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# Dynamic kinetic asymmetric arylation and alkenylation of ketones

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Despite the importance of enantioenriched alcohols in medicinal chemistry, total synthesis, and materials science, the efficient and selective construction of enantioenriched tertiary alcohols bearing two contiguous stereocenters has remained a substantial challenge. We report a platform for their preparation through the enantioconvergent, nickel-catalyzed addition of organoboronates to racemic, nonactivated ketones. We prepared several important classes of α,β-chiral tertiary alcohols in a single step with high levels of diastereo- and enantioselectivity through a dynamic kinetic asymmetric addition of aryl and alkenyl nucleophiles. We applied this protocol to modify several profen drugs and to rapidly synthesize biologically relevant molecules. We expect this nickel-catalyzed, base-free ketone racemization process to be a widely applicable strategy for the development of dynamic kinetic processes.

The development of general stereoselective methods with simultaneous control of contiguous stereocenters is critical to the efficient discovery and manufacture of new drugs. Enantioenriched alcohols constitute an important class of compounds that are found in a myriad of pharmaceutical agents and bioactive natural products (*1*, *2*). A variety of protocols for the asymmetric addition of organometallic nucleophiles or hydride reagents to carbonyls has enabled the efficient and stereoselective synthesis of alcohols with a single stereocenter (*3*–*5*). However, efficient methods for the preparation of alcohols bearing two adjacent stereocenters remain relatively underdeveloped. In particular, synthetic approaches to chiral tertiary alcohols with stereocenters at the α and β positions from simple and easily available precursors are rare, despite the frequent presence of this structural motif in bioactive molecules and drugs (Fig. 1A and fig. S1) (*6*–*8*). A typical method for the synthesis of α,β-chiral tertiary alcohols is the diastereoselective nucleophilic addition to enantiopure α-stereogenic ketones (Fig. 1B) (*9*, *10*). However, these precursors are difficult to prepare and potentially suffer from racemization during carbonyl addition reactions or during storage. Moreover, the stereocontrolled addition to the carbonyl group is generally nontrivial, and the results may be difficult to predict in many cases (*10*). In addition, to obtain reasonable levels of diastereoselectivity, reactions need to be conducted under low-temperature conditions with highly basic and nucleophilic organometallic reagents (for example, Mg or Li), which limit the type of compatible substrates and functional groups. In this context, it would be more desirable to use readily available racemic ketones and air- and moisture-stable nucleophiles for the general construction of stereodefined α,β-stereogenic tertiary alcohols in an enantioconvergent manner (Fig. 1C).

Among general approaches for achieving an enantioconvergent synthesis of tertiary alcohols with contiguous stereocenters, the dynamic kinetic asymmetric transformation (DyKAT) of racemic α-chiral ketones through the addition of air- and moisture-stable organoboronate reagents provides an elegant and efficient solution that is applicable to synthesize complex and functionalized targets (*11*–*18*). In general, to achieve a selective and efficient DyKAT, the first requirement is that the substrate racemization must be rapid [with a high $k_{rac}$ (rate of racemization) in the equilibration between enantiomeric starting materials (*S*)-SM and (*R*)-SM] (Fig. 1D). In addition, there is a second prerequisite: the reaction of the chiral catalyst with one enantiomer of the substrate must occur with high stereoselectivity and at a substantially higher rate than the other enantiomer ($k_S \gg k_R$) to give the enantioenriched product. As one enantiomer of substrate is selectively consumed, the equilibrium shifts to allow both enantiomers of the racemic starting material to eventually convert into the chiral product. Thus, in principle, the maximum theoretical yield of a DyKAT process is 100%, which is superior to processes that are based on kinetic or classical resolutions with yields limited to 50%. The dynamic kinetic asymmetric hydrogenation of carbonyls has been well studied and even performed on more than a 100-ton scale annually to provide an ideal asymmetric synthesis of secondary alcohols, and important contributions have been made by the groups of Noyori (*19*), Zhou (*20*), Johnson (*21*), Zhang (*22*), and others (*23*). By contrast, dynamic kinetic asymmetric ketone additions to furnish chiral tertiary alcohols bearing adjacent stereocenters have been less explored. Currently, the DyKAT chemistry of ketones is limited to the addition of activated ketones (α-keto esters) to form complex glycolates, a technique developed by the Johnson group (*24*, *25*). However, to date, dynamic kinetic asymmetric additions to nonactivated ketones for general synthesis of chiral tertiary alcohols remain unreported.

Several factors have impeded the development of a protocol for enantioconvergent addition of nonactivated ketones (Fig. 1D). First, the racemization of nonactivated substrates through enolization is sluggish and requires strong bases, making it difficult to develop functional group–tolerant conditions that meet the kinetic requirements for a DyKAT. Second, the attenuated electrophilicity and increased steric hindrance of simple ketones lead to diminished reactivity for addition reactions in general. Third, the control over the diastereoselectivity and enantioselectivity for unactivated ketones is more challenging. For these reasons, almost all DyKATs of ketones use substrates bearing electron-withdrawing functional groups (such as ester or halogen groups) at the α-position of the ketone, and simple ketones are seldom used. However, we considered that developing a distinct reactivity paradigm for racemization and using a nontraditional carbonyl activation mode with a judicious choice of chiral ligand would address these longstanding critical challenges.

