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Homogenous Catalysis Hot Paper

Enantioconvergent Deacylative Functionalization toward α-Quaternary Nitriles

*Minghao Zhang and Zhongxing Huang**

Abstract: The use of readily available prochiral or racemic quaternary carbons to access enantioenriched ones offers a promising alternative to conventional synthesis from tertiary or planar substrates. Unlike desymmetrization, which modifies an existing substituent with limited reactivity, a functional group swap can install a new motif, which is structurally distinct and non-derivable from the replaced group. However, achieving enantioconvergence in these quaternary-to-quaternary transformations is challenging, especially for acyclic stereocenters. Here, we report that acyl groups of β-ketonitriles can be stereoselectively replaced by allyl, propargyl, or benzyl moieties using easily accessible alcohols under palladium catalysis. The deacylative functionalization proceeds through a retro-Claisen-type elimination of ketonitrile with alkoxide and the absence of diastereoisomerism in the resulting ketenimine anion assists the subsequent asymmetric addition. Together with the pair of α-substituents, the retained nitrile and the incoming alkyl motif instill significant derivatization potential into the enantioenriched quaternary stereocenters.

Introduction

Forging optically active quaternary carbons remains a major challenge in asymmetric catalysis.[1–3] Conventional bottom-up synthesis often relies on the asymmetric addition and substitution of unsaturated bonds and tertiary stereocenters, respectively (Figure 1a).[4,5] Besides the planar-to- and tertiary-to-quaternary conversion, prochiral and racemic quaternary carbons are increasingly recognized as alternative reactants. These quaternary-to-quaternary syntheses benefit from the facile, modular construction of tetrasubstituted carbons via sequential substitution of bulk chemical feedstocks, especially active methylene compounds.[6] When built with a pair of enantiotopic motifs, desymmetric functional group interconversion (FGI) of the prochiral carbon generates a quaternary stereocenter.[7–9] However, these asymmetric conversions have a restricted scope of functional groups derivable from their parents (e.g., aldehyde or alcohol from ester via reduction) and are less effective for equally available racemic carbons due to the capped productivity of resolution. Instead, an enantioconvergent functional group swap (FGS) that can introduce a structurally distinct substituent that is inaccessible from the replaced one is highly sought after but underexplored.

As exemplified in the preparation of α-quaternary nitrile, one of the most versatile tetrasubstituted carbons, early efforts were highly dependent on tertiary reactants (Figure 1b). Nevertheless, an electron-withdrawing α-substituent is often needed for stereoselective substitution[10–15] while direct access to quaternary stereocenters from nonactivated nitriles is underdeveloped[16–18] and frequently entails preparation of silyl ketene imines (SKIs).[19–27] Meanwhile, quaternary carbons have emerged as promising substrates. Particularly, desymmetrization of easily accessible disubstituted malononitriles has proved effective in giving assorted cyclic and acyclic quaternary stereocenters.[28–35] Sporadic reports have also emerged using racemic α-quaternary nitriles via decarboxylative pathways.[36–39] Here, we aim to unlock an enantioconvergent quaternary-to-quaternary pathway from equally available racemic β-ketonitriles via a deacylative functionalization (DaF) that swaps in allyl, propargyl, or benzyl motifs.

Central to our strategy is a retro-Claisen reaction that eliminates an acyl group with alkoxide to generate a pair of enolate and ester electrophiles for catalytic alkylation (Figure 1c). The mode of mutual activation was first demonstrated by Tunge and immediately sparked interest in constructing enantioenriched stereocenters.[40] However, high enantioconvergence was hard to achieve, presumably due to the nonstereoselective enolate formation, a complication also encountered in other FGSs, including decarboxylative functionalization.[41–43] As a result, limited successful examples often proceed through cyclic enolates with fixed conformation.[44–47] Here, we envision that the lack of *E*/*Z* isomerism for ketenimine anions eliminated from β-ketonitriles can benefit the enantiocontrol of the following addition, thus

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Additional supporting information can be found online in the Supporting Information section

