

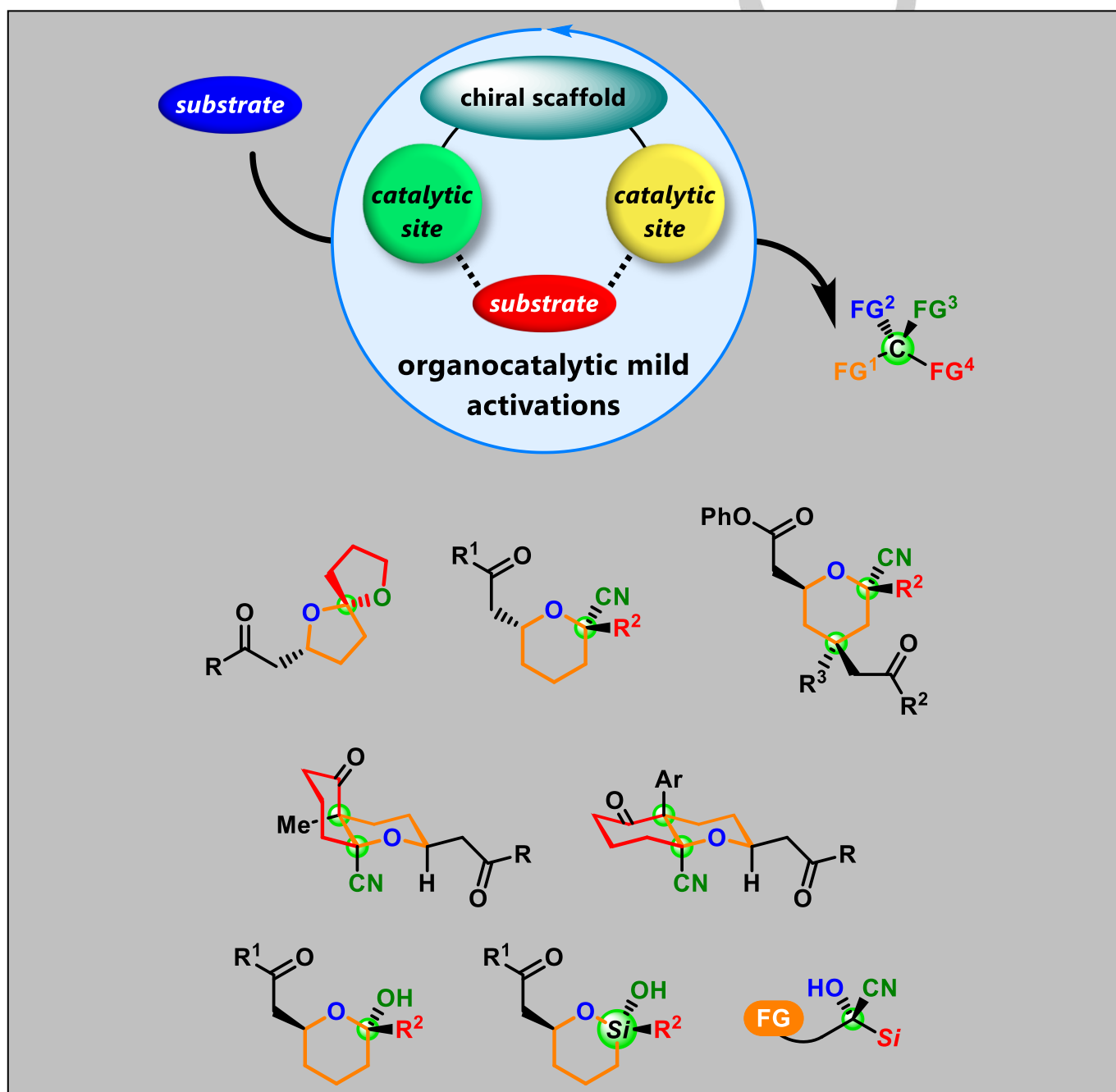


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Organocatalytic Access to Tetrasubstituted Chiral Carbons Integrating Functional Groups

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Abstract: Three-dimensional organic structures containing sp^3 carbons bearing four non-hydrogen substituents can provide drug-like molecules. Although such complex structures are challenging targets in synthetic organic chemistry, efficient synthetic approaches will open a new chemical space for pharmaceutical candidates. This review provides an account of our recent achievements in developing organocatalytic approaches to attractive molecular platforms based on optically active sp^3 carbons integrating four different functional groups. These methodologies include asymmetric cycloetherification and cyanation of multifunctional ketones, both of which take advantage of the mild characteristics of organocatalytic activation. Enzyme-like but non-enzymatic organocatalytic systems can be used to precisely manufacture molecules containing complex chiral structures without substrate specificity problems. In addition, these catalytic systems control not only stereoselectivity but also site-selectivity and do not induce side reactions even from substrates with rich functionality.

1. Introduction

Three-dimensional organic structures containing abundant sp^3 -hybridized carbons often display drug-like properties.¹ In addition, sp^3 carbons bearing four non-hydrogen substituents are promising structural platforms from several viewpoints, including pharmacological properties, shape diversity, and patentability.² However, such complex structures are challenging targets in synthetic organic chemistry. If efficient synthetic approaches to accessing these complex structures are available, they will open a new chemical space for pharmaceutical candidates. We have developed asymmetric synthetic reactions based on the multipoint recognition of molecular conformations using organocatalysts.³ In these reactions, organocatalysts activate substrates via mild noncovalent interactions, and their cooperative actions at multiple catalytic sites are essential even in intrinsically rapid intramolecular cyclizations. These catalyst systems are effective for recognizing specific molecular conformations of substrates through multipoint interactions, thereby leading to the selective construction of absolute and relative product configurations. Several strategies have been developed to construct tetrasubstituted chiral carbons in enantio- and diastereoselective cycloetherification reactions (Figure 1). These strategies have led to the construction of tetrasubstituted chiral carbons bearing multiple functional structures, including heterocycles and various functional groups. Moreover, by expanding the synthetic concepts, we explored the

enantioselective cyanation of multifunctional ketones to afford densely functionalized tetrasubstituted chiral carbons (Figure 2). The mild characteristics of organocatalysis contribute to not only enantioselectivity but also site-selectivity, and also prevent side reactions caused by the rich functionalities of the substrates. Thus, these synthetic methods provide access to further attractive molecular platforms based on sp^3 -hybridized carbons integrating four different functional groups while controlling the absolute configurations. This review provides an account of our recent achievements in developing organocatalytic access to tetrasubstituted chiral carbons integrating multiple functional groups.