Toward this goal, we recently developed a series of bulky yet flexible $C_2$-symmetric chiral *N*-heterocyclic carbenes (NHC) (*26*), namely 1,3-bis(4-methyl-2,6-bis((*R*)-1-phenylethyl)phenyl)-4,5-dihydro-1*H*-imidazol-3-ium-2-ide (SIPE)– and 7,9-bis(4-methyl-2,6-bis((*R*)-1-phenylethyl)phenyl)-7*H*-acenaphtho[1,2-*d*]imidazol-9-ium-8-ide (ANIPE)–type ligands (*27*–*29*). We successfully applied the ligands to several challenging asymmetric transformations, including a highly enantioselective nickel-catalyzed arylation of ketones with organoboronates (*30*). A rare enantioselective $\eta^2$-coordinating activation of ketone carbonyls and the subsequent cross-coupling–like mechanism is the key to enable a general synthesis of chiral tertiary alcohols (*31*). Recently, we made the discovery that under base-free conditions, Ni-ANIPE complex can rapidly catalyze the racemization process of a chiral nonactivated ketone [(*R*)-**1b**], with the enantiomeric excess (ee) of (*R*)-**1b** decreasing from 98 to 0% in 15 minutes in the presence of 5 mol % Ni-**L1** at 30°C (Fig. 1E, reaction 1). We reasoned that electron-donating NHC-ligated Ni(0) species facilitate oxidative cyclization to form an $\eta^2$ Ni-ketone complex, which could undergo a reversible β-H elimination

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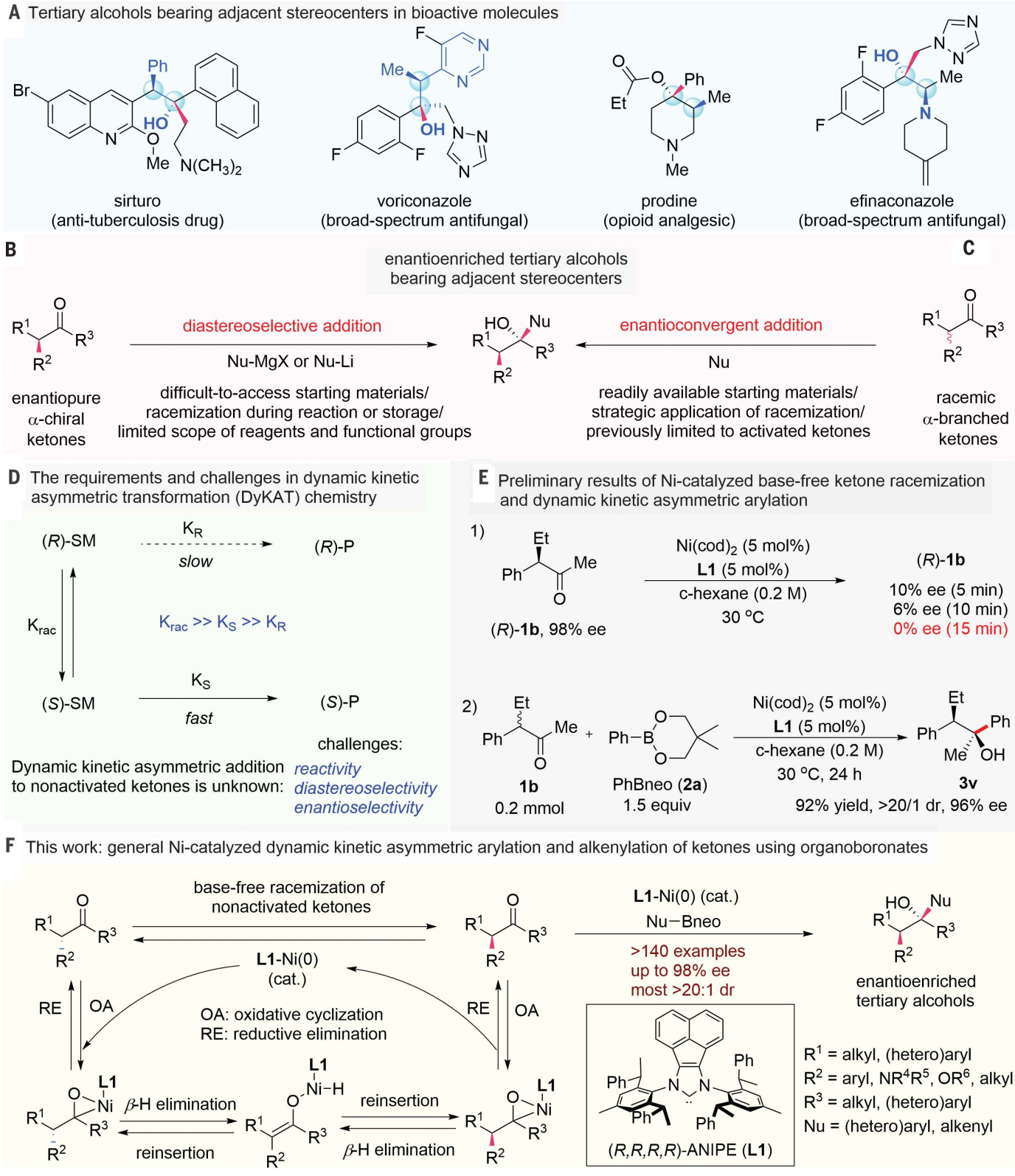


**Fig. 1. Bioactive tertiary alcohols, their synthesis by traditional diastereoselective addition, and this work's DyKAT strategy.** (**A**) Representative drugs demonstrating the ubiquitous nature of chiral tertiary alcohols in bioactive organic molecules. (**B** and **C**) Contrasting traditional methods and our proposed enantioconvergent approaches to enantioenriched tertiary alcohols bearing adjacent stereocenters. (**D**) The requirements and challenges of dynamic kinetic asymmetric addition to nonactivated ketones. (**E**) The discovery of a rapid nickel-catalyzed racemization of unactivated ketones and its application in DyKAT chemistry. (**F**) A nickel catalyst for general enantioconvergent addition of racemic nonactivated ketones to generate various chiral tertiary alcohols bearing two contiguous stereocenters.