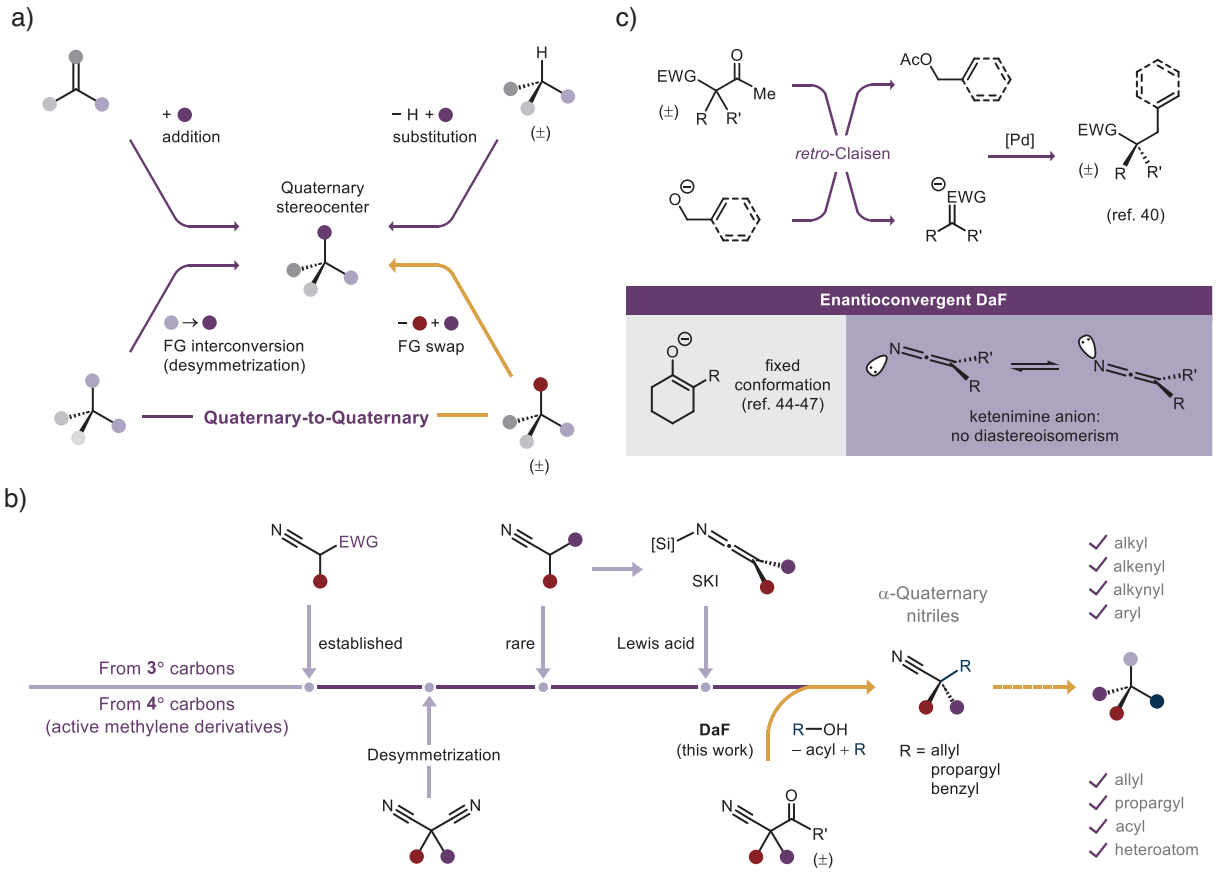


Figure 1. Catalytic preparation of quaternary stereocenters. a) General reaction paradigms toward quaternary stereocenters. b) Preparation of α-quaternary nitriles. c) Asymmetric deacylative functionalization.

unlocking the challenging access to acyclic quaternary stereocenters via DaF. Together with the versatility of the native nitrile and the set of incoming functional groups, the enantioconvergent quaternary-to-quaternary conversion would expedite the preparation of assorted tetrasubstituted carbons.