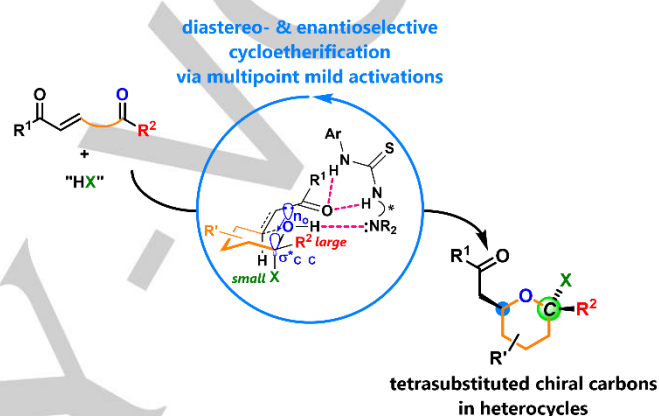


Figure 1. Construction of tetrasubstituted chiral carbons in enantio- and diastereoselective cycloetherification.

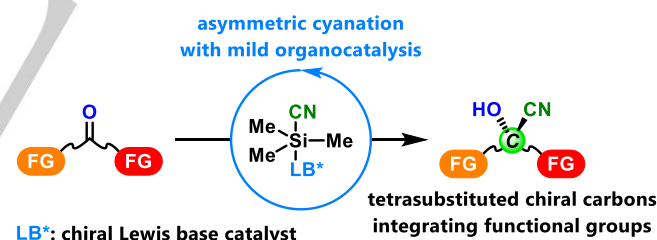


Figure 2. Enantioselective cyanation of multifunctional ketones.

2. Intramolecular Oxy-Michael Addition to Construct Multiple Stereogenic Centers Including Tetrasubstituted Chiral Carbons

2.1. Intramolecular Hetero-Michael Addition

Intramolecular hetero-Michael addition reactions allow the straightforward construction of heterocycles, which are ubiquitous scaffolds found in a range of bioactive natural products and pharmaceuticals.⁴ However, efficient enantioselective catalysis has not been established.⁵ To address this issue, we focused on bifunctional organocatalysts, enabling synergistic multipoint activations via mild hydrogen bonding (Figure 3). Multipoint

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recognition of substrates provides an effective chiral environment for cyclization. In addition, the catalysis based on mild noncovalent interactions gives rise to an effective system, in which no reaction can proceed without the simultaneous activations at multiple catalytic sites.⁶ By using bifunctional organocatalysts bearing hydrogen-bond donor and acceptor moieties on an effective chiral scaffold, including aminothioureas and phosphoric acids, we have accomplished the enantioselective syntheses of various heterocycles.⁷

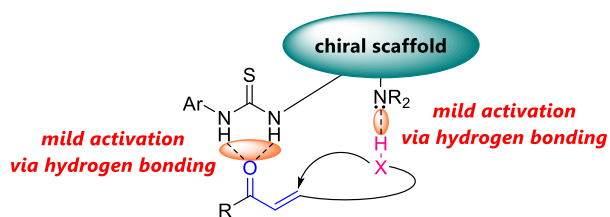
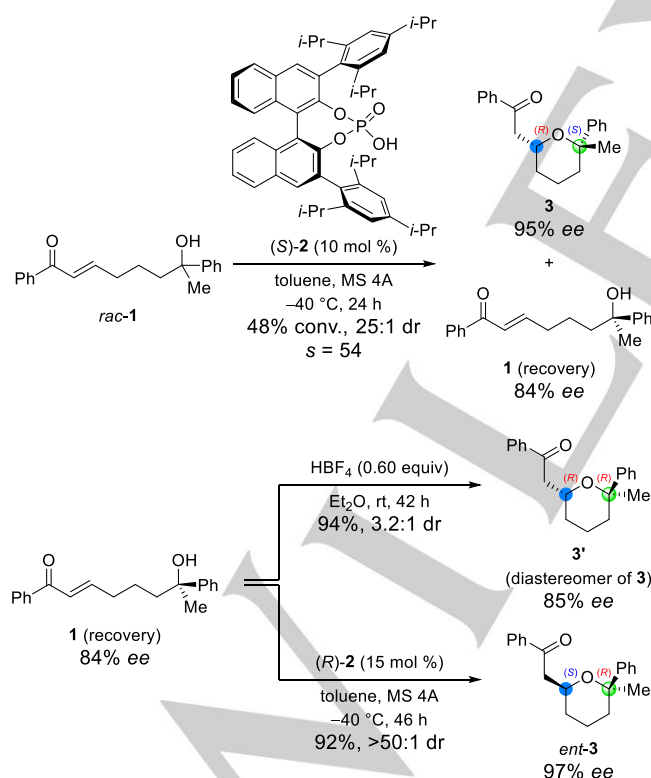


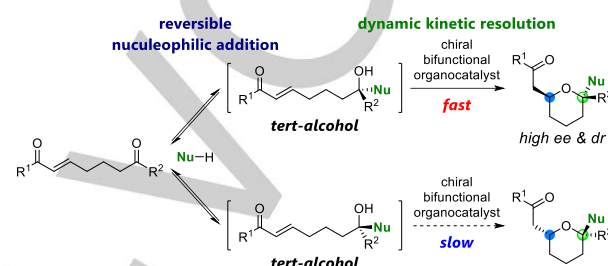
Figure 3. Asymmetric intramolecular hetero-Michael addition reactions using bifunctional organocatalysts.

2.2. Intramolecular Oxy-Michael Addition to Construct Multiple Stereogenic Centers Including Tetrasubstituted Chiral Carbons



Scheme 1. Asymmetric cycloetherification via KR and stereodivergent synthesis of THPs with two chiral centers.