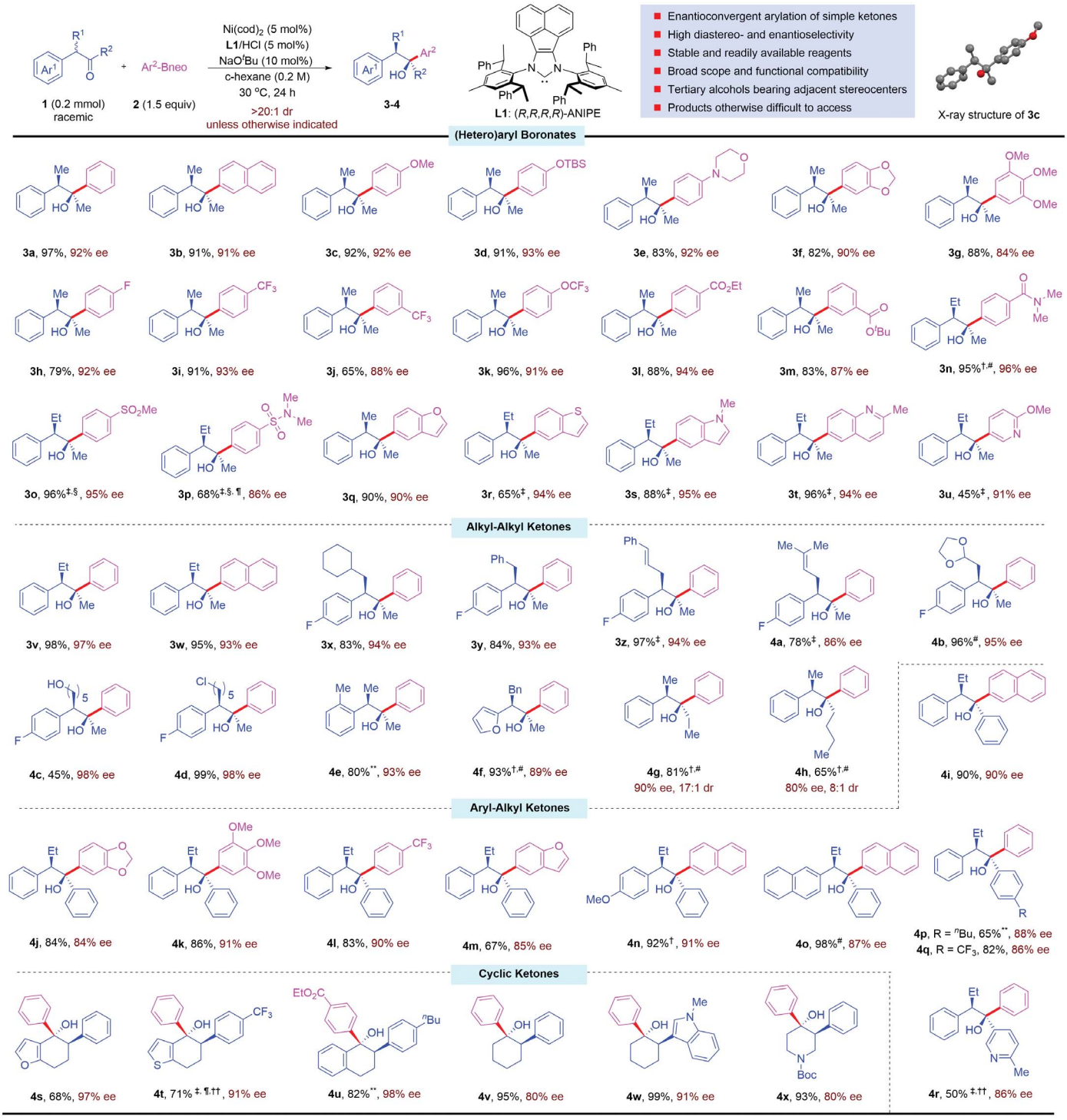


**Fig. 2. Scope of nickel-catalyzed enantioconvergent arylation of α-aryl ketones.** The yields of isolated products on a 0.2 mmol scale are shown. Values ee and dr were determined with HPLC and NMR analysis. The relative and absolute stereochemistries of products are shown according to the x-ray structure of **3c**. †10 mol % catalyst, 20 mol % NaO$^t$Bu; ‡10 mol % catalyst, 20 mol % NaO$^t$Bu, 50°C, 48 hours; §toluene as the solvent; ¶80°C. #50°C; **48 hours; ††Ti(O$^i$Pr)$_4$ was added (supplementary materials).

and reinsertion to rapidly racemize the ketone (Fig. 1F). We considered that these exceptionally rapid and mild racemization conditions would constitute a promising platform for the development of DyKATs that use α-chiral ketones as substrates. Moreover, given the excellent levels of stereocontrol that have previously been achieved with ligands in the ANIPE family, we speculated that Ni-ANIPE would be a general and highly selective catalyst for the enantioconvergent addition of sp$^2$ carbon nucleophiles into racemic, non-activated ketones. A preliminary test of the feasibility with racemic ketone **1b** with phenylboronic acid neopentylglycol ester (PhBneo;