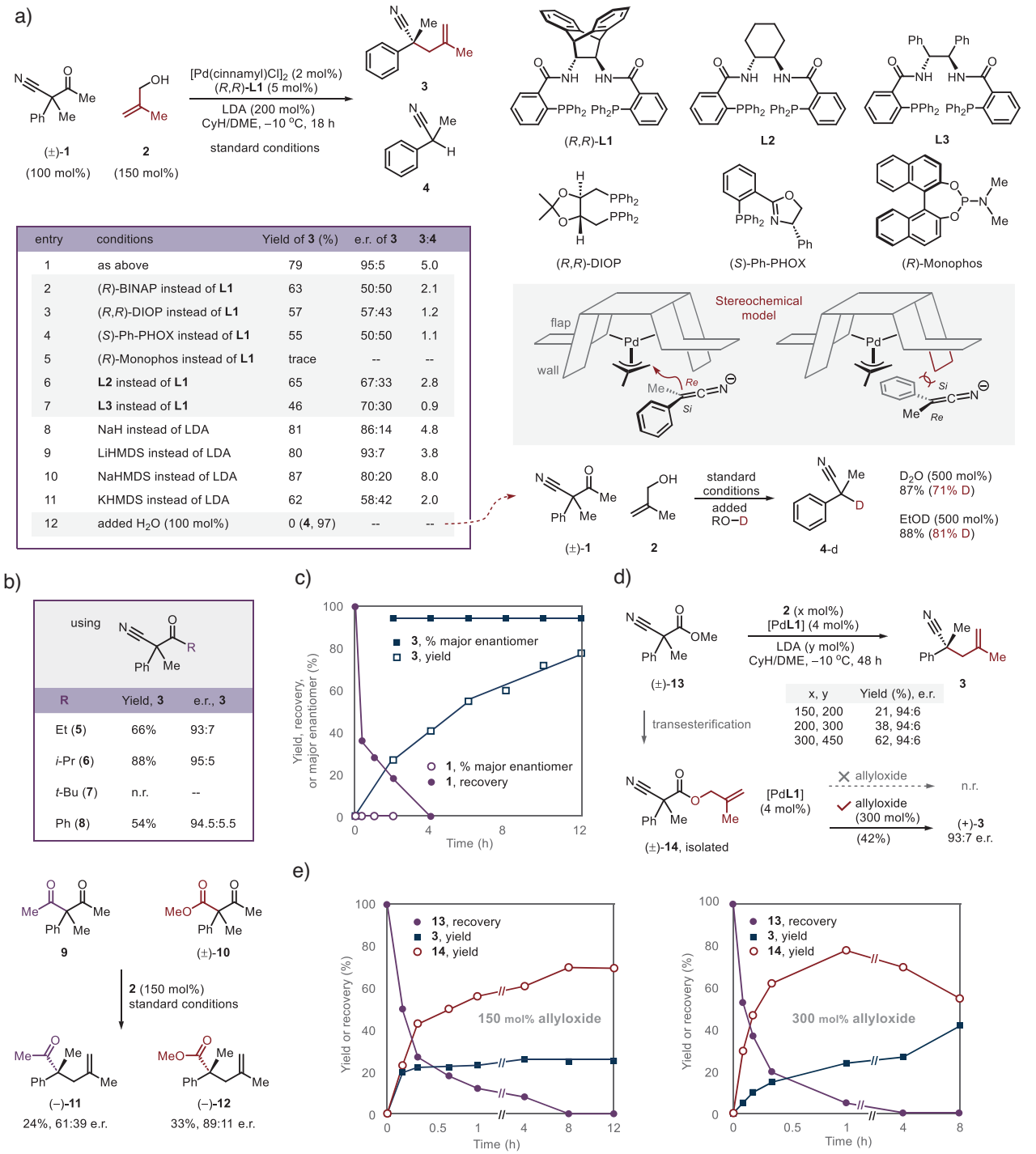
Results and Discussion

Conditions of Asymmetric Deacylative Allylation

Indeed, the nitrile substituent proved effective in implementing enantiocontrol. The DaF of racemic disubstituted β-ketonitriles **1** with allyl alcohol **2** gave an acyclic quaternary stereocenter (**3**) in high enantiopurity with chiral palladium catalyst (Figure 2a, entry 1). Although common mono- and bidentate ligands showed only negligible stereoselectivity (entries 2–5), classic Trost ligands stand out with **L1** identified as the optimal (entries 6 and 7). The high enantioselectivity and absolute configuration (vide infra, **29** and **73**) can be explained by the classic "flap-wall" model of palladium complexes with these ligands,[48] where the nucleophilic attack from the *Si* face of ketenimine anion is disfavored due to the steric repulsion between the large phenyl ring and one of the lowered flaps (i.e., the wall). The choice of base is also critical, as its strength modulates alkoxide generation and the identity of cation affects the stereocontrol of allylic substitution (entries 8–11). Meanwhile, α-tertiary nitrile **4** was observed as the major byproduct and determined to be racemic. It supposedly arises from the competing protonation of ketenimine anion in the absence of a palladium catalyst. The sensitivity of the allylation to adventitious moisture was further evidenced by the detrimental effect of added water at a stoichiometric level (entry 12). However, the isolation of the labeled protonation product **4**-d from added deuterium oxide or deuterated ethanol serves as indirect evidence for the ketenimine anion intermediate.

Besides acetyl, the FGS is compatible with structurally diverse acyl motifs, including propionyl (**5**), isobutyryl (**6**), and benzoyl (**8**) groups (Figure 2b). However, β-ketonitrile with a hindered pivaloyl substituent (**7**) failed to react. Although diketone **9** and β-ketoester **10** can also participate in the deacylative allylation, the stereocontrol was weaker compared with ketonitrile, presumably due to the diastereoisomerism of enolate intermediates.

The enantioconvergence of the deacylative allylation is manifested by its kinetic profile (Figure 2c). The recovered β-ketonitrile (**1**) remained racemic till its full consumption, while the enantiopurity of the quaternary product (**3**) was unchanged throughout the allylation. Meanwhile, two partly overlapping but independent stages can be clearly observed. Consistent with the proposed deacylation/substitution



entry	conditions	Yield of 3 (%)	e.r. of 3	3:4
1	as above	79	95:5	5.0
2	(*R*)-BINAP instead of **L1**	63	50:50	2.1
3	(*R*,*R*)-DIOP instead of **L1**	57	57:43	1.2
4	(*S*)-Ph-PHOX instead of **L1**	55	50:50	1.1
5	(*R*)-Monophos instead of **L1**	trace	--	--
6	**L2** instead of **L1**	65	67:33	2.8
7	**L3** instead of **L1**	46	70:30	0.9
8	NaH instead of LDA	81	86:14	4.8
9	LiHMDS instead of LDA	80	93:7	3.8
10	NaHMDS instead of LDA	87	80:20	8.0
11	KHMDS instead of LDA	62	58:42	2.0
12	added H_2O (100 mol%)	0 (**4**, 97)	--	--

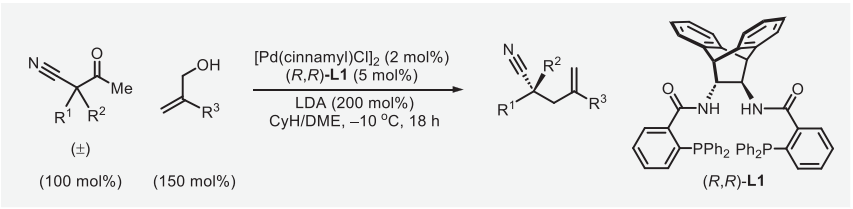
R	Yield, 3	e.r., 3
Et (**5**)	66%	93:7
i-Pr (**6**)	88%	95:5
t-Bu (**7**)	n.r.	--
Ph (**8**)	54%	94.5:5.5

Figure 2. Enantioconvergent deacylative allylation of β-ketonitrile. a) Palladium-catalyzed asymmetric deacylative allylation. b) Compatibility of assorted ketonitriles, diketones, and β-ketoesters. c) Kinetic profile of the deacylative allylation. The yield and recovery were determined by crude H-NMR. The percentage of major enantiomer is determined by chiral HPLC. d) Decarboxylative allylation of cyanoacetic ester. e) Kinetic profiles of the decarboxylative allylation. The yield and recovery were determined by crude H-NMR. The percentage of major enantiomer is determined by chiral HPLC. LDA, lithium diisopropyl amide. Cy, cyclohexyl. DME, dimethoxyethane. HMDS, hexamethyldisilazide. n.r., no reaction.

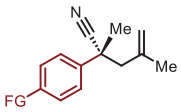
sequence, after ketonitrile was fully eliminated, the enantioenriched product continued to generate from the accumulated ketenimine anion intermediate. We were also able to isolate ester electrophiles generated during the DaF and their successful coupling with branched nitriles under identical conditions illustrated the feasibility of the retro-Claisen/substitution pathway (Supporting Information Section 7).

Enantioconvergent *decarboxylative* functionalization was also attempted (Figure 2d).[41] Although disubstituted cyanoacetic ester **13** did yield the allylation product under standard conditions, the yield was low with considerable

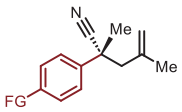
Table 1: Allylated quaternary stereocenters from DaF[a)]



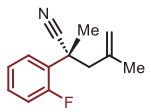
Aryl substituents



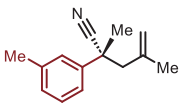
FG =
H (+)-**3**, 73%, 95:5 e.r.
Me (+)-**15**, 68%, 95:5 e.r.
t-Bu (+)-**16**, 55%, 95:5 e.r.
F (+)-**17**, 80%, 93:7 e.r.
Cl (+)-**18**, 69%, 90:10 e.r.
Br (+)-**19**, 53%, 88:12 e.r.