Organocatalytic intramolecular oxy-Michael addition has been proved to be effective for the construction of multiple stereogenic centers, including tetrasubstituted chiral carbons. Chiral phosphoric acid catalyst (*S*)-**2** allowed the cycloetherification via kinetic resolution (KR)⁸ of racemic alcohols (Scheme 1).⁹ Notably, tertiary alcohols are also applicable, although their KR is rare, and the use of (*S*)-**2** afforded tetrahydropyran (THP) **3**, bearing a tetrasubstituted chiral carbon. In addition, the recovered optically active alcohol **1** was converted to diastereomer **3'** and enantiomer *ent*-**3**, which demonstrated the divergent syntheses of various stereoisomers, taking advantage of KR methods.

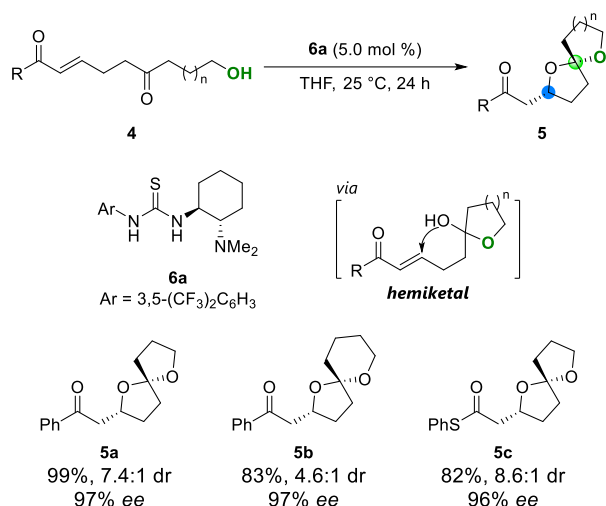


Scheme 2. Design of asymmetric cycloetherification via DKR of chiral tertiary alcohols.

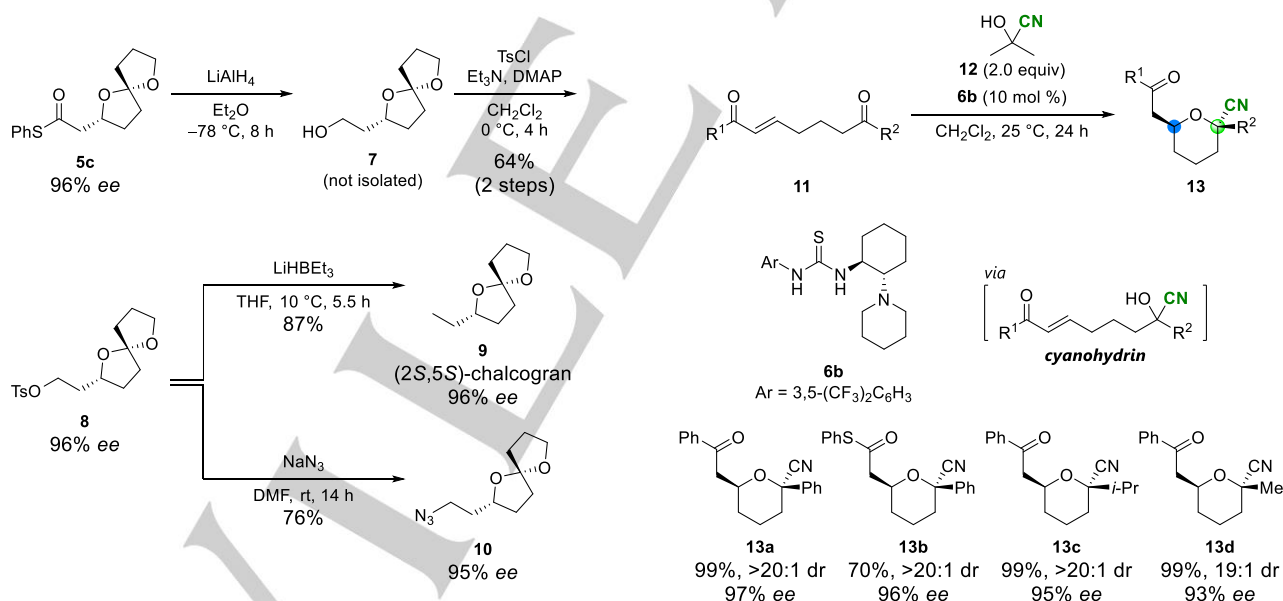
On the other hand, the quantitative synthesis of a specific stereoisomer requires dynamic kinetic resolution (DKR).¹⁰ In particular, the construction of tetrasubstituted chiral carbons should involve in-situ racemization of tertiary alcohols; however, they are not amenable to redox process, which is useful for secondary alcohols, and their racemization typically requires harsh conditions, which are not compatible with asymmetric catalysis. In particular, intramolecular cyclizations become even faster under such harsh conditions, and it is difficult to control the stereoselectivity through multipoint recognition of molecular conformations, even though mild organocatalysis is employed. Thus, we designed a system involving the reversible addition of nucleophiles to ketones to realize formal racemization of tertiary alcohols under mild conditions. Organocatalytic enantio- and diastereoselective cycloetherification of reversibly generated chiral tertiary alcohols via DKR enabled the simultaneous construction of multiple stereogenic centers, including tetrasubstituted chiral carbons (Scheme 2).

Firstly, cyclization of hemiketals reversibly generated via intramolecular addition of a pendant alcohol yields chiral spiroketals with high enantioselectivities (Scheme 3).¹¹ Spiroketal frameworks bearing an alkyl group at their 2-positions are found in a range of insect pheromones, and the products are potentially useful as agricultural chemicals. This method enables the asymmetric synthesis of spiro[4.4]nonanes and sipro[4.5]decanes. In addition, spiroketal **5c** bearing a thioester group was efficiently synthesized and used for further transformation. The reduction of **5c** with lithium aluminium hydride followed by tosylation afforded the corresponding tosylate **8** without erosion of the enantiomeric excess. Subsequent reduction with lithium triethylborohydride gave optically active (2*S*,5*S*)-chalcogran (**9**), which is a

pheromone of the six-spined spruce bark beetle *Pityogenes chalcographus* (Scheme 4). Compound **8** was also treated with sodium azide to afford **10**, containing a pheromone framework bearing an azide tag, which could expand the utility of the bioactive structure by allowing its facile introduction into various compounds by means of well-established ligation methods based on click chemistry.¹²



Scheme 3. Asymmetric synthesis of spiroketals.