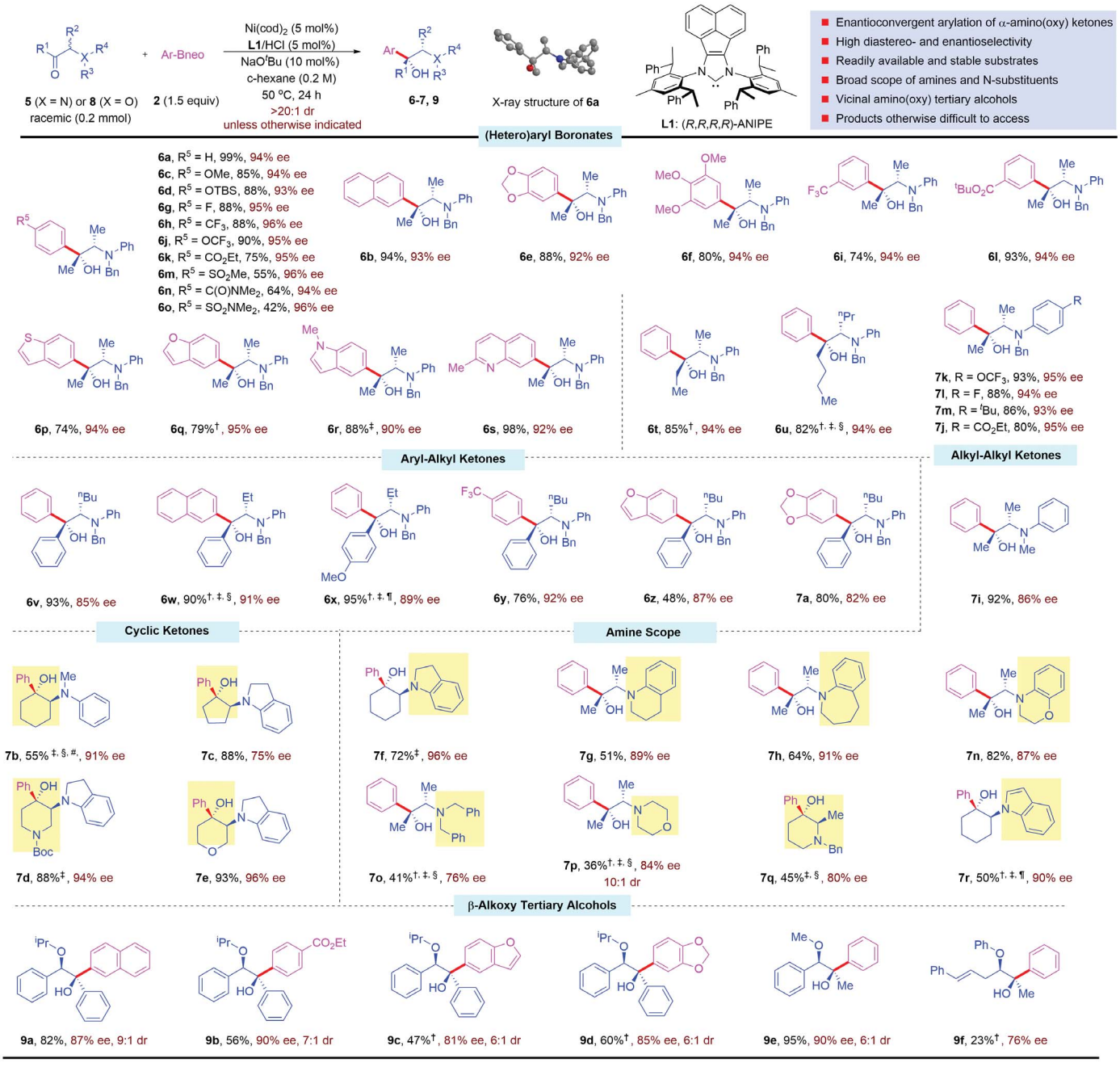


**Fig. 3. Scope of nickel-catalyzed enantioconvergent arylation of α-amino or α-oxy ketones.** The yields of isolated products on a 0.2 mmol scale are shown. Values ee and dr were determined with HPLC and NMR analysis. The relative and absolute stereochemistries of products are shown according to the x-ray structure of **6a**. †10 mol % catalyst, 20 mol % NaO$^t$Bu; ‡Ti(OiPr)$_4$ was added; §60°C; ¶80°C; #1.0 equiv NaO$^t$Bu (supplementary materials).

**2a**) delivered product **3v** in 92% yield with 96% ee and complete [>20:1 diastereomeric ratio (dr)] diastereocontrol (Fig. 1E, reaction 2). On the basis of these key preliminary findings, we report enantioconvergent addition (including arylation and alkenylation) of boronate esters into nonactivated ketones to deliver enantioenriched tertiary alcohols with adjacent stereocenters in high diastereo- and enantioselectivities and chemical yields (Fig. 1F). In a single operation, multiple important classes of challenging and value-added tertiary alcohols—including α-aryl tertiary alcohols, tertiary allylic alcohols, α,β-amino alcohols, β-alkoxy alcohols, and β,β-dialkyl alcohols, compounds that previously required multistep synthetic procedures to access—were prepared directly from readily available and inexpensive organoboronates and racemic ketones.

## Reaction optimization

To develop the enantioconvergent arylation of ketone, we selected **2a** and ketone **1a** as the model substrates using imidazolium chloride and base as the ligand for nickel catalyst, instead of free NHC (supplementary materials). After extensive investigation of reaction parameters, we identified the optimized reaction condition as **1a** (1.0 equiv), **2a** (1.5 equiv), 5 mol % of Ni(cod)$_2$ and NHC (**L1**/HCl, readily prepared on 50 g scale) (supplementary materials), and 10 mol % of NaO$^t$Bu (sufficient for in situ deprotonation of imidazolium chloride, but insufficient to promote racemization) in cyclohexane at ambient temperature (30°C)