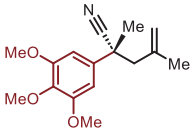
FG = OMe (+)-**20**, 71%, 96:4 e.r.
[8 mmol] 1.17 g, 68%, 95:5 e.r.
[20 mmol] 2.30 g, 53%, 95:5 e.r.
OCF_3 (+)-**21**, 63%, 90:10 e.r.
OMOM (+)-**22**, 51%, 96:4 e.r.
OTIPS (+)-**23**, 49%, 96.5:3.5 e.r.
SMe (+)-**24**, 60%, 92.5:7.5 e.r.



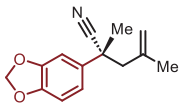
(+)-**25**, 41%, 91.5:8.5 e.r.



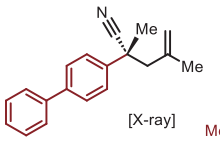
(+)-**26**, 90%, 95:5 e.r.



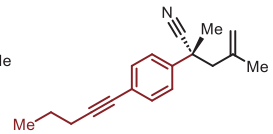
(+)-**27**, 78%, 95:5 e.r.



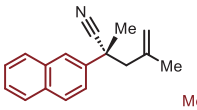
(+)-**28**, 87%, 95:5 e.r.



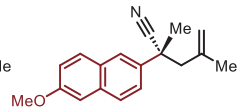
(+)-**29**, 64%, 93:7 e.r.



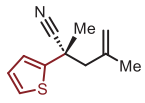
(+)-**30**, 61%, 90:10 e.r.



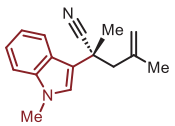
(+)-**31**, 90%, 92:8 e.r.



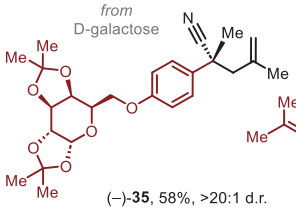
(+)-**32**, 81%, 94:6 e.r.[b]



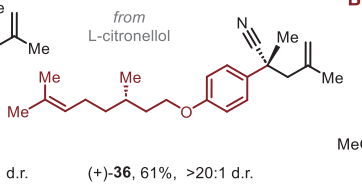
(+)-**33**, 72%, 90:10 e.r.



(+)-**34**, 42%, 97:3 e.r.

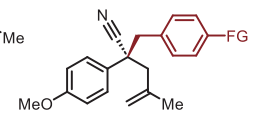


(–)-**35**, 58%, >20:1 d.r.

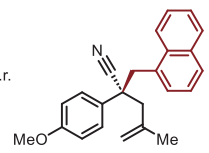


(+)-**36**, 61%, >20:1 d.r.

Benzyl substituents

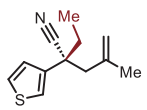


FG =
H (–)-**39**, 81%, 91.5:8.5 e.r.
CF_3 (–)-**40**, 62%, 90:10 e.r.
Cl (–)-**41**, 67%, 90:10 e.r.
NO_2 (–)-**42**, 58%, 90:10 e.r.
CN (–)-**43**, 62%, 89:11 e.r.

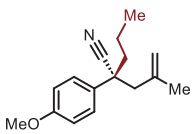


(–)-**44**, 60%, 94.5:5.5 e.r.

Alkyl substituents

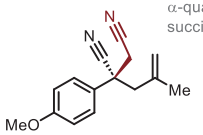


(+)-**37**, 61%, 92:8 e.r.

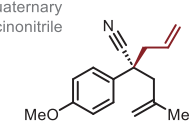


(+)-**38**, 57%, 90.5:9.5 e.r.

α-quaternary succinonitrile

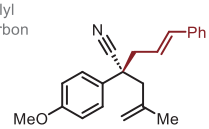


(+)-**45**, 71%, 93.5:6.5 e.r.



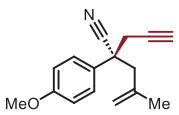
(+)-**46**, 62%, 92:8 e.r.

diallyl 4° carbon



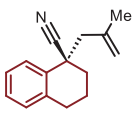
(–)-**47**, 69%, 90:10 e.r.

allyl-propargyl 4° carbon

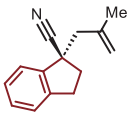


(+)-**48**, 57%, 92:8 e.r.

Cyclic ketonitriles

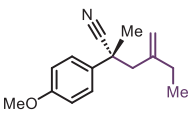


(+)-**49**, 76%, 93:7 e.r.[b]

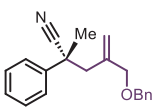


(+)-**50**, 65%, 86:14 e.r.[b]

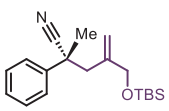
Allyl nucleophiles



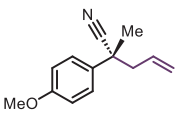
(+)-**51**, 61%, 95:5 e.r.



(+)-**52**, 78%, 90.5:9.5 e.r.[b]



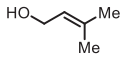
(+)-**53**, 64%, 90:10 e.r.[b]

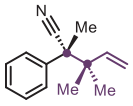


(+)-**54**, 60%, 87.5:12.5 e.r.

