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Controlled *meta*-Selective C−H Mono- and Di-Olefination of Mandelic Acid Derivatives

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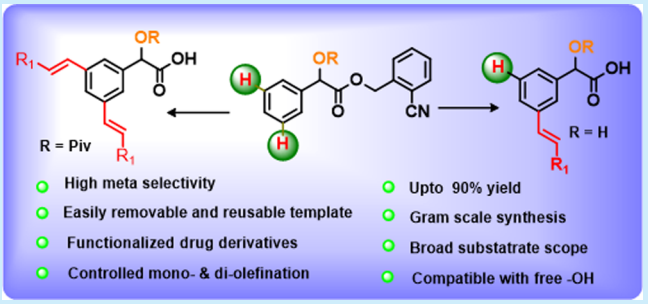
ABSTRACT: Mandelic acids represent a key structural motif present in many drug molecules. Herein, we report the controlled *meta*-selective mono- and diolefination of mandelic acids by the careful design of the substrate and oxidant. Furthermore, free *meta*-functionalized mandelic acid was generated by selectively removing the template under mild basic conditions. The synthesis of functionalized homatropine and cyclandelate drug derivatives was demonstrated. Kinetic isotope effects revealed C−H activation as the rate-limiting step.



Mandelic acid derivatives are biologically important molecules that are widely present in many drugs and natural products, such as homatropine, cyclandelate,[1] cefalexin, etc.[2] Although several derivatives of mandelic acid have been reported, they are mostly limited to functionalization on the side chain with limited examples for fuctionalized phenyl rings. In 2015, Yu et al. reported the *ortho*-C−H functionalization (olefination, arylation, iodination, and acetoxylation) of protected mandelic acid derivatives;[3] however, to date there have been no general reports for the *meta*-selective C−H functionalizations of mandelic acids. Given the importance of these structural motifs, it is highly desirable to develop a practical method for remote *meta*-C−H functionalization.

Directed C−H bond functionalization is an important strategy in organic synthesis to introduce different functional groups on the *ortho*-position of an aromatic ring.[4] On the other hand, *meta*-C−H bond functionalization is less studied and challenging owing to the distance between the *meta*-C−H bond and the directing group and as well as the electronic effects.[5] Different strategies have been developed in the past decade to achieve *meta*-selectivity using transient mediators,[6] directing group templates,[7] steric or electronically biased properties of substrates and catalysts, etc.[8] Among these, the directing-group-assisted U-shaped nitrile-containing end-on template developed by Yu et al. for *meta*-selective C−H bond functionalization via the formation of a 10−12 membered cyclophane-like pretransition state is an important technique.[9] This strategy was later developed and studied by several other groups, including Maiti, Tan, and Li, for the *meta*-selective C−H functionalization of hydrocinnamic acid, benzyl alcohol, benzylamine, benzoic acids, arylacetic acids, and others using end-on nitrile-, pyrimidine-, and pyridine-based templates.[7,10] In many cases, the template synthesis is slightly complex and requires harsh conditions for its removal.[11] Again, in most cases the templates were not reusable since a different functional group was generated during the deprotection.[12] Although the *meta*-selective C−H functionalizations of arylacetic acids have been reported, they are mostly limited to α,α'-unsubstituted derivatives, with limited examples for α,α'-alkyl-substituted derivatives. Mandelic acid (α-hydroxy phenylacetic acid) derivatives were generally not a suitable reacting partner for these transformations. Herein, we report the *meta*-selective controlled mono- and diolefination of mandelic acid derivatives with a high selectivity using an easily removable and reusable template (Scheme 1).

We started our screening with mandelic acids that contained nitrile, pyrimidine, oxazole, or amide directing groups as templates with $Pd(OAc)_2$, Ac-Gly-OH, AgOAc, and HFIP for *meta*-C−H olefination. Interestingly, substrate **1a**, containing a 2-cyano benzyl template, gave the expected *meta*-olefinated product in a good yield (79%) and high *meta*-selectivity (*meta*:others > 11:1) with no diolefinated byproduct. Screening other reaction conditions, such as temperature, catalyst loading, ligands, solvents etc. (see the Supporting Information), showed the current conditions ($Pd(OAc)_2$ catalyst, Ac-Gly-OH ligand, AgOAc oxidant, and HFIP solvent) to be optimal. A higher ligand loading (60 mol %) was required to drive the reaction to completion. With the optimized conditions in hand, we carried out the olefination of **1a** with different olefin partners. Gratifyingly, excellent *meta*-selectivity

