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Enantioselective Cascade Formal Reductive Insertion of Allylic Alcohols into the C(O)−C Bond of 1,3-Diketones: Ready Access to Synthetically Valuable 3-Alkylpentanol Units

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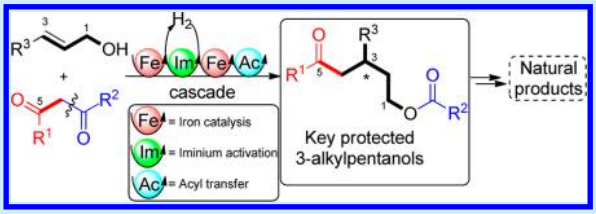
Supporting Information

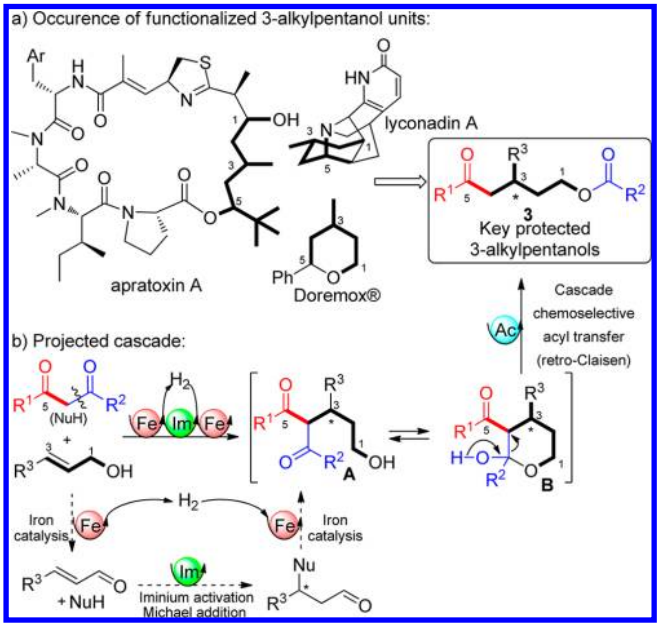
ABSTRACT: An unprecedented cascade reaction combining dual iron−amine-catalyzed enantioselective functionalization of allylic alcohols and chemoselective acyl transfer is presented. It allows, from diketones and allylic alcohols, preparation of efficiently functionalized γ-chiral alcohols in up to 96% yield and 96:4 er. The interest of this redox-, atom-, and step-economomical approach was further demonstrated in the short synthesis of several key fragments of biologically active natural products or odorant molecules.



Enantioselective access to functionalized chiral building blocks in a minimum number of operations is key for the development of sustainable fine chemistry. To orient researcher's efforts, several concepts such as the atom economy from Trost, the step economy from Wender, or the redox economy from Baran have recently been introduced.[1] These guidelines all tend to reach the same goal of a limited economical and thus environmental impact of newly developed synthetic strategies and methodologies. Although tremendous progress was achieved in the last decades, some crucial chiral building blocks still require lengthy and costly sequences for their preparation. This is the case for optically active functionalized 3-alkylpentanol units found in important biologically active natural products such as apratoxin A and lyconadin A or in Doremox, a constituent of the rose scent commercialized by Firmenich. All these chiral units should be readily available from key protected γ-alkyl alcohols **3** (Scheme 1a, R^3 = Me).[2]

The two main difficulties to access this important 3-alkylpentanol motif **3** rely, first, on the selective generation of the appropriate defined function (ketone and protected alcohol), often requiring functional group interconversion, namely redox transformations and protecting group manipulations that inevitably lengthen the synthetic strategy. Second, the control of the absolute configuration of these γ-chiral alcohols constitutes a real synthetic challenge that requires innovative approaches.[3] Stereoselective cascade reactions able to generate molecular complexity and functional diversity in a limited number of operations can bring a unique answer to these two synthetic problems.[4] Here, we propose a conceptually new shortcut solution based on the combination of our recent enantioselective functionalization of allylic alcohols[5] with an intramolecular product-driven acyl transfer.[6] The initial allylic alcohol transformation proceeds through an iron-catalyzed hydrogen transfer generating the corresponding α,β-unsaturated aldehyde that upon iminium activation gives the expected

Scheme 1. Some Examples of the Occurrence of 3-Alkylpentanol Units and Projected Cascade



enantioselective Michael addition. The resulting chiral transient saturated aldehyde is then reduced by the in situ generated iron hydride to the key hydroxy diketone **A**, triggering the final retro-Claisen step.