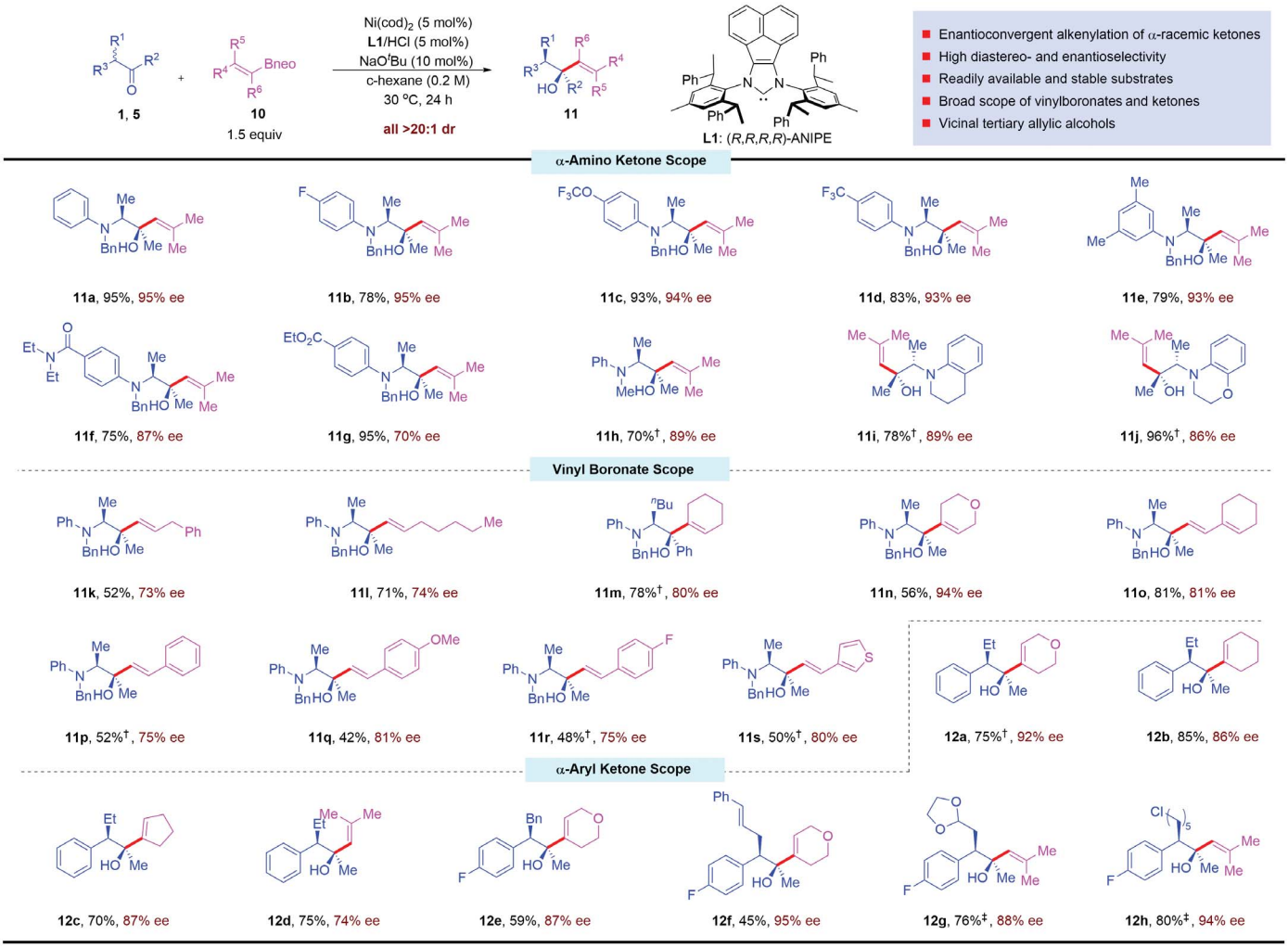


**Fig. 4. Scope of nickel-catalyzed enantioconvergent alkenylation of racemic ketones.** The yields of isolated products on a 0.2 mmol scale are shown. †50 mol % $Ti(OiPr)_4$ was added; ‡10 mol % catalyst, 20 mol % $NaO^tBu$, 50°C.

for 24 hours (Fig. 2). The tertiary alcohol **3a** (Fig. 2) was obtained in quantitative yield with 92% ee and >20:1 dr. A completely base-free condition with free NHC (**L1**) gave comparable results (supplementary materials). We found a series of commonly used chiral phosphine and NHC ligands to be ineffective for this arylation reaction, probably because of the low reactivity of the bulky ketone substrate and difficult enantiodiscrimination of the dialkyl substituents. Increasing the amount of $NaO^tBu$ substantially lowered the chemical yield, and three equivalents of base completely inhibited the reaction (supplementary materials). We reasoned that a significant excess of the base could build up a high concentration of the enolate form of the ketone substrate, resulting in no desired arylation but an aldol side reaction. Control experiments without ligand or nickel catalyst led to no reaction, suggesting the critical role of the Ni-NHC catalyst (supplementary materials).

### Arylation substrate scope

With the optimized reaction conditions, we first explored the scope of arylboron components for this DyKAT protocol (Fig. 2, **3a** to **3u**). Both electron-rich and electron-poor arylboronates readily underwent arylation, giving rise to tertiary alcohol products in high yields and diastereo- and enantioselectivities (**3a** to **3p**, 84 to 96% ee, >20:1 dr). Many functional groups such as ether (**3c**), silyl ether (**3d**), tertiary amine (**3e**), fluorine (**3h**), trifluoromethyl (**3i** and **3j**), trifluoromethoxy (**3k**), ester (**3l** and **3m**), amide (**3n**), sulfone (**3o**), and sulfonamide (**3p**) were compatible with the arylation reaction. Arylboronic esters bearing pharmaceutically important heterocycles such as benzofuran (**3q**), benzothiophene (**3r**), indole (**3s**), quinolone (**3t**), morpholine (**3e**), and pyridine (**3u**) all served as competent substrates that create products in good to excellent yields with high diastereo- and enantioselectivities (88 to 94% ee, >20:1 dr).

Subsequently, we surveyed the scope of ketone substrates (Fig. 2, **3v** to **4x**). Ketones with different α-substituents—including methyl, ethyl, bulky cyclohexylmethyl, benzyl, cinnamyl, and prenyl groups—could all be converted to desired tertiary alcohols in high yield and with high ee (**3v** to **4a**, 86 to 97% ee, >20:1 dr). Substrates containing an acetal, a free hydroxyl group, and an alkyl chloride underwent an arylation reaction to afford complex alcohol products in good yields and with excellent ee (**4b** to **4d**, 95 to 98% ee, >20:1 dr). Then, we investigated the ketone substrates substituted with different α-aryl groups and found that electron-rich, -neutral, and -poor substituents (**3x** to **4e**, **4n**, **4t**, **4o**, and **4u**) were all compatible with this transformation. Moreover, substrates bearing furan (**4f**) and *N*-methylindole (**4w**) also worked well. Dialkyl ketones with different chain lengths were also suitable partners for this reaction, albeit with a slight loss of diastereo- and enantioselectivity as the chain grew (**4g** to **4h**, 80 to 90% ee, 8:1 to 17:1 dr).