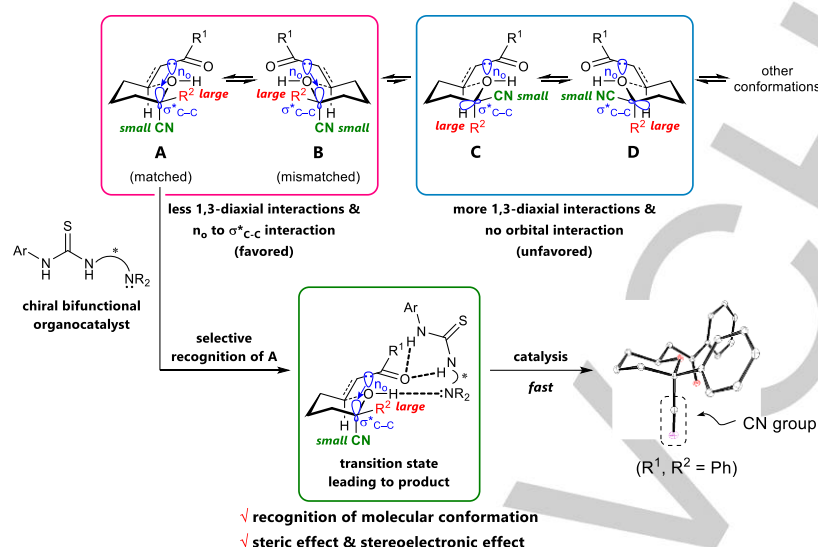
Scheme 4. Synthesis of chalcogran and its derivative.

and electronic properties to preferentially reside in the axial position: it is known to have a small A value (conformational energy) because of its linear structure¹⁴ and is capable of inducing an anomeric effect because of its electronegativity.¹⁵ Moreover, the diverse chemistry of a cyano group also expands the utility of the resulting products as synthetic intermediates.¹⁶

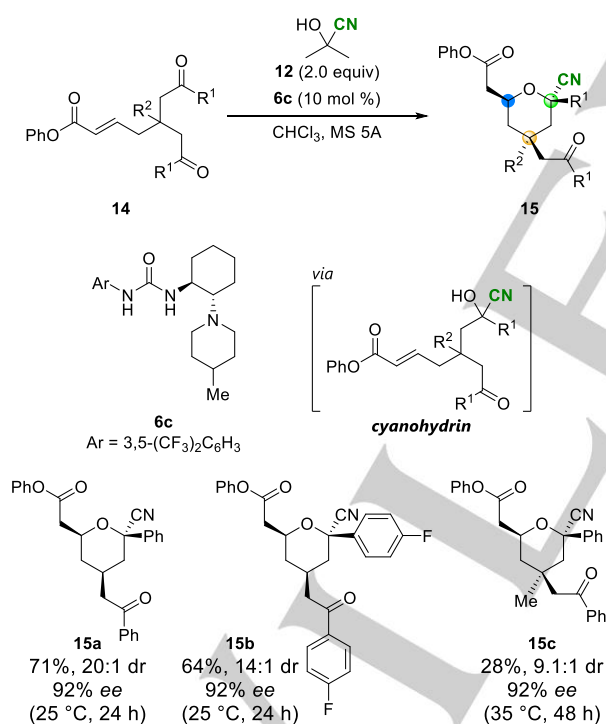
The reactions of substrates **11** with acetone cyanohydrin (**12**) in the presence of bifunctional organocatalyst **6b** afforded in quantitative yields and excellent enantio- and diastereoselectivities THPs **13** involving the simultaneous construction of two chiral centers, one of which was fully substituted (Scheme 5).¹⁷ The stereoselectivities are rationalized as follows (Scheme 6). The chiral bifunctional organocatalyst can form hydrogen bonds with a specific chair-like conformation (**A**) from the isomers generated during interconversions between the enantiomers of cyanohydrin intermediates in various conformations (**A–D** and other conformations). This complex immediately catalyzes the subsequent asymmetric oxy-Michael addition from the recognized conformation. It is also important that the cyano group in the axial position is favored mainly by its small steric effects, and two stereogenic centers are controlled in one operation. It is noteworthy that a methyl-substituted ketone also yielded THP **13d** with high enantio- and diastereoselectivity despite the relatively small difference in size between the methyl and cyano groups, reinforcing that some assistance was also provided by the anomeric effect induced by the cyano group in the chair-like oxygen-containing cyclic conformation.

Scheme 5. Asymmetric cycloetherification via DKR of chiral cyanohydrins.

Next, aiming for the DKR of tertiary alcohols generated via the reversible addition of a carbon nucleophile, we selected hydrogen cyanide as a suitable carbon nucleophile because asymmetric cyanation of ketones is a powerful method for the construction of tetrasubstituted chiral carbons.¹³ In addition, a cyano group embedded in saturated six-membered rings has fascinating steric