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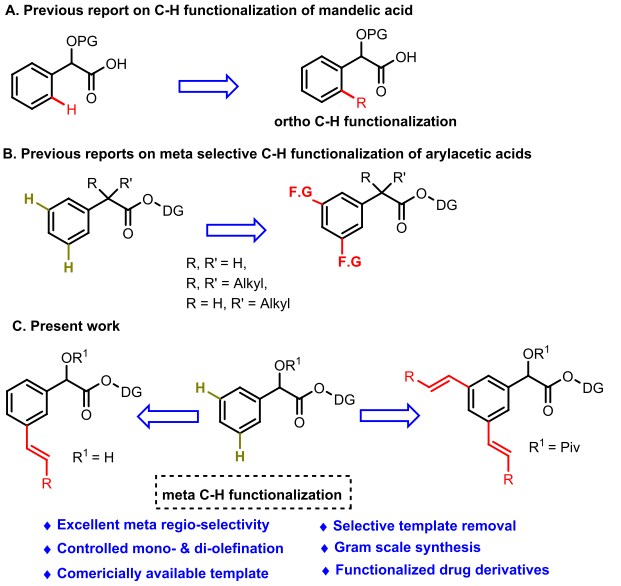
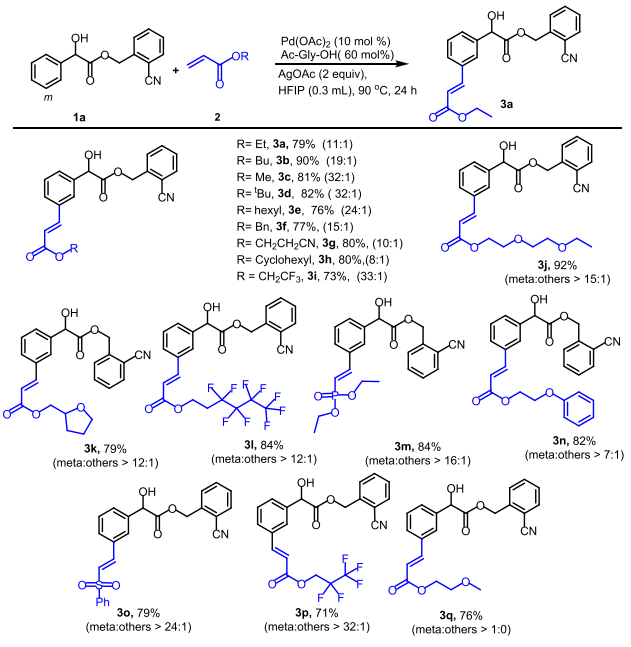
Scheme 1. Previous Reports on the C−H Functionalization of Mandelic Acid and Present Work



was achieved in most cases to afford the olefinated products **3a**−**3q** in good to excellent yields (71%−90%). Interestingly, olefins, such asphenyl vinyl sulfone, and vinyl phosphonate ester gave the resultant products in good yields and with excellent *meta*-selectivities (Scheme 2).

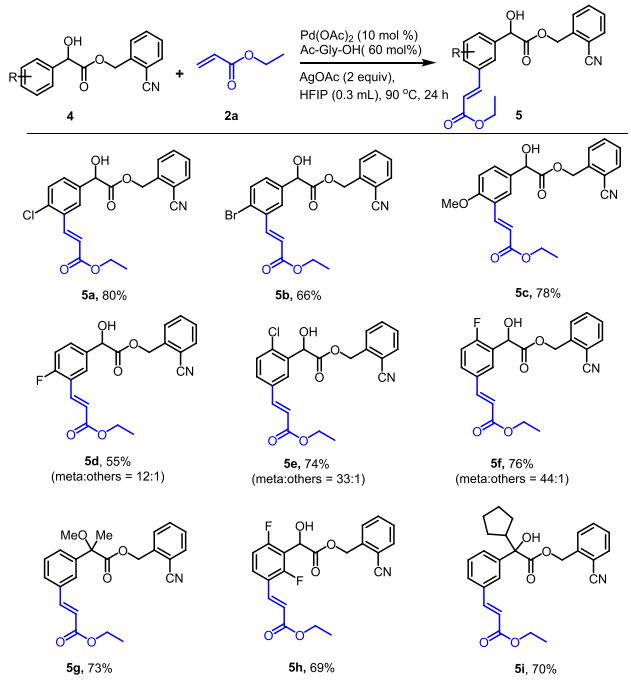
In order to show the synthetic versatility of this method, different mandelic acid derivatives were studied next. In most cases, the resultant products were obtained in good to excellent yields, giving the *meta*-isomer exclusively in some cases. Substituents such as *p*-Cl, *p*-Br, and *p*-OMe groups (**5a**, **5b**, and **5c**, respectively) were all well tolerated and gave the resultant products in good selectivities except for compound **5d**, which contained a *p*-F substituent and afforded a mixture of mono- and diolefination products (mono:di = 3:1), albeit with good *meta*-selectivity. Furthermore, sterically hindered substrates **5e**, **5f**, and **5h** containing *o*-Cl, *o*-F, and *o*-difluoro substituents, respectively, also provided the desired olefinated products in good yields and with high *meta*-selectivities. It is noteworthy that compounds **5g** and **5i**, which contained *α*-methyl and cyclopentyl substituents, respectively, also furnished the resultant products in good yields with a high regioselectivity (Scheme 3).