The strategy for an efficient acyl transfer relies on the high reactivity of 1,3-diketones toward Michael addition.[7] These pronucleophiles bear a noninnocent activating acyl group (R^2CO)

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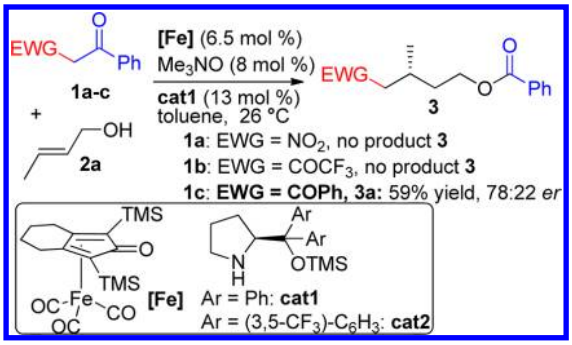
that should be transferred afterward via a retro-Claisen reaction from lactol **B**, cyclic isomer of adduct **A** resulting from the dual catalysis (Scheme 1b). This unprecedented, enantioselective overall quadruple cascade, involving dual borrowing hydrogen/iminium catalysis/retro-Claisen fragmentation, would result in a formal fully atom-, step- and redox-economic chemoselective reductive insertion of a 3-substituted allylic alcohol into a C(O)−C bond of the 1,3-diketone substrates (Scheme 1b).[8]

To validate the proof of concept for this domino process, dual iron−amine catalysis/acyl transfer, we subjected different pronucleophiles **1** and crotyl alcohol (**2a**) to activation by iron cyclopentadienone [**Fe**] as borrowing hydrogen complex,[9] Me_3NO to generate the active iron catalyst (liberating CO_2 and Me_3N)[9d] and **cat1** in toluene (Scheme 2).