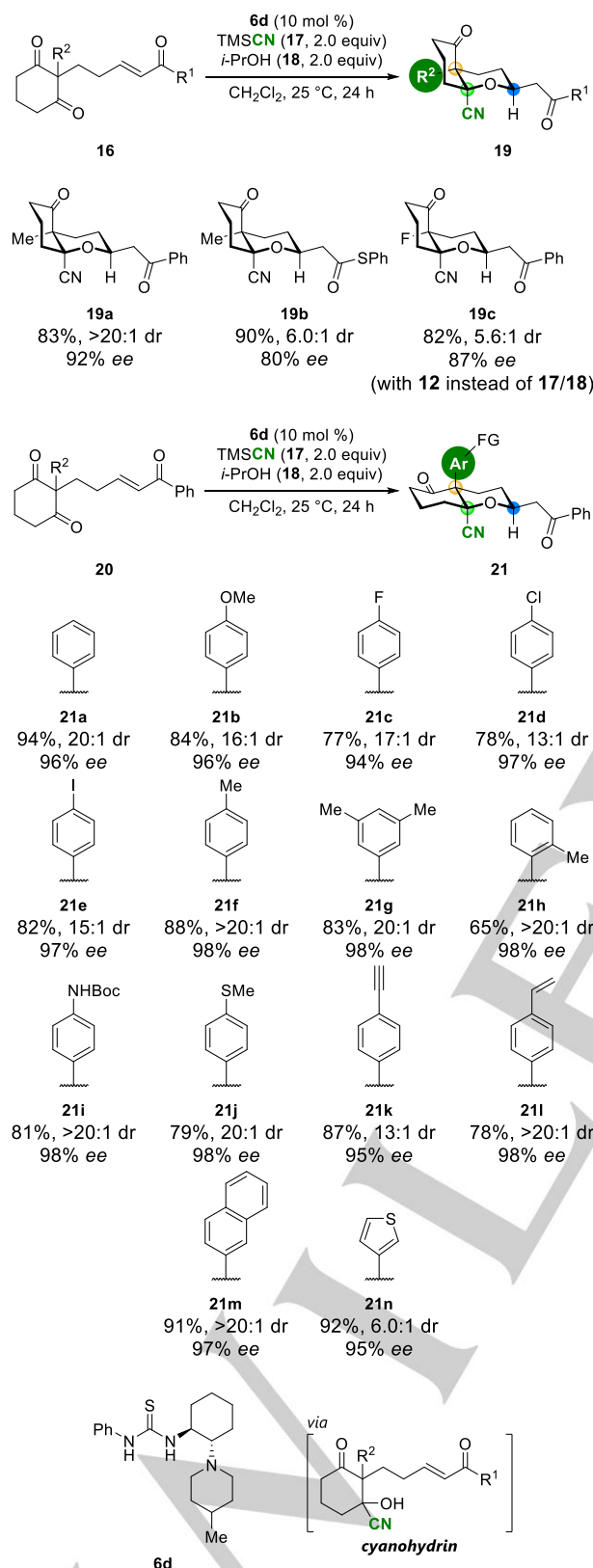
Scheme 6. Rationale for the stereoselectivity.



Scheme 7. Asymmetric concomitant construction of three chiral carbons in THP synthesis.

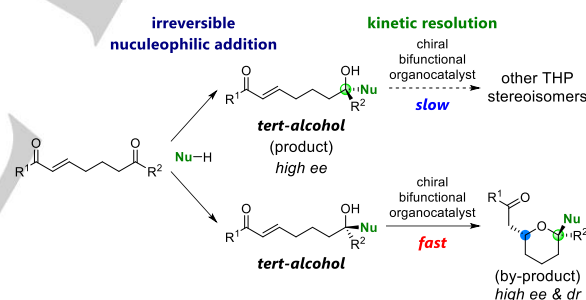
The methodology also enabled enantio- and diastereoselective cycloetherification of cyanohydrins generated in situ from achiral 1,5-diketone-bearing enones **14** involving the simultaneous construction of three stereogenic centers, including tetrasubstituted chiral carbon centers (Scheme 7).¹⁸ In this method, THP **15c**, containing two tetrasubstituted stereogenic centers, was also synthesized with high enantio- and diastereoselectivity, albeit in modest yield. In addition, the resulting products contained multiple synthetically important functional groups in different oxidation states (ketone, ester, and cyano groups). Hence, this synthetic method facilitated the construction of complex heterocyclic architectures.

Furthermore, the enantio- and diastereoselective cycloetherification of 1,3-cyclohexanedione-bearing enones involving the in-situ generation of chiral cyanohydrins represent the first catalytic asymmetric approach to oxadecalin derivatives containing three stereogenic centers including contiguous tetrasubstituted chiral carbons at their bridge heads of the fused ring systems (Scheme 8).¹⁹ Depending on the class of substituents on the 1,3-diketones, both *cis*- and *trans*-decalin-type scaffolds **19** and **21** were synthesized with good-to-excellent stereoselectivities. Based on the high stereoselectivity in the reactions of aryl group-containing 1,3-diketones **20**, a range of functional groups were integrated on the chiral quaternary carbon moieties of *trans*-oxadecalin derivatives **21**, facilitating the synthesis of densely functionalized and complex heterobicyclic configurations containing multiple tetrasubstituted chiral carbons, which are otherwise difficult to access and thus expand the chiral chemical space. In addition, the diastereoselectivities decreased considerably when triethylamine was used as the catalyst instead of **6d**, indicating that both the enantioselectivity and diastereoselectivity were controlled to a large degree by the chiral bifunctional organocatalyst, which taps the potential of fully catalyst-controlled stereodivergent strategies.



Scheme 8. Asymmetric construction of contiguous tetrasubstituted chiral carbons in oxadecalin synthesis.

Furthermore, enantio- and diastereoselective cycloetherification also enabled the KR of chiral tertiary alcohols, which are irreversibly generated in situ (Scheme 9). Chiral cyanohydrins were irreversibly generated from acylsilanes because they have higher electrophilicity than typical ketones, and the KR of the acylsilane cyanohydrins was attained (Scheme 10).²⁰ The cyclization selectively occurred from one enantiomer of cyanohydrin in the presence of the bifunctional organocatalyst, and the other enantiomer was selectively synthesized. To the best of our knowledge, this is the first example of a non-enzymatic catalytic asymmetric approach to optically active acylsilane cyanohydrins. The bifunctionality of the catalysts containing thiourea and tertiary amino groups on the optimized molecular skeleton is crucial not only for attaining high stereoselectivity but also for obtaining the desired acylsilane cyanohydrin **23** in high yield, avoiding product degradation via Brook rearrangement to provide **25**. Catalysts **6e** and **6f** were much better than catalysts **6b** and **26**. The obtained products contain a densely functionalized tetrasubstituted stereogenic carbon center bearing silyl, cyano, and hydroxy groups and can be employed in the synthesis of chiral organosilanes, which has recently attracted increasing attention as a pharmaceutical candidate. Therefore, this method offers a new avenue for the catalytic asymmetric construction of synthetically challenging tetrasubstituted chiral carbons that can serve as structural platforms for integrating multiple functionalities on a chiral carbon center.^{1,2}

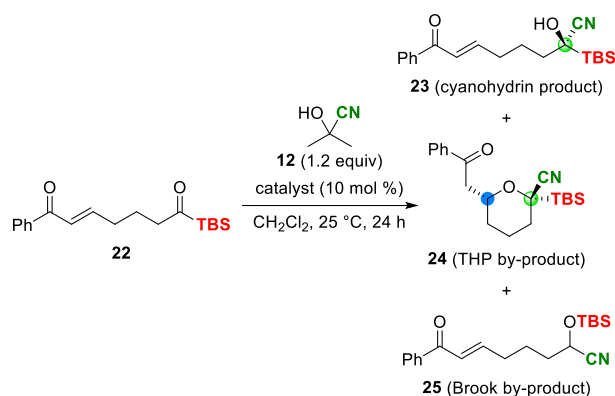


Scheme 9. Design of KR of chiral tertiary alcohols via asymmetric cycloetherification.