Scheme 2. *meta*-C−H Olefination of Mandelic Acid[a]



[a]Reaction conditions are as follows: **1a** (0.1 mmol), **2a** (0.15 mmol), $Pd(OAc)_2$ (0.01 mmol), Ac-Gly-OH (0.06 mmol), AgOAc (0.2 mmol), and HFIP (0.3 mL). Isolated yields. Ratio of *m*:(*p* + *o*) was determined by ^{1}H NMR spectra.

Scheme 3. *meta*-C−H Olefination of Substituted Mandelic Acid[a]



[a]Reactions conditions are as follows: **4** (0.1 mmol), **2a** (0.2 mmol), $Pd(OAc)_2$ (0.01 mmol), Ac-Gly-OH (0.06 mmol), AgOAc (0.2 mmol), and HFIP (0.3 mL). Isolated yields. Ratio of *m*:(*p* + *o*) was determined by ^{1}H NMR spectra.

We next focused on diolefination of mandelic acid, as it can give direct access to tri-substituted and other highly substituted derivatives. Controlling the mono- versus diselectivity is a common issue in many C−H functionalization reactions.[12a,13] We started the screening with the templates that were already synthesized. Surprisingly, the reaction gave only mono-olefinated products even with excess oxidant and olefin partners under the standard conditions. After some screening, we observed that protecting the hydroxyl group of mandelic acid and using Ag_2CO_3 as the oxidant afforded the diolefination of mandelic acid. Accordingly, substrate **6a** gave the best yield (80%) and a high *meta*-selectivity (>44:1) (see the Supporting Information).

With the optimized conditions in hand, we studied different olefin partners and mandelic acid derivatives to show the synthetic versatility of the method. In most cases, good yields and a high *meta*-selectivity were observed. Interestingly, even when the mandelic acid side chain was sterically crowded, the diolefinated product **7h** was obtained exclusively. Acrylates,

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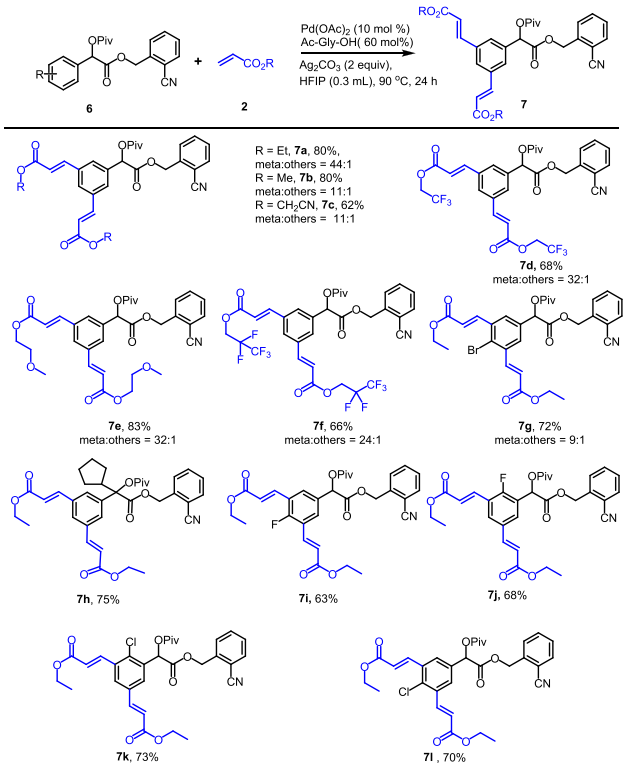
such as methyl, ethyl, methoxy ethyl, etc., afforded the diolefinated products in high selectivities and good yields. Subsequently, we examined substituted mandelic acid derivatives, which afforded highly functionalized tetra-substituted benzene derivatives (**7g**, **7i**, **7j**, **7k**, and **7l**), showing the synthetic versatility of the method (Scheme 4).

