at a much faster rate than that catalyzed by Mg(ClO4)2·6H2O, but the yield of 3a was lower (1 h, 67% yield vs. 7 h, 92% yield). These findings are fully in accordance with the concept of a hidden Brønsted acid67,68 in the reaction, the addition of 10 or 20 mol% noncoordinating base 2,6-di-tert-butylpyridine 22 to the reaction of 1a and 2a was undertaken. Almost no reaction occurred, even when the reaction time was extended to 20 h.

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Fig. 5 Late-stage hydrodifluoroalkylation of natural products and drug derivatives. Reaction conditions: alkenes (0.3 mmol), 2a (0.45 mmol), Mg (ClO4)2·6H2O (10 mol%), and ClCH2CH2Cl (3 mL) in air at room temperature. aIn all, 3 mol% Mg(ClO4)2·6H2O, 3 equiv. 2a. bIn all, 20 mol% Mg(ClO4)2·6H2O, 3 equiv. 2a.

Late-stage diversification

Flavononid derivative 11, 1 h, 42%a

Estrone derivative 12, 15 h, 77%

Camphorsultam derivative 15, 24 h, 51%b

Glucose derivative 16, 5 h, 77%b

reaction of α-methylstyrene 1b with 2a was conducted (Fig. 6). Under the catalysis of 3 mol% Mg(ClO4)2·6H2O at r.t., 1.29 g of 3b was obtained in 78% yield—better than the 62% yield of the small-scale reaction reported earlier (see Fig. 3). The resulting ketone 3 is a versatile difluoro synthon capable of undergoing a variety of diversifying reactions. For instance, upon treatment with tert-BuOK or diethylaminosulfur trifluoride, the α,α-difluorinated benzyol moiety of 3a could be converted into a CF2H or CF2CF2Ph moiety, which has important applications in drugs, agrochemicals, and advanced materials15,66. Furthermore, the ketone moiety of 3 could be transformed into an ester or an alcohol via oxidation, reduction, or a nucleophilic addition reaction, as demonstrated by the synthesis of ester 19, secondary alcohol 20, and tertiary alcohol 21 bearing an ethynyl group.

Considering that α,α-difluoroketones are interesting targets for the development of pharmaceutical agents59, we initially evaluated the in vitro cytotoxic activity of some samples in human colorectal cancer cells (HCT116) using CCK-8 assay. We were delighted to find that the selected compounds had good growth-inhibitory activity at 30 µM and the half-maximal inhibitory concentration (IC50) values of cytotoxic effects ranged from 4.22 to 58.25 µM, depending on their structures (see the Supplementary Information for details). These preliminary results demonstrate that the thus obtained α-branched difluoroketones are potentially valuable in anticancer drug development, and once again, lay stress on the importance of diversity-oriented synthesis of α,α-difluoroketones.

Preliminary mechanistic study. The inexpensive catalyst, mild conditions, simple and easy-to-handle reaction system, broad scope, and good functional group tolerance make this Markovnikov hydrodifluoroalkylation reaction potentially useful. These attractive features intrigued us to investigate the possible reaction mechanism. First, to examine whether Mg(ClO4)2·6H2O acted as a hidden Brønsted acid67,68 in the reaction, the addition of 10 or 20 mol% noncoordinating base 2,6-di-tet-butylpyridine 22 to the reaction of 1a and 2a was undertaken. Almost no reaction occurred, even when the reaction time was extended to 20 h.

On the other hand, the model reaction proceeded smoothly in the presence of 10 or 20 mol% HClO4 (aq. 70%), affording product 3a in 67% or 71% yield, respectively, within 1 h (Fig. 7a). The reaction catalyzed by 10 mol% HClO4 (aq. 70%) proceeded at a much faster rate than that catalyzed by Mg(ClO4)2·6H2O, but the yield of 3a was lower (1 h, 67% yield vs. 7 h, 92% yield). These findings are fully in accordance with the concept of a hidden Brønsted acid catalyst67,68, supporting the idea that the HClO4 released from Mg(ClO4)2·6H2O is, in reality, the active catalyst. This decreases the hydrolysis of difluoroensylsilane and the dimerization of alkenes by slowing down the reaction rate, through gradually releasing HClO4 from Mg(ClO4)2·6H2O, and thereby ensuring a higher yield, compared with the direct use of HClO4 (aq. 70%) as the catalyst.