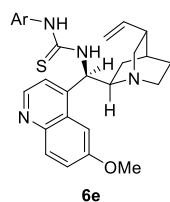
While various asymmetric cyclizations of cyanohydrins have been accomplished on the basis of the properties of a cyano group, a hydroxy group is also a potent small and electronegative functional group; indeed, it is partially located in the axial position on the anomeric carbons of saccharides in nature. Inspired by these concepts, the first desymmetrization^{8c,21} of *gem*-diols to form chiral hemiketal carbons was accomplished via organocatalytic enantio- and diastereoselective cycloetherification (Scheme 11).²² This transformation afforded optically active tetrahydropyran derivatives containing a chiral hemiketal carbon, a ubiquitous scaffold found in a variety of bioactive natural products and pharmaceuticals. To achieve the construction of the chiral hemiketal carbons, it is also necessary to suppress the formation of dihydropyran by-product **29**, which was formed via intramolecular oxy-Michael addition of an enol

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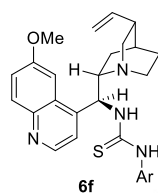
form of **11**.²³ The presence of water in the reaction proved to be important not only for generating the *gem*-diols but also for controlling the interconversion between the desired products **27** and by-products **29** (Scheme 12). In addition, this method enabled the catalytic desymmetrization of silanediols as an asymmetric route to chiral silicon centers, which are challenging synthetic targets in asymmetric catalysis (Scheme 13).



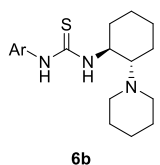
catalyst:



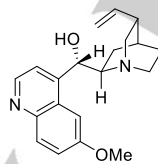
23: 49%, 96% ee
24: 48%, 8.0:1 dr, 86% ee
25: <1%



23: 44%, -97% ee
24: 53%, 6.6:1 dr, -86% ee
25: <1%



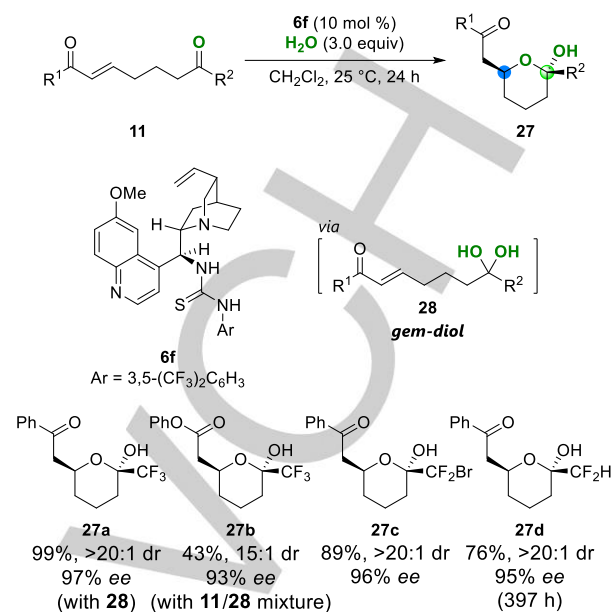
23: 5%, -66% ee
24: 61%, 12:1 dr, -50% ee
25: 34%



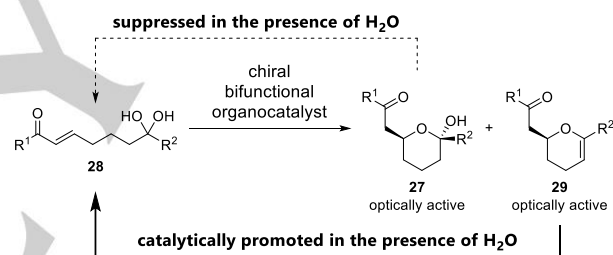
23: <1%
24: <1%
25: >95%

Ar = 3,5-(CF₃)₂C₆H₃

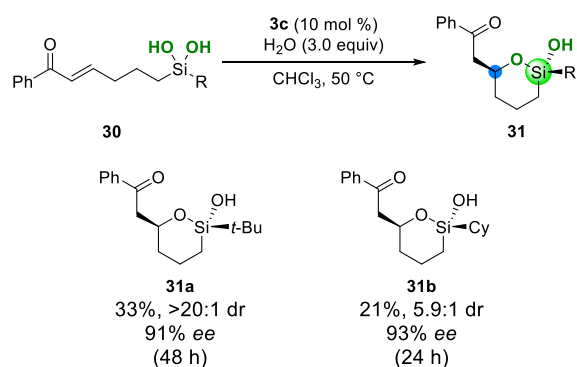
Scheme 10. KR of acylsilane cyanohydrin via asymmetric cycloetherification.



Scheme 11. Desymmetrization of *gem*-diols via asymmetric cycloetherification.