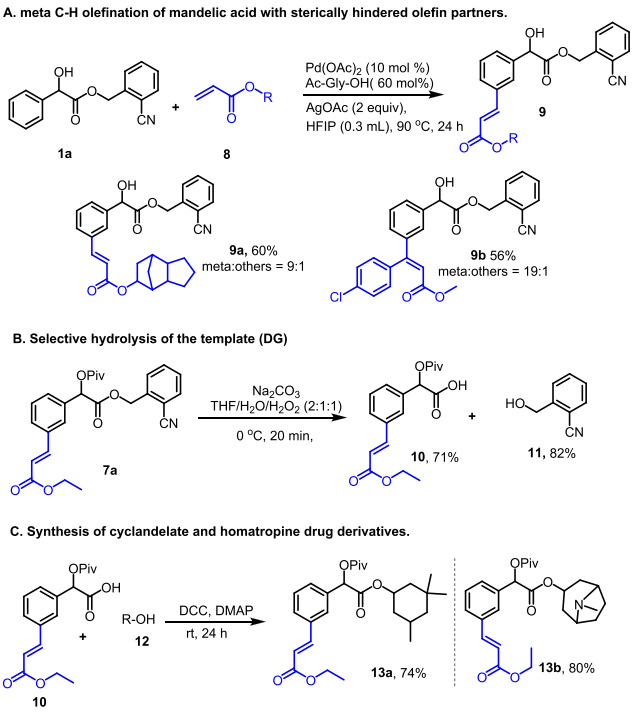
Scheme 4. *meta*-C−H Diolefination of Protected Mandelic Acid[a]



[a]Reaction conditions are as follows: **6** (0.1 mmol), **2** (0.3 mmol), $Pd(OAc)_2$ (0.01 mmol), Ac-Gly-OH (0.06 mmol), Ag_2CO_3 (0.2 mmol), and HFIP (0.3 mL). Isolated yield. Ratio of *m*,*m*:*m*,(*p* + *o*) was determined by ^{1}H NMR spectra.

To further demonstrate the synthetic utility of the protocol, sterically hindered octahydro-1*H*-4,7-methanoinden-5-yl acrylate, **8a** was selectively *meta*-olefinated to furnish product **9a,** a key structural motif present in many drug molecules, in a good yield. Similarly, the sterically hindered olefin **8b** also afforded the mono-olefinated product **9b** in a high yield and *meta*-selectivity (Scheme 5a). To demonstrate the reusability of the template, we carried out the selective hydrolysis of the benzyl ester template in the presence of pivaloyl and acrylic esters in compound **7a.** After some initial screening (Table S9), we found that using Na_2CO_3/H_2O_2 at 0 °C in THF/H_2O gave the desired product **10** in a 71% yield along with template **11** (82%), which can further be reused for the synthesis of the starting materials (Scheme 5b). To further demonstrate the synthetic utility of this method, we coupled carboxy-(pivaloyloxy)methyl)phenyl)acrylic acid **10** with 3,3,5-trimethylcyclohexanol (mixture of *cis*- and *trans*-isomers) **12a** to afford the *meta*-functionalized cyclandelate drug derivative **13a** in a 74% yield. Similarly, coupling compound **10** with tropine **12b** afforded the desired *meta*-functionalized homatropine drug derivative **13b** in an 80% yield (Scheme 5c). Next, to show the scalability of this methodology, we demonstrated the

Scheme 5. Synthetic Applications of the Methodology



gram-scale synthesis of mono- and diolefinated mandelic acid derivatives under similar reaction conditions without any significant change in the yield or selectivity (see the Supporting Information).

We then conducted mechanistic studies to understand the underlying mechanism for the controlled formation of mono- and diolefinated products. We carried out a competition experiment between *p*-trifluoro and *p*-methoxy mandelic acid esters **4j** and **4c**, respectively, and the resultant products **5j** and **5c** were obtained in a 2:3 ratio, showing that electron-rich substrates are more reactive than electron-poor substrates (Scheme 6a). These results indicate the possibility of a base-assisted internal electrophilic-type substitution (BIES) or another similar mechanism for the C−H activation step.[14] Intermolecular kinetic isotopic effect (KIE) experiment between **1a** and **1a-D** afforded compounds **3a** and **3a-D**, with K_H/K_D = 4.3. A similar K_H/K_D value was also obtained for the parallel KIE experiment (see the Supporting Information). This high K_H/K_D value indicates a primary kinetic isotopic effect (KIE) and C−H activation as the rate-determining step (Scheme 6b).