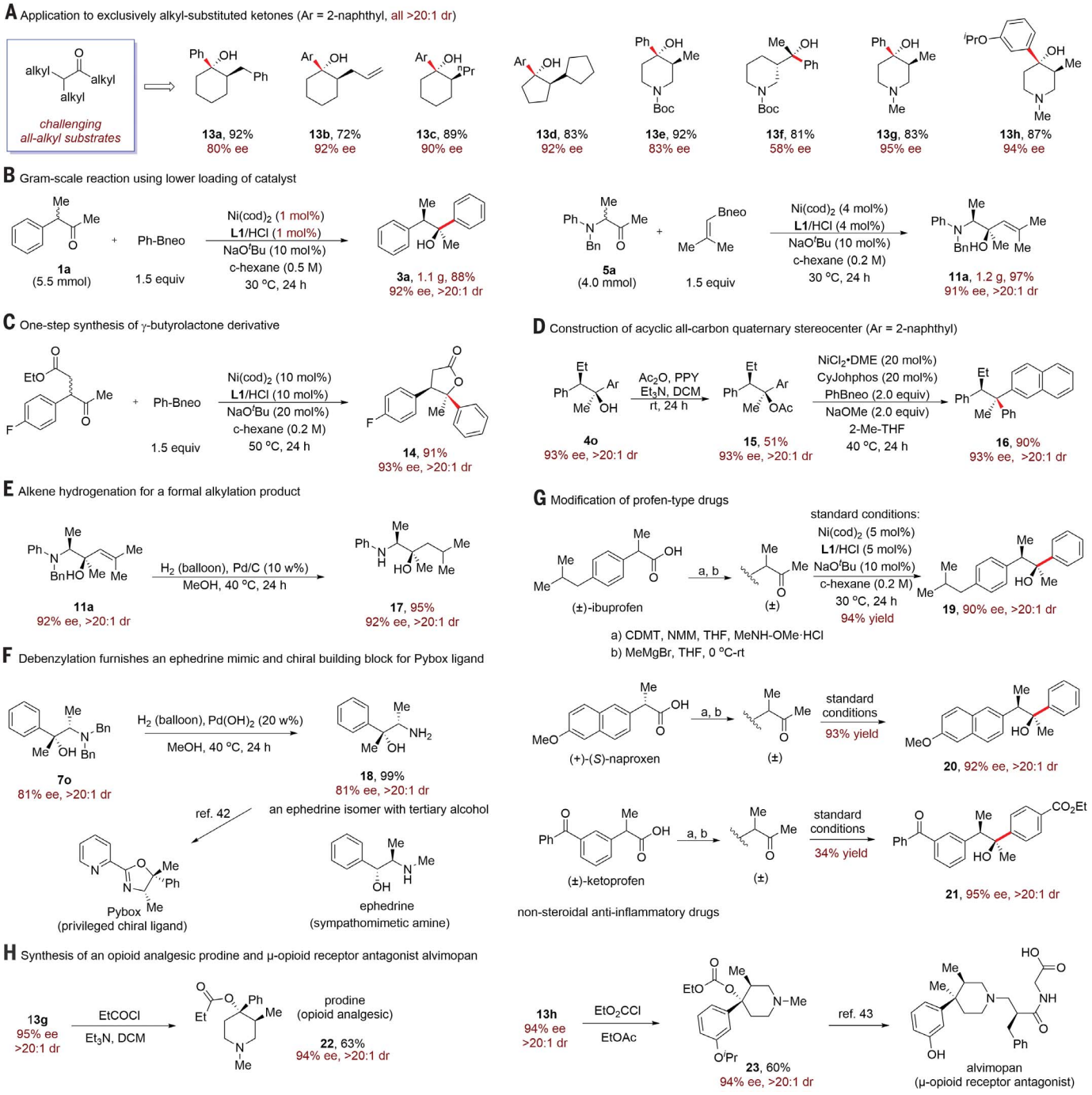


**Fig. 5. Application of the DyKAT arylation to exclusively alkyl-substituted ketones, synthetic elaboration, and drug modification.** (**A**) Reactions with challenging α,α-dialkyl ketones. (**B**) Gram-scale arylation and alkenylation reaction. (**C**) One-step synthesis of a γ-butyrolactone derivative. (**D**) Stereoretentive construction of an acyclic all-carbon quaternary stereocenter. (**E**) Combination of vinylation and hydrogenation for a formal alkylation reaction. (**F**) Synthesis of an ephedrine mimic. (**G** and **H**) Application of the enantioconvergent arylation strategy in modifying profen-type drugs and synthesizing prodine and alvimopan (supplementary materials).

We also examined the reactivity of aryl ketone substrates (**4i** to **4r**). Commercially available 1,2-diphenylbutan-1-one effectively underwent enantioconvergent arylation with different arylboronates to give diaryl-substituted tertiary alcohols in moderate to excellent yield with high levels of diastereo- and enantioselectivity, despite the potential low reactivity caused by extremely hindered substrates (**4i** to **4r**, 84 to 91% ee, > 20:1 dr). Especially aryl ketones bearing heterocycles—such as pyridine (**4r**), furan (**4s**), and thiophene (**4t**)—were all suitable substrates (86 to 97% ee, >20:1 dr). Aside from acyclic ketones, various α-stereogenic cyclic ketones also performed well to afford highly complex tertiary alcohols bearing adjacent stereocenters (**4s** to **4x**, 80 to 98% ee, >20:1 dr). Last, the absolute and relative configuration of **3c** was determined by means of x-ray crystallographic diffraction analysis. Ketones with α-aryl α-alkyl substituents