Scheme 2. Influence of the Electron-Withdrawing Group over the Reactivity

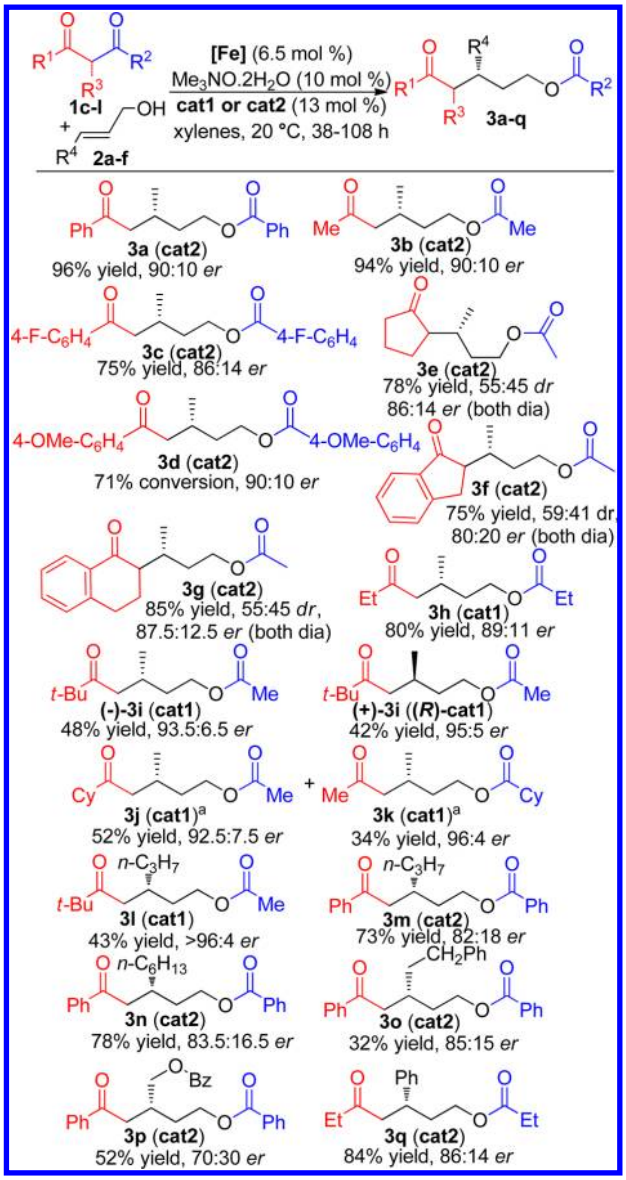


Activation by strong electron-withdrawing groups (EWG = NO_2, **1a** or $COCF_3$, **1b**) resulted in no product formation. While supposedly more reactive than ketoesters, the fact that these two molecules do not react in the dual catalytic system suggests that they probably inhibit the initial hydrogen transfer by coordinating to the iron catalyst. Gratifyingly, turning to 1,3-diketone **1c** (EWG = COPh), the designed process cleanly occurred directly providing, under mild conditions, the protected alcohol **3a** in 59% yield and a promising 78:22 er (Scheme 2).

Encouraged by the observed promising cascade using symmetrical 1,3-diketone **1c** and given the synthetic potential of this process, reaction conditions were carefully optimized. Extensive screening (see the Supporting Information) revealed that the use of 13 mol % of silylated diarylprolinols either **cat1** or **cat2**[10] depending on the diketone used, xylenes as solvent and $Me_3NO{\cdot}2H_2O$ as initiator gave the best results (Scheme 3). Under these conditions, using **cat2**, **3a** was obtained in 96% yield and 90:10 er.

With these optimized conditions in hand, systematic variation of the substrates was then carefully examined. Gratifyingly, structurally different diketones **1c−l** and allyl alcohols **2a−f** provided the expected rearranged products under mild conditions (Scheme 3). It must be pointed out that while for **1c** the fragmentation was spontaneous at room temperature, using other diketones, conversion of the intermediate lactol **B** was sometimes incomplete at this temperature. Fortunately, upon evaporation of the solvent with the rotavapor bath adjusted at 40 °C, clean evolution to the rearranged form was observed after 5−15 min. Using crotyl alcohol (**2a**) (R^4 = Me), the nature of the diketone could be modified efficiently giving rise to the cascade products in yields ranging from 34 to 96%. 2,4-Pentanedione furnished the expected protected product **3b** in 90:10 er and 94% yield. Electron-withdrawing or donating

Scheme 3. Scope of the Cascade Dual Iron/Amine Catalysis and Acyl Transfer



groups (*p*F, or *p*OMe) could be placed on symmetrical aryl diketones giving the cascade products **3c** and **3d** in 86:14 and 90:10 er, respectively. When starting from unsymmetrical cyclic *α*-acetyl ketones, only the chemoselective migration of the acetyl group was observed in this transformation (**3e−g**). A moderate diastereoselectivity was obtained, while the er ranged from 80:20 to 87.5:12.5 for the formation of **3e−g**. The moderate diastereocontrol might be explained by the nature of the diastereocontrolling step, namely the protonation of the product after the fragmentation.