Furthermore, *meta*−*meta* diolefination was confirmed by blocking one of the *meta*- positions of mandelic acid. Accordingly, the reaction of the *m*-Cl mandelic acid derivative under the standard conditions for diolefination afforded only mono-olefinated product **7m**. This shows that diolefination happens at *meta*−*meta* positions and not in *ortho*−*meta* or *para*−*meta* positions (Scheme 6c). Furthermore, to prove that the mono-olefinated product is a possible intermediate in the diolefination reaction, sequential hetero-diolefination was performed using the mono-olefinated product **7g′** (which was obtained as a byproduct in diolefination of **7g**) and 2-cyanoethyl acrylate to afford the diolefinated product **7n** in a 71% yield. These results suggest that the reaction may proceed in a stepwise manner (Scheme 6d). Similarly, to understand the role of protecting groups, substrate **4g** containing a methyl

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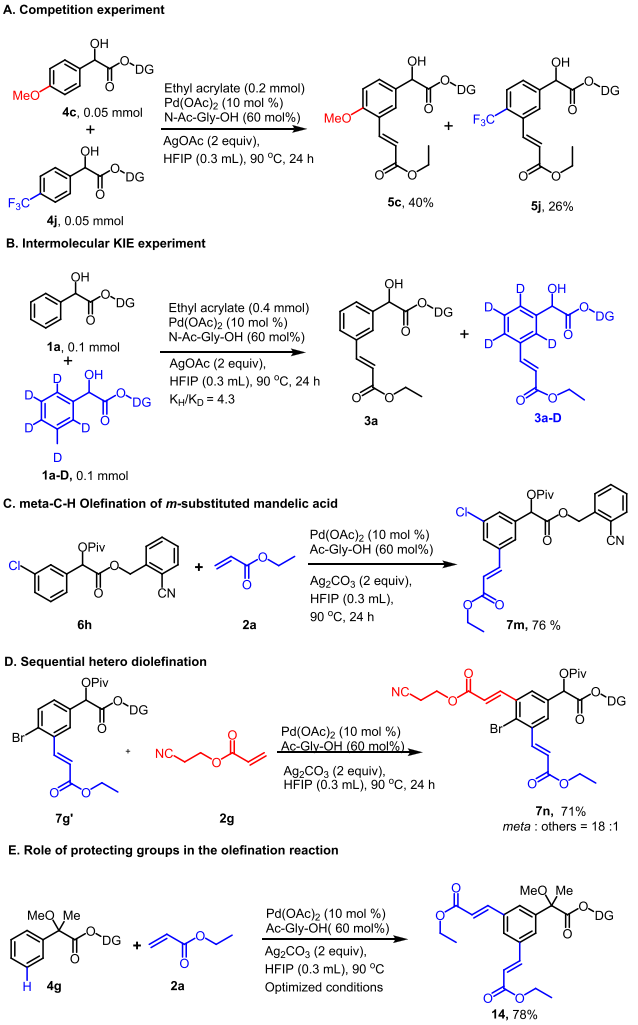
Scheme 6. Mechanistic Studies for the *meta*-C−H Olefination of Mandelic Acid



protection was treated with ethyl acrylate under the standard diolefination conditions to afford the desired *meta*-diolefinated product **14** in a 78% yield (Scheme 6e).

This result shows that the carbonyl (C═O) of the pivaloyl or acetyl protecting group does not coordinate with the catalyst to drive the reaction but rather prevents the free hydroxyl group of mandelic acid from interfering in the second olefination reaction. Alternatively, the bulky protecting groups may favor the second olefination (diolefination) reaction by bringing the directing group and the *meta*-C−H bond of mandelic acid close by decreasing their bond angle (Thorpe−Ingold effect) or increasing the concentration of the reactive rotamer, which is commonly called the reactive rotamer effect.[15] Similarly, silver carbonate being more basic than silver acetate also may favor the diolefination reaction. Hence, the synergetic effect of both the protecting groups and the oxidant plays a key role in determining the selectivity.

In summary, we have developed the *meta*-selective controlled mono- and diolefination of mandelic acid using an end-on nitrile template. A wide range of mandelic acid derivatives and acrylates were well-tolerated and afforded the final mono- and diolefinated products in good yields and high selectivities. Interestingly, free −OH groups were compatible with the mono-olefination reactions. More importantly, templates could be easily removed under basic conditions and could be reused again to make the substrates. Moreover, *meta*-olefination was extended to sterically hindered and disubstituted olefins to form the corresponding *meta*-olefinated mandelic acid derivatives in high selectivities. Finally, *meta*-functionalized homatropine and cyclandelate drug derivatives were demonstrated using this strategy.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02080.

Experimental procedures, characterization data, and ^{1}H NMR and ^{13}C NMR spectra for all products (PDF)

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Notes

The authors declare no competing financial interest.

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