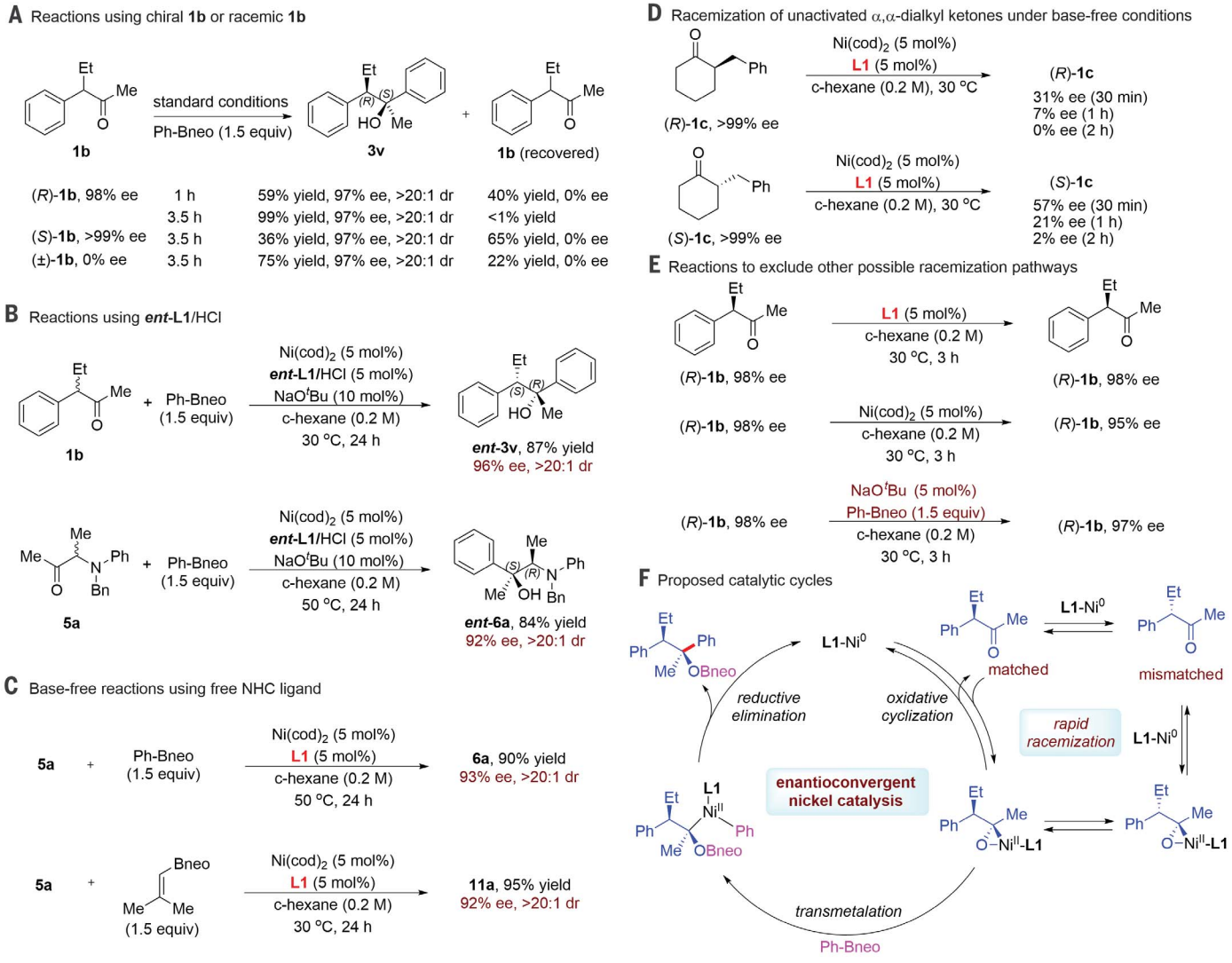


**Fig. 6. Control experiments and proposed catalytic cycles.** (**A**) Reactions with chiral and racemic ketone substrates to support the rapid racemization process and identify match or mismatch substrates. (**B**) Reactions with enantiomeric ligand to obtain the enantiomeric products. (**C**) DyKAT arylation and vinylation of ketones under base-free conditions. (**D**) Fast racemization of unactivated α,α-dialkyl ketones under base-free conditions. (**E**) Reactions to exclude other possible racemization pathways. (**F**) Proposed catalytic cycles.

are rarely used in DyKATs because of their low acidity. However, our use of these less activated substrates in this method allowed the expedient synthesis of complex compounds that could be difficult to access by other approaches.

### Extension to α-amino or α-oxy ketones

Optically pure amino alcohols are prominent structural motifs prevalent in pharmaceuticals and bioactive natural products (Fig. 1A). Furthermore, these compounds are also used as chiral auxiliaries, ligands, and catalysts in asymmetric synthesis. The asymmetric hydrogenation of amino ketones is the most efficient for synthesizing chiral amino alcohols. Dynamic kinetic asymmetric hydrogenation of racemic α-amino ketones to vicinal amino secondary alcohols has also been developed (*32*). However, asymmetric catalytic construction of vicinal amino tertiary alcohols is rare, despite this functionality being an essential building block for synthesis and privileged substructure in marketed antifungal agents (Fig. 1A). Typically, this moiety is synthesized through diastereoselective organometallic addition to laboriously prepared chiral α-amino ketones (*33*). Enantio- and diastereoselective catalytic nitroaldol reactions of ketones are few (*34*), even though the subsequent reduction of the nitro group to amine is required. Moreover, the direct catalytic asymmetric synthesis of 1,2-amino tertiary alcohols is limited in the scope of coupling partners (*35*). To date, the only general enantioselective method is the 2-azadiene-ketone reductive coupling recently reported by Li *et al.* (*36*). However, these methods require substrates with *N*-protecting groups that inherently affect the step or redox economy. Therefore, a straightforward and general approach that enantioselectively assembles tertiary amino alcohols with various desired amine substituents is highly sought after.