The proton source for this hydrodifluoroalkylation was then investigated. Because of the absence of external agents as the
proton source, we questioned whether the proton came from the crystal water of Mg(ClO₄)₂·6H₂O. If so, the use of a combination of anhydrous Mg(ClO₄)₂ with deuterium oxide (D₂O) would give the deuterated difluoroalkylated product. We indeed found that the reaction of α-ethylstyrene 1a with 2a worked well in the presence of 10 mol% anhydrous Mg(ClO₄)₂ and 1 equiv. D₂O, to furnish the deuterated product 23 in 82% yield (Fig. 7b). This result suggested that the proton in this hydrodifluoroalkylation mainly originates from the crystal water of Mg(ClO₄)₂·6H₂O. Meanwhile, partial proton transfer might originate from the trace amount of water in the reaction system, thus decreasing the ratio of deuterated product 23. Unfortunately, when 2 equiv. of D₂O was added, almost no alkylated adduct was isolated. Besides, under the standard conditions, tertiary alcohol 24 reacted with 2a to afford product 3a in 19% yield, as well as the elimination product olefin (E)-4a in 42% yield (Fig. 7c), further demonstrating that the reaction under consideration proceeds via the carbocation intermediate. The lower yield in this case was in accordance with the above-observed deleterious effect of water. Based on these results, we came to a conclusion that the reaction could only tolerate trace amount of water, the crystal water of the catalyst, and that in the atmosphere of the reaction vessel (totally less than 2 equiv.), possibly because the presence of excess water will trap the carbocation intermediate, or lead to the hydrolysis of difluoroenoxysilane dominated.

Discussion

In conclusion, we have realized a regioselective Markovnikov hydrodifluoroalkylation of simple alkenes with difluoroenoxysilanes, which is fully complementary to the well-established anti-Markovnikov radical processes. This represents a straightforward and effective strategy to access valuable α-difluoroalkylated ketones with a quaternary or tertiary carbon at the β-position. Remarkably, the mild reaction conditions, the inexpensive and easy-to-handle catalyst, and the broad scope of alkenes, including mono-, di-, tri-, and tetrasubstituted alkenes, make our methodology potentially very useful. The value of this methodology is further demonstrated by the late-stage diversification of natural products and drug derivatives, as well as versatile product transformations to functionalized fluorine-containing molecules. Preliminary biological studies indicate that these difluorinated ketones are promising therapeutic agents for colorectal cancer. The application of this methodology and the development of a catalytic enantioselective version is currently ongoing in our laboratory.

Methods

General procedure for the hydrodifluoroalkylation of simple alkenes. Under an air atmosphere, to a 5.0-mL vial were added Mg(ClO₄)₂·6H₂O (9.9 mg, 0.03 mmol, 10 mol%) and anhydrous Mg(ClO₄)₂ (10 mol%), 20 h, NR. The resulting mixture was stirred at room temperature until full consumption of alkenes by TLC analysis. The reaction mixture was then concentrated under reduced pressure. The crude residue was purified by flash column chromatography to provide the desired products. Full experimental details and characterization of compounds can be found in the Supplementary Information.

Caution. Attention should be paid when handling perchlorate salts because they are potentially explosive when used in the presence of combustible substances at high temperature. It has been documented that magnesium perchlorate has high thermal stability (>300–500 °C), and actually can be dried under vacuum at 160 °C without any accident[45,50]. In addition, exposure to nominal levels of such perchlorate does not adversely affect health and safety, as evidenced by The National Fire Protection Association that ranks magnesium perchlorate as barely hazardous for health, and as an oxidizing product but not as an explosive one.

Data availability

X-ray crystallographic data for compound 3a (CCDC 1938421) and 8k (CCDC 1938418), are freely available from the Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures. All other data in support of the findings of this study are available within the article and its Supplementary Information or from the corresponding author upon reasonable request.
Received: 11 May 2020; Accepted: 5 October 2020; Published online: 30 October 2020

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Acknowledgements

This work was supported by the National Natural Science Foundation of China (Grant nos. 21725203 and 21901074), the Ministry of Education (PCSIRT), and the Fundamental Research Funds for the Central Universities is highly appreciated.

Author contributions

X.-S.H. and J.Z. conceived the project. X.-S.H. and J.-X.H. performed the experiments. X.-S.H. and J.-S.Y. analyzed experimental data. S.-Z.D. performed the biological activity studies. Q.-H.Z. analyzed the NMR data of deuterium experiments. J.-S.Y. and J.Z. directed the project and co-wrote the paper.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary information is available for this paper at https://doi.org/10.1038/s41467-020-19387-4.

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Peer review information Nature Communications thanks the anonymous reviewer(s) for their contribution to the peer review of this work.

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