Other acyclic aliphatic-1,3-diketones could also be efficiently applied in the cascade giving the products **3h−l** in 89:11 to 96:4 er. Use of unsymmetrical monoacetyl diketones proceeded with variable chemoselectivity, always in favor of the acetyl migration, leading to **3i−l** with good er. The more substituted the R^1 group, the higher the selectivity.[11] For example, with *tert*-butyl methyl 1,3-diketone, the acetyl migration is total leading to compounds **3i,l**, while a separable 1.6/1 mixture of **3j** and **3k** is obtained in an excellent enantiocontrol (92.5:7.5 to 96:4 er) from the corresponding cyclohexyl methyl 1,3-diketone.[12] Finally, the

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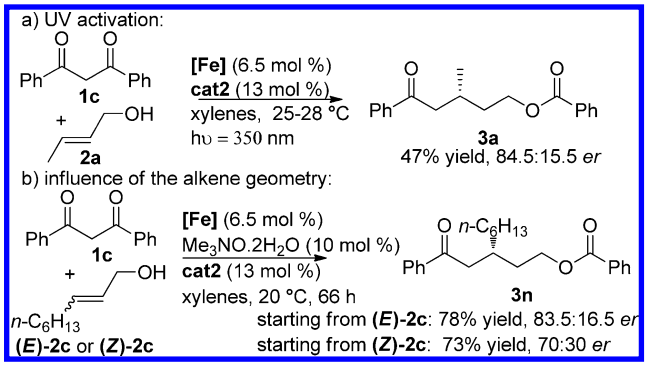
nature of the allylic alcohol could be varied leading to structurally different products **3l**−**q**, in 32 to 84% yield and 70:30 to 96:4 er.

The combination of the dual catalytic process with the acyl transfer is interesting in terms of its mechanism. As already mentioned, the presence of the electron-withdrawing ketone is absolutely required for the spontaneous fragmentation since ketoesters do not rearrange.[5a] But if one reduces too strongly the electron density on the pro-nucleophile, no more reaction occurs (Scheme 2). This suggests that electron-poor diketones or nitroketone coordinate to the metal, inhibiting its catalytic properties.[13]

Interestingly, when Me_3NO is removed from the mixture and replaced by UV activation (350 nm to remove one CO from the initial iron complex),[14] the overall dual-catalysis/acyl transfer cascade does take place in 47% yield (Scheme 4a). In addition,

Scheme 4. Cascade Process under UV Activation and Difference in Reactivity between (*E*)-2c and (*Z*)-2c

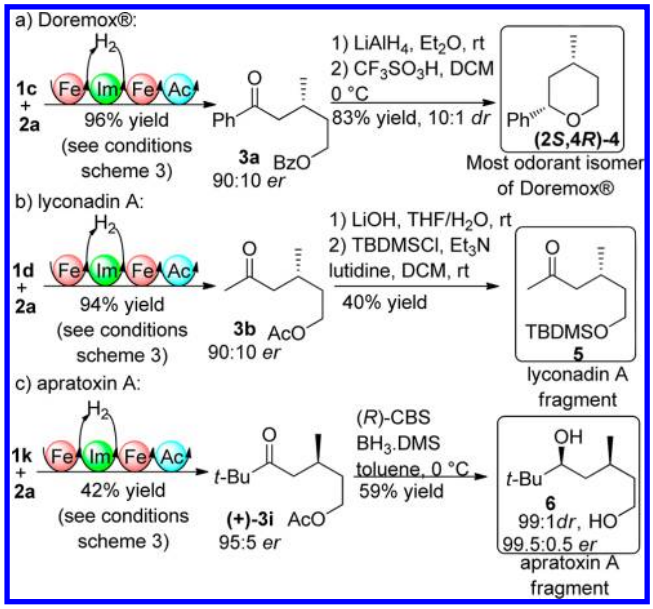


84.5:15.5 er was observed under these conditions, a result close to the one obtained using Me_3NO as initiator. This suggests that beside from generating the active iron complex, Me_3NO and the Me_3N generated in this iron activation do not take part in the different steps of the catalytic cycle. This probably indicates that it is the enol form of the diketone (observed by NMR) and not a deprotonated form, which adds to the iminium ion intermediate. Similarly, the acyl transfer occurs simply by thermal activation, without the involvement of either Me_3N or **cat2**. Control experiments comparing the reactivity profile of both *E* and *Z* starting allylic alcohol **2c** gave the same enantiomer of the product **3n** in, respectively, 83.5:16.5 and 70:30 er (Scheme 4b). This indicates that in the case of (*Z*)-allyl alcohols, even though the lifetime of the *α*,*β*-unsaturated aldehyde is short, isomerization to the parent (*E*)-*α*,*β*-unsaturated aldehyde via dienamine formation predominantly occurs prior to nucleophilic Michael addition.[15]

Given the apparent interest of the series of functionalized *γ*-chiral protected alcohols readily obtained from raw materials through this cascade, wide arrays of potential synthetic applications seem possible. To fully demonstrate this potential, we decided to apply it to the synthesis of structurally different attractive natural products fragments or odorant molecule (Scheme 5).