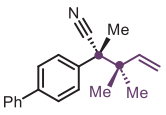
Vicinal Quaternary carbons

from

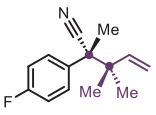




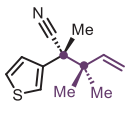
(+)-**55**, 54%, 89.5:10.5 e.r.
b:l = 10:1



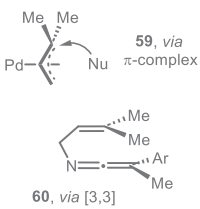
(–)-**56**, 72%, 91.5:8.5 e.r.
b:l > 20:1



(+)-**57**, 55%, 87.5:12.5 e.r.
b:l = 7.5:1



(+)-**58**, 51%, 91:9 e.r.
b:l = 7.5:1



[a)] Unless noted otherwise, the deacylative allylation was run using β-ketonitrile (0.3 mmol), $[Pd(cinnamyl)Cl]_2$ (0.006 mmol, 2 mol%), (*R*,*R*)-**L1** (0.015 mmol, 5 mol%), and LDA (0.6 mmol, 200 mol%) in a mixture of cyclohexane and DME at –10 °C for 18 hours. (See Sections 4 and 5 of Supporting Information for details). [b)] β-benzoylnitriles were used as reactants instead of β-acetylnitriles. FG, functional group. MOM, methoxymethyl; TIPS, triisopropylsilyl; Bn, benzyl; TBS, *tert*-butyldimethylsilyl.

formation of allyl ester **14** via transesterification. Contrary to reported mechanisms of allyl esters involving an oxidative addition/decarboxylation/allylation sequence,[39] isolated **14** was examined to be inert in the presence of the current palladium catalyst alone. However, it can give the allylation product (**3**) with additional allyloxide, indicating the possibility of reactivation via a retro-Claisen pathway. Indeed, reactions of methyl ester **13** with excess allyloxide gave much improved yields, and their kinetic profiles are consistent with the reactivation (Figure 2e). After the decarboxylative allylation and transesterification consumed most of the allyloxide, the growth of the enantioenriched quaternary carbon (**3**) stalled (left graph). In contrast, a continuous generation of products from allyl ester (**14**) was observed with excess nucleophiles (right graph). It is worth noting that the decarboxylative allylation exhibits an equally high enantioconvergence with its deacylative counterpart, highlighting the broad applicability of ketenimine anions for excellent enantiocontrol.

Scope of Deacylative Allylation

The enantioconvergent allylation can harness the easy preparation of β-ketonitriles by accommodating assorted types of substituents (Table 1). Aromatic rings with substituents of distinct electronic properties (**15**–**24**) and at different positions (**25**–**28**) are all compatible. These functional groups include halogens (**17**–**19**) and protected phenols (**22**, **23**, and **28**) that can be easily converted to build up the structural complexity of the quaternary stereocenter. Meanwhile, extended scaffolds, such as biphenyl[49] (**29**) and phenylacetylene (**30**), did not meddle with the enantiocontrol. Besides substituted phenyls, ketonitriles with fused arenes (**31**), including those derived from naproxen (**32**) and heteroaromatic rings (**33** and **34**), can also participate. It is worth noting that when intrinsically chiral moieties derived from galactose (**35**) and citronellol (**36**) were incorporated to give diastereomeric mixtures of ketonitrile reactants, good stereoconvergence was still obtained.

The deacylative allylation is also flexible to the alkyl substituent of ketonitriles. Elongation of the alkyl chain has a negligible effect on the enantioselectivity (**37** and **38**), while various substituents on a benzyl group were all tolerated (**39**–**44**). The broad compatibility has allowed the preparation of several challenging chiral structures. For example, β-ketonitrile with a cyanomethyl group afforded α-quaternary succinonitrile **45**, an enantioenriched equivalent of 1,4-dicarbonyl compounds that often require umpolung chemistry to access. Native allyl and propargyl substituents were also accommodated to give diallyl (**46** and **47**) and allyl-propargyl (**48**) stereocenters, respectively. These enantioenriched carbons set an ideal stage for ring closure via metathesis or cycloisomerization but are often difficult to prepare due to the high similarity between the pair of unsaturated alkyl chains. On the other hand, cyclic quaternary stereocenters (**49** and **50**) can also be directly accessed via deacylative allylation.

Diversely shaped and functionalized allyloxides can promote the DaF. Besides alkyl-substituted allylic alcohol (**51**), those with additional, protected alcohol (**52** and **53**) can also participate and open opportunities for further structural elaboration. Unsubstituted allylic alcohol is compatible as well, albeit with a diminished enantioselectivity (**54**). When prenol was used, congested and vicinal quaternary carbons were obtained in both good regio- and enantioselectivity (**55**–**58**). These results stand in contrast to the previous non-asymmetric deacylative allylation that favored linear products.[40] Although multiple pathways are feasible for C─C bond formation between ketenimine anion and palladium-allyl complex,[50] addition to the more crowded site of a π complex (**59**) is rare, while the high enantioselectivity observed here excludes a reductive elimination followed by a noncatalytic $^{[3]}\sigma$-rearrangement (**60**). Instead, the tail-to-tail bond formation of chiral palladium σ-complex **61** is more likely to ensure both good regio- and enantioselectivity.

Extension to Deacylative Propargylation and Benzylation

Slightly modified conditions can be used to enable a rare deacylative propargylation enantioselectively (Table 2a), with the alkyne motif bringing in distinct derivatization potential compared to allylation. Although aryl-substituted propargyl alcohols of diverse electronic properties and shapes can all participate in the DaF (**62**–**67**), its compatibility with an alkenyl substituent allowed the incorporation of an enyne moiety (**68**). On the other hand, propargyl alcohols with an alkyl substituent are less effective. For example, the susceptibility to isomerization of a methyl-substituted propargyl alcohol (**69**) under basic conditions led to a quaternary nitrile with an allene (**70**).[51] When the isomerization site was fully blocked, the deacylative propargylation product was obtained stereoselectively but in limited yield, presumably due to the increased sterics (**71**).