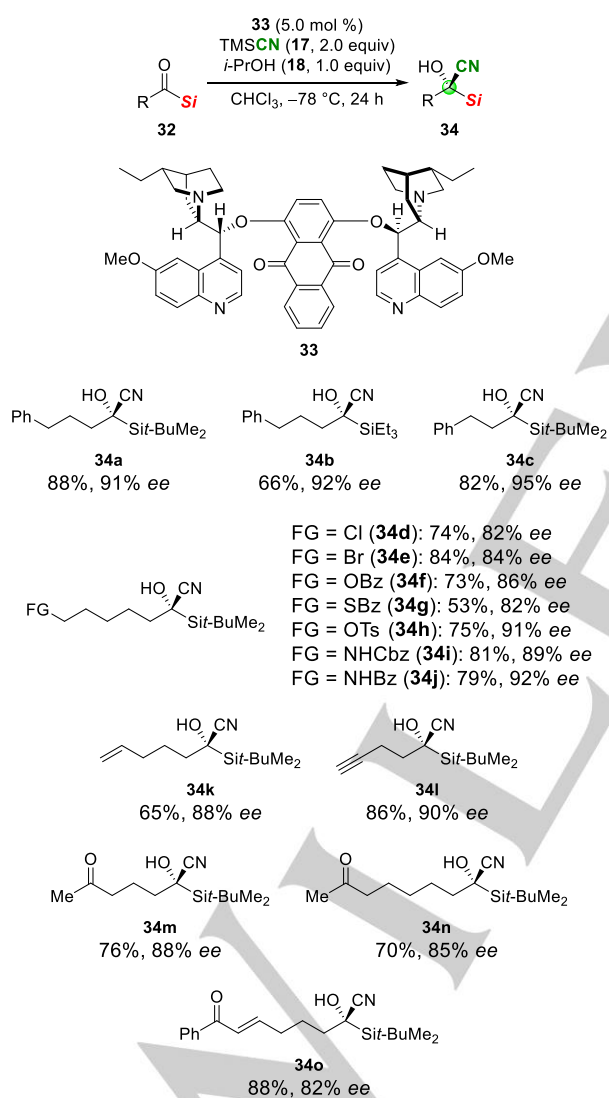
Scheme 12. Effects of H₂O.



Scheme 13. Desymmetrization of silanediols via asymmetric cycloetherification.

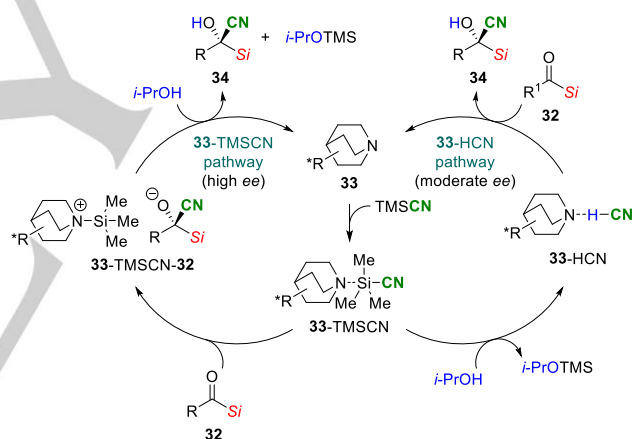
3. Cyanation of Multifunctional Ketones

Catalytic asymmetric cyanation of ketones represents a straightforward method for the construction of tetrasubstituted chiral carbon centers,¹³ which are of particular interest in synthetic^{21a,24} and medicinal^{1,2} chemistry. Indeed, owing to the synthetic utility of optically active tertiary alcohols bearing cyano groups,^{16,25} significant advances have been made in their asymmetric synthesis.^{13,24} The asymmetric cyanation of acylsilanes affords densely functionalized tetrasubstituted chiral carbon centers bearing silyl, cyano, and hydroxy groups. However, the application of this method has been limited to a few enzymatic approaches that employ only one substrate because of its substrate specificity.²⁶



Scheme 14. Non-enzymatic catalytic asymmetric cyanation of acylsilanes.

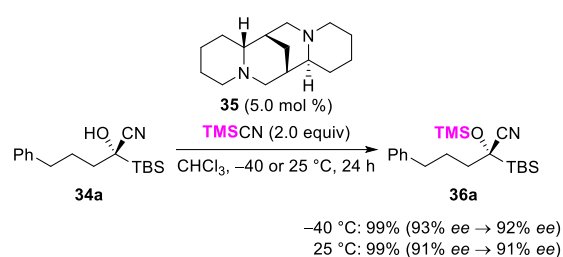
As mentioned above, we previously reported the KR of the chiral cyanohydrins generated in situ from the acylsilanes involving the organocatalytic asymmetric cyclization under nearly neutral conditions, which prevents the occurrence of the Brook rearrangement (Scheme 10).²⁰ However, the maximum yield is ~50% due to the principle of KR, and the substrate structures are limited as they are required to undergo a 6-membered ring formation via intramolecular oxy-Michael addition. To solve these issues, it is desirable to develop a non-enzymatic asymmetric cyanation of acylsilanes via enantioselective 1,2-addition reactions. We supposed that organocatalysis is effective not only for achieving high enantioselectivity but also for preventing side reactions, and Lewis base-catalyzed enantioselective cyanation of acylsilanes was developed (Scheme 14).²⁷ To the best of our knowledge, this is the first non-enzymatic catalytic method that leads to quantitative yields of optically active acylsilane cyanohydrins. This method does not require any specific substrate structure, and various functional groups are tolerated, overcoming the limitations imposed by substrate specificity in conventional enzymatic methods. In addition, site-selective cyanation of substrates containing multiple carbonyl moieties was also attained (**34m**, **34n**, and **34o**).



Scheme 15. Proposed catalytic pathways.

Catalytic pathways were proposed based on several experimental results (Scheme 15). There are two possible catalytic cycles. The **33**-TMSCN complex was generated as a common intermediate. In the **33**-TMSCN pathway, the **33**-TMSCN complex cyanates **32**, and the alcohol additive removes the silyl group to regenerate **33**. In contrast, in the **33**-HCN pathway, the alcohol additive initially reacts with the **33**-TMSCN complex to generate HCN, which is then activated by **33** and cyanates **32**. Although the **33**-HCN pathway also provides more than 80% enantiomeric excess, it is relatively lower than that of the **33**-TMSCN pathway. The use of bulky *i*-PrOH inhibited the generation of HCN, and the **33**-TMSCN complex was more involved in the **33**-TMSCN pathway to provide high enantioselectivity. In the **33**-TMSCN pathway, *i*-PrOH scavenges the TMS group from **33**-TMSCN-**32** to regenerate **33** and protonates the resulting alkoxide to provide **34**.