As a first application of the discovered cascade, we synthesized the (2*S*,4*R*) isomer of Doremox, the most odorant isomer (Scheme 5a).[16] This odorant molecule was previously prepared in an enantioselective manner in six- to nine-step synthetic sequences.[2a] From **3a**, obtained in 90:10 er from easily available starting materials, reduction of both ketone and ester[17] followed

Scheme 5. Synthetic Applications of the Cascade



by diastereoselective acid promoted cyclization[18] efficiently gives, as the major product (10:1 dr), the expected cyclic pyran **4**.

We next turned to the synthesis of key fragments of two distinct bioactive natural products with both remarkable cytotoxic activities, namely lyconadin A and apratoxin A.[19] From **3b**, obtained in 90:10 er by the cascade from 2,4-pentanedione and crotyl alcohol (**2a**), protecting group exchange provides **5** in a straightforward three-step sequence (Scheme 5b). Compound **5** was previously applied to the synthesis of lyconadin A, but its preparation required six steps from expensive (*R*)-1-methyl hydrogen 3-methylglutarate.[20]

Finally, the C1−C5 fragment of apratoxin A was then prepared according to the synthetic sequence presented in Scheme 5c. Following the disclosed cascade, (+)-**3i**, obtained in 95:5 er using (***R***)-**cat1** to obtain the appropriate configuration at C3, was reduced with (*R*)-CBS directly, giving upon hydrolysis in one single operation the corresponding diol **6** (99:1 dr and 99.5:0.5 er). Compound **6** is a known precursor of apratoxin A but previously required 5−11 steps depending on the strategy used for its preparation.[2g−i]

In conclusion, we have developed the first example of enantioselective dual iron−amine catalysis acyl-transfer cascade for the synthesis of enantioenriched *γ*-chiral alcohols directly from simple achiral diketones and allylic alcohols. The efficient combination of the different activation modes, an iron-catalyzed borrowing hydrogen and an iminium catalysis together with the final retro-Claisen fragmentation, allow the preparation of these valuable building blocks in up to 96% yield and 96:4 er. The designed process occurs under mild conditions, fulfills the principles of redox, step- and atom-economies, and in addition avoids the handling of toxic *α*,*β*-unsaturated aldehydes. This strategy gives access in one single operation to synthetically useful functionalized building blocks possessing distinct functions directly from commercially or easily prepared substrates. The efficiency of this approach was demonstrated in the rapid synthesis of several natural product fragments or odorant molecules. Given the considerable synthetic shortcuts provided by this methodology, we are convinced that it will in the near future find widespread applications in natural product synthesis.

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■ ASSOCIATED CONTENT

Supporting Information

Reaction optimization, experimental procedures, characterization of compounds, and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(11) Use of 1-phenyl-1,3-butanedione (R^1 = Ph, R^2 = Me, R^3 = H) gave the product in a 1/1 mixture of Bz and Ac products.

(12) The difference in er between **3j** and **3k** might reflect a different enantiocontrol between the two diastereomers formed prior to the rearrangement.

(13) Unfortunately, attempts at observing such coordination between a 1,3-diketone and the activated iron complex have remained inconclusive.

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(16) Doremox is sold as a racemic mixture. For the initial patent, see: Firmenich. US Patent 005 219 836A, June 15, 1993.

(17) Under these conditions, reduction performed at rt gives 1.3:1 dr while reducing the temperature to 0 °C gives 1.55:1 dr of the corresponding alcohol.

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