The palladium catalyst can also promote asymmetric DaF using readily available benzyl alcohols (Table 2b).[52] Given the challenging dearomative formation of η^3-benzyl complex, the identity of the acyl group eliminated from ketonitrile to form benzyl electrophile is crucial.[53] Indeed, no deacylative benzylation was observed from β-acetylnitrile, while the reactivity was revived with its benzoyl counterpart (**72**), presumably due to the easier ionization of benzyl benzoate than acetate. Diversely substituted benzyl alcohols (**73**–**79**), including those with fused rings (**76**) and heterocycles (**77**–**79**), are all compatible with the DaF. For furyl methanol, the dearomative alkylation product (**80b**) was also observed, consistent with an electrophilic palladium η^3-complex. Meanwhile, cyclic β-benzoylnitriles are also tolerated under the benzylation conditions (**81**).

Derivatization and Access to Bioactive Molecules

Enabling the enantioconvergence aside, the nitrile motif can bring along its rich reactivity to the enantioenriched α-quaternary nitrile (Figure 3a). Common hydrolysis, reduction,

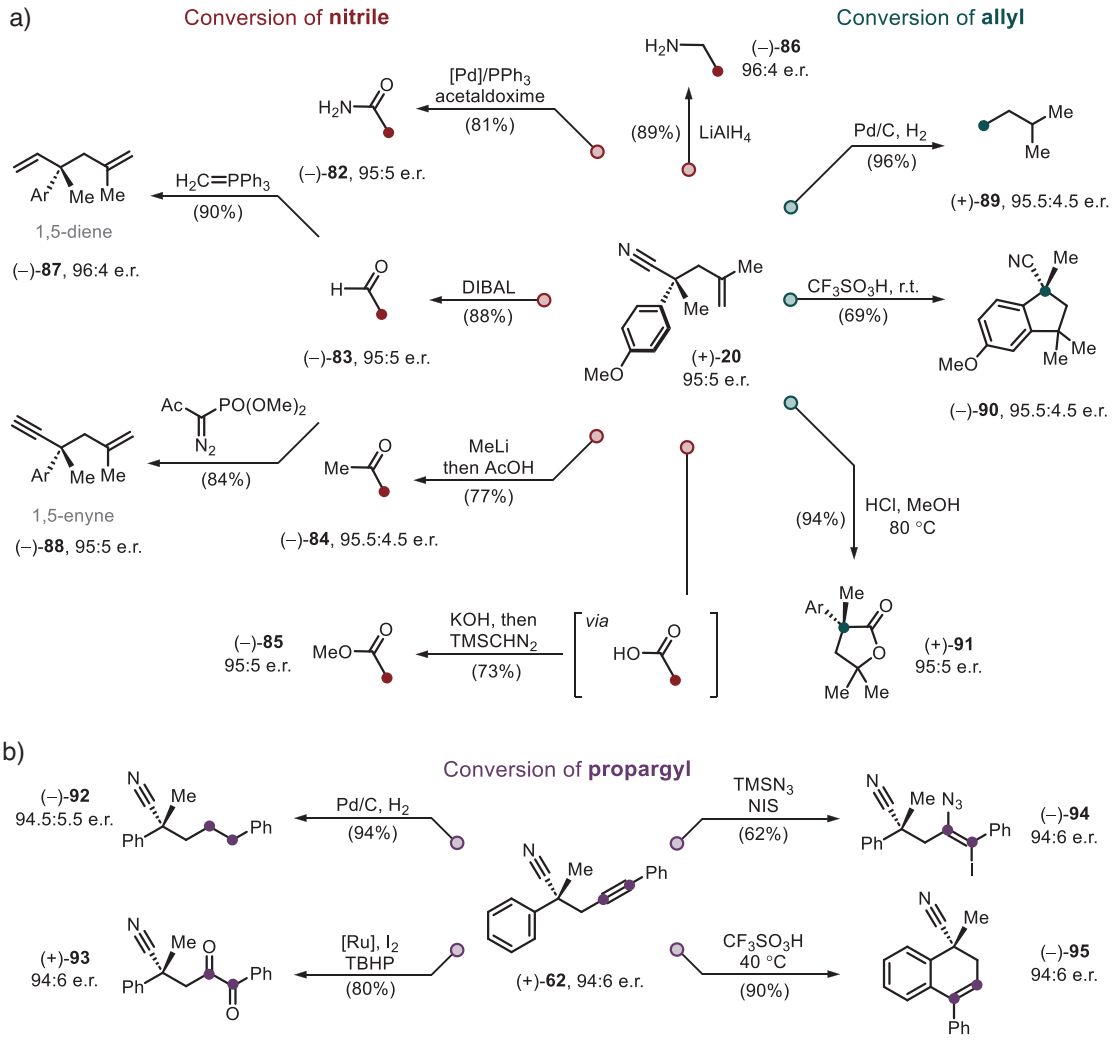


Figure 3. Derivatization to enantioenriched polyfunctionalized structures. a) Conversion of α-allyl nitriles. b) Transformations of the alkyne in the deacylative propargylation product. DIBAL, diisobutylaluminum hydride. Ac, acetyl. TMS, trimethylsilyl. TBHP, *tert*-butyl hydroperoxide. NIS, *N*-iodosuccinimide.

and addition conditions can be applied to give amide (**82**), aldehyde (**83**), ketone (**84**), ester (**85**, via acid), and primary amine (**86**). From this panel of functional groups, molecular complexity can be further built up to polyfunctionalized structures easily, such as 1,5-diene (**87**) and -enyne (**88**).