Protocols have also been established to transform the resulting cyanohydrin products because they remain susceptible to Brook rearrangement. In addition, they are difficult to protect because of the adjacent bulky silyl group, which is consistent with the formation of non-silylated product **34** when cyanation was performed using catalyst **33**. Thus, an active catalyst is necessary for protection under mild conditions, which avoids the Brook rearrangement, and sparteine-catalyzed silylation of the product alcohols was developed (Scheme 16). This is a valuable handle for synthetic applications. For example, indium-catalyzed hydration of nitrile **36a** to the corresponding amide was possible, while unprotected **34a** only provided the Brook side product under the same conditions. The sparteine-catalyzed silylation further expands the synthetic utility of optically active acylsilane cyanohydrins, a variety of which are now available through the **33**-catalyzed cyanation we developed.



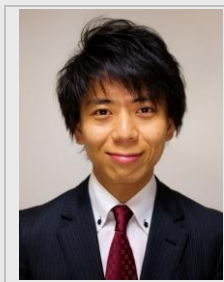
Scheme 16. Sparteine-catalyzed silylation of acylsilane cyanohydrin.

The synthetic methods in Schemes 14 and 16 provide tetrasubstituted chiral carbon centers that integrate multiple functional groups, including functionalized alkyl groups as well as silyl, cyano, and hydroxy groups. Thus, an efficient catalytic approach was developed to prepare potential building blocks for the synthesis of pharmaceutically relevant chiral organosilanes.


4. Summary and Outlook

We have developed a range of organocatalytic approaches to tetrasubstituted chiral carbons integrating functional groups through asymmetric cycloetherification and cyanation of multifunctional ketones. Both methodologies take advantage of the mild characteristics of the organocatalytic activation. In cycloetherification, multipoint mild activations through noncovalent interactions, including hydrogen bonding, imparted the recognition of a specific molecular conformations of the substrates, thereby leading to the selective construction of the absolute and relative configurations of the products. Enzyme-like but non-enzymatic organocatalytic systems are associated with the chemistry of molecular imprinting,²⁸ which, in this case, precisely manufactures small molecules with complex chiral structures. In the cyanation of the acylsilanes, the mild characteristics of organocatalysis resulted in not only high enantioselectivities but also excellent site-selectivities. It is also important that the catalytic systems successfully prevent side

reactions caused by the rich functionality of the substrates. The developed catalytic method clearly solved the substrate specificity problem of conventional enzymatic methods. These results suggest that organocatalytic concepts are versatile for the asymmetric integration of four different functional groups on sp^3 hybridized carbons, which rapidly expands the pharmaceutically potential chemical space.



Keisuke Asano completed his Ph.D. at Kyoto University (Japan) in 2012 under the supervision of Professor Seiji Matsubara. He was appointed as an assistant professor at Kyoto University in 2012 and joined the group of Professor Jun-ichi Yoshida before moving back to the group of Professor Seiji Matsubara in 2013. He was promoted to an associate professor in Hokkaido University (Japan) and is working with Professor Daisuke Uruguchi since 2022. He received The 30th Inoue Research Award for Young Scientists (2014), Eisai Award in Synthetic Organic Chemistry, Japan (2014), Special Young Lecturer in the 95th CSJ Annual Meeting (2015), Poster Award in the 39th Naito Conference (2015), The 68th The Chemical Society of Japan Award for Young Chemists (2019), Thieme Chemistry Journals Award 2020 (2020), The 12th Inoue Science Research Award (2020), and The 10th JACI Prize for Encouraging Young Researcher (2021). His current research interests focus on the synthesis and analysis of biomolecules using organocatalytic reactions.



Seiji Matsubara was born in Kobe in 1959. He received his Ph.D. in 1986 from Kyoto University under the supervision of Professor Hitosi Nozaki and Professor Kiitiro Utimoto. He was also a student of Université de Lausanne for a year (1984–1985) under the supervision of Professor Manfred Schlosser. He was appointed as an assistant professor in 1986, an associate professor in 1995, and a full professor in 2006 at Kyoto University. He was also a postdoctoral fellow at Stanford University (1988–1989, Professor Barry M. Trost). His awards include The 3rd Inoue Research Award for Young Scientists (1987), Incentive Award in Synthetic Organic Chemistry, Japan (1998), Asian Core Program Lectureship Award, Korea and Malaysia (2014), and The 34th The Chemical Society of Japan Award for Creative Work (2017).

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Keywords: Organocatalyst • Tetrasubstituted chiral carbon • Functional group • Cycloetherification • Cyanation

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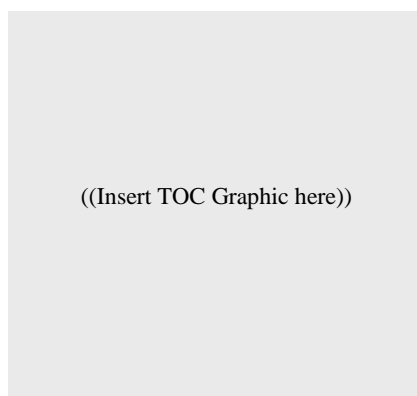
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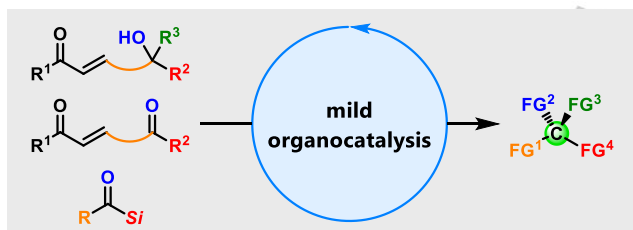
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*Keisuke Asano,* Seiji Matsubara***Page No. – Page No.****Organocatalytic Access to Tetrasubstituted Chiral Carbons Integrating Functional Groups**

Tetrasubstituted chiral carbons are drug-like structural platforms. Organocatalysis allows for the facile construction of optically active tetrasubstituted chiral carbons integrating multiple functional groups. The methodologies include asymmetric cycloetherification and cyanation of multifunctional ketones, taking advantage of the mild characteristics of organocatalytic activation. The enzyme-like but non-enzymatic catalytic systems control not only stereoselectivity but also site-selectivity without substrate-specificity problems, and also prevent side reactions even from substrates with rich functionality.