The olefin and alkyne from the allylation and propargylation can contribute greatly to the structural diversification as well. The hydrogenation of them can complement the scope of the current DaF by generating saturated alkyl groups of distinct shapes (**89** and **92**). On the other hand, they can also be converted to motifs of higher complexity via oxidation[54] (**93**) and difunctionalization[55] (**94**). In addition to functional group interconversion, these unsaturated bonds are amenable to ring closure together with other substituents of the quaternary stereocenter. For example, benzo-fused rings can be produced from both allylated and propargylated products in the presence of acid (**90** and **95**). Intriguingly, under distinct acidic conditions, the hydrolysis of nitrile triggers a lactone formation with the allyl group (**91**).

These facile interconversions, together with subsequential transformations, released the full power of the DaF to access bioactive molecules containing an enantioenriched tetrasubstituted carbon (Figure 4). For example, the pair of native and incoming allyl motifs in **96** can coordinate an olefin metathesis to give a cyclic quaternary stereocenter (**97**). The following functional group interconversions of nitrile (**98**), nucleophilic substitution (**99**), and hydrogenation completed the enantio- and diastereoselective route toward a rare cyclic triazole fungicide (**100**).[56,57] Meanwhile, two allyl groups of a similar product (**101**) can each proceed through a Friedel–Crafts alkylation with the phenyl substituent to directly generate a calcium channel blocker as a perfume ingredient (**102**).[58] Notably, the hydrogenated acenaphthylene scaffold contains a quaternary stereocenter on two similar fused rings, which differ only by a methylene unit, making it particularly challenging to prepare stereoselectively. A similar ring closure of **3**, when accompanied by a nucleophilic addition to nitrile (**103**), gave a chiral flavorant containing a polysubstituted indane (**104**).[59]

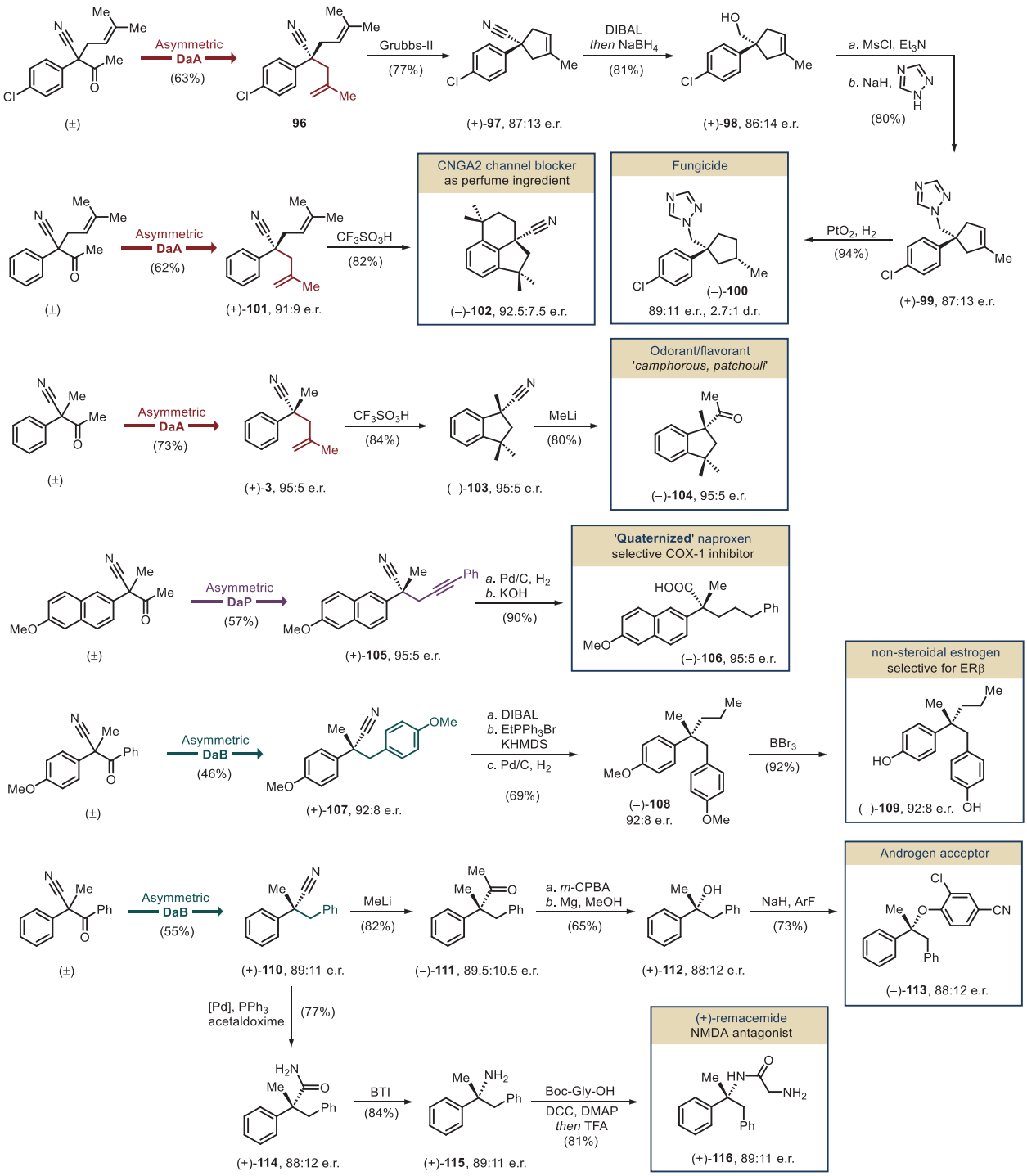
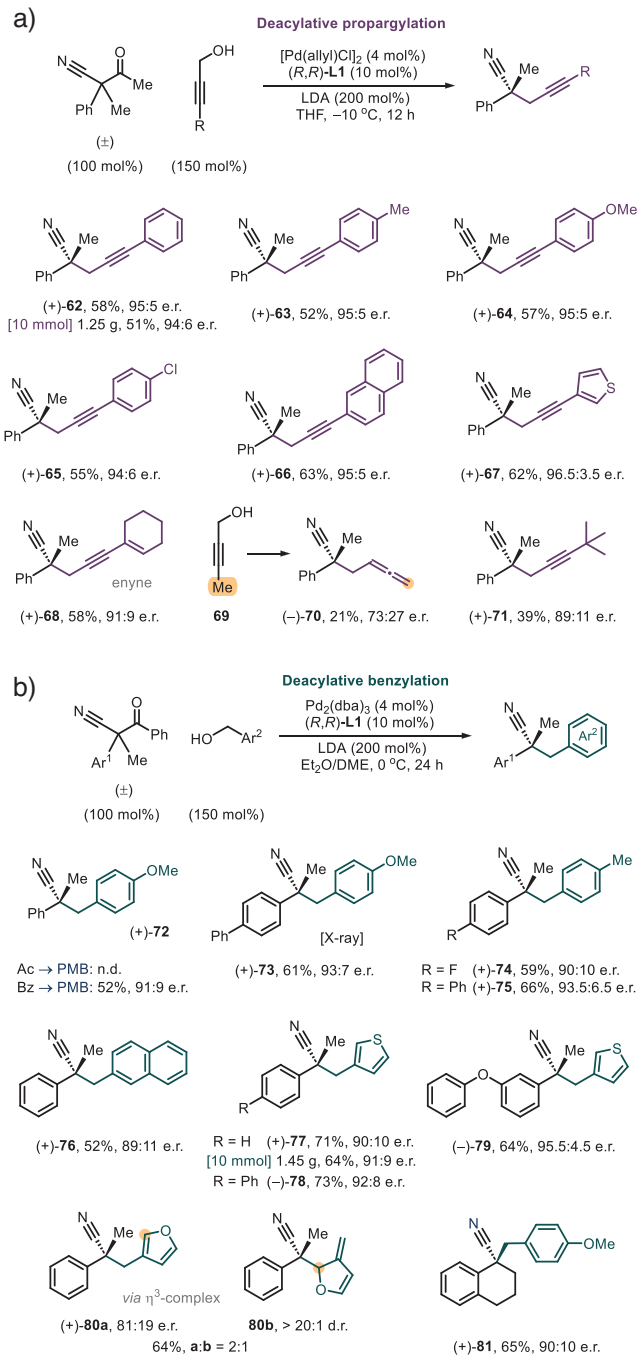


Figure 4. Access to bioactive molecules from asymmetric DaF. DaA/P/B, deacylative allylation/propargylation/benzylation. Ms, methanesulfonyl. HMDS, hexamethyldisilazide. *m*-CPBA, *meta*-chloroperoxybenzoic acid. BTI, bis(trifluoroacetoxyiodo)benzene. DCC, dicyclohexylcarbodiimide. DMAP, dimethylaminopyridine.

As the direct, asymmetric alkylation of α-tertiary nitriles is notoriously difficult, the quaternary-to-quaternary allylation and propargylation followed by hydrogenation can serve as effective surrogates. As such, an enantioenriched naproxen analog with a linear alkyl substituent (**106**) was prepared via asymmetric propargylation (**105**). The quaternary molecule is a selective COX-1 inhibitor and thus can potentially avoid side effects caused by conventional, nonselective NSAIDs.[60]

Although less diverse in reactivity compared with allyl and propargyl, benzyl groups are prevalent substituents of stereocenters in bioactive molecules. The conversion of the nitrile motif in the benzylation product **107** successfully afforded a trialkylated quaternary stereocenter (**108**) en route

Table 2: Scope of asymmetric deacylative propargylation and benzylation[a)]



[a)] Unless noted otherwise, the deacylative propargylation was run using β-ketonitrile (0.3 mmol), $[Pd(allyl)Cl]_2$ (0.012 mmol, 4 mol%), (*R*,*R*)-**L1** (0.03 mmol, 10 mol%), and LDA (0.6 mmol, 200 mol%) in THF at –10 °C for 12 h. The deacylative benzylation was run using β-ketonitrile (0.3 mmol), $Pd_2(dba)_3$ (0.012 mmol, 4 mol%), (*R*,*R*)-**L1** (0.03 mmol, 10 mol%), and LDA (0.6 mmol, 200 mol%) in a mixture of Et_2O and DME at 0 °C for 24 h (see Sections 4 and 5 of Supporting Information for details). Ac, acetyl. PMB, *para*-methoxybenzyl.

to a bisphenol estrogen selective for ERβ (**109**).[61] The DaF also demonstrated flexibility in synthesizing heteroatom-substituted congested stereocenters. For example, after the quaternary product **110** was converted to a methyl ketone (**111**), a Baeyer–Villiger oxidation followed to give tertiary alcohol **112** with stereoretention. Subsequent nucleophilic aromatic substitution led to an ethereal androgen acceptor (**113**).[62] Enantioenriched α-tertiary amines are also accessible. Sequential hydrolysis of **110** to amide (**114**), hypervalent iodine-mediated Hofmann rearrangement (**115**), and condensation with glycine generated enantioenriched remacemide (**116**).

Conclusion

In summary, the enantioconvergence of a DaF toward chiral nitriles has been achieved. Following the mutual activation of β-ketonitriles and alcohols through elimination, chiral palladium catalysts can leverage the lack of diastereoisomerism in ketenimine anion intermediates to facilitate stereoselective allylation, propargylation, and benzylation. Consequently, the challenging access to acyclic quaternary stereocenters is now unlocked. The quaternary-to-quaternary approach complements conventional bottom-up synthesis from tertiary and planar reactants. Meanwhile, its capability to swap in structurally distinct substituent inconvertible from the removed one overcomes the limitation of desymmetric functional group interconversion using prochiral quaternary carbons.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Active methylene compound • Allylation • Enantioconvergent • Quaternary stereocenter

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