We therefore focused on the enantioconvergent synthesis of tertiary amino alcohols using a racemic α-benzyl(phenyl)amino ketone (**5a**) and PhBneo (**2a**) as the model substrate. After a quick screening of reaction parameters (supplementary materials), we identified the optimal reaction conditions as otherwise conserved except for the temperature, which we simply elevated to 50°C. With the conditions established, we first investigated the scope of arylboron coupling partners for this enantioconvergent arylation reaction. As shown in Figure 3 (**6a** to

**6s**), a wide variety of arylboronates with both electron-donating and electron-withdrawing substituents readily participated in the reaction, affording vicinal amino tertiary alcohols in high yelds and enantioselectivities with complete diastereocontrol (**6a** to **6o**, 92 to 96% ee, >20:1 dr). Moreover, functional groups including ether (**6c**, **6e**, and **6f**), silyl ether (**6d**), fluoride (**6g**), trifluoromethyl (**6h** and **6i**), trifluoromethoxy (**6j**), ester (**6k** and **6l**), sulfone (**6m**), amide (**6n**), and sulfonamide (**6o**) were well compatible under the arylation conditions. In addition to arylboronates, heteroarylboronates bearing benzothiophene (**6p**), benzofuran (**6q**), indole (**6r**), and quinolone (**6s**) were all viable substrates giving products in good yield with excellent enantio- and diastereoselectivities (90 to 95% ee, >20:1 dr).

We next examined the scope of racemic α-amino ketone substrates (Fig. 3, **6t** to **7r**). Dialkyl ketones with longer alkyl chains, such as ethyl and butyl groups, delivered tertiary amino alcohols in similarly high yields and selectivities (**6t** to **6u**, 94% ee, >20:1 dr). A series of exceptionally bulky aryl-alkyl ketones proceeded effectively, with heteroaryl and arylboronates providing complex vicinal amino diaryl tertiary alcohols in 82 to 92% ee and excellent diastereoselectivities (**6v** to **7a**, >20:1 dr). Cyclic α-amino ketones such as cyclohexanone, cyclopentanone, tetrahydropyranone, and piperidinone were all feasible coupling components affording cyclic amino tertiary alcohols in a single operation with high yield and selectivities (**7b** to **7f** and **7q**, 75 to 96% ee, >20:1 dr). Subsequently, we assessed the scope and type of the α-amino substituent. As we expected, various substrates containing alkyl-aryl amines with different substituents (**7i** to **7m**, 86 to 95% ee, >20:1 dr) and dialkyl amino groups successfully delivered products (**7o** to **7q**, 76 to 84% ee, 10:1 to >20:1 dr), albeit with diminished reactivity and selectivity in some cases. Substrates with medicinally important saturated or unsaturated *N*-heterocycles such as indoline (**7c** to **7f**), dihydroquinoline (**7g**), tetrahydrobenzoazepine (**7h**), dihydrobenzooxazine (**7n**), morpholine (**7p**), piperidine (**7q**), and indole (**7r**) all effectively underwent the enantioconvergent arylation reaction furnishing cyclic amino tertiary alcohols. These products, especially those containing cyclic amines, are very challenging to synthesize by methods with substrates with *N*-protecting groups. Additionally, the relative and absolute configuration of the product (**6a**) was confirmed with x-ray crystallography.

Chiral β-alkoxy alcohols are essential chiral building blocks in asymmetric synthesis. Asymmetric ketone hydrogenation has been reported to prepare β-alkoxy secondary alcohols (*20*). However, enantioselective catalytic synthesis of β-alkoxy tertiary alcohols remains elusive. We found that the coupling of commercially available racemic benzoin isopropyl ether and several functionalized aryl or heteroaryl boronates in our standard nickel-catalyzed conditions proceeded effectively, producing complex β-alkoxy tertiary alcohols in good yields with synthetically useful diastereo- and enantioselectivities [**9a** to **9d**, 81 to 90% ee, 6:1 to 9:1 dr (Fig. 3)]. Less hindered dialkyl α-oxy-ketones also performed well, although a homoallylic ether substrate showed lower reactivity when we used a bulkier ANIPE-type ligand (**9e** to **9f**, 76 to 90% ee, 6:1 to >20:1 dr) (supplementary materials).

### Asymmetric alkenylation

Enantioenriched allylic alcohols are among the most important structural units in organic synthesis. They are found in a myriad of bioactive molecules and drugs; they are vital chiral synthons that undergo diverse transformations to afford various stereodefined targets of value in chemistry. Consequently, the asymmetric synthesis of allylic alcohols has been a critical topic for methodology development for decades (*37*). However, the enantioselective synthesis of tertiary allylic alcohols is still challenging. Recent progress on asymmetric vinylation of ketones, arguably the most efficient method, has been achieved with stepwise-preformed vinyl zinc (*38*), enyne (*39*), or vinyl boronic acid (*40*). Nonetheless, these reactions are limited to sensitive organometallic vinyl sources, activated ketones, or the preparation of dienyl allylic alcohols. The established systems are not amenable to synthesizing chiral vicinal tertiary allylic alcohols. Thus, a general and practical asymmetric vinylation of ketones, especially one with readily available reagents and capable of simultaneous construction of two stereocenters, is in high demand.

To this end, we focused on expanding our arylation reaction to enantioconvergent vinylation of racemic ketones (Fig. 4). We found that the vinylation reaction between α-amino ketones (**5**) and a trisubstituted alkenylboronate performed well to give vicinal amino tertiary allylic alcohol (**11a**) in nearly quantitative yield with 95% ee and >20:1 dr. Regarding the scope of α-amino substituents, a range of alkyl aniline containing functional groups—such as fluorine (**11b**), trifluoromethoxy (**11c**), trifluoromethyl (**11d**), amide (**11f**), and ester (**11g**), as well as *N*-heterocycles including dihydroquinoline (**11i**) and dihydrobenzooxazine (**11j**)—were all readily incorporated into the amino allylic alcohol products in high yields with 70 to 95% ee and >20:1 dr. As for the scope of vinylboronates, both acyclic or cyclic substrates and alkyl-, alkenyl-, and aryl-substituted vinyl substrates all successfully coupled with α-amino ketones to deliver products in 73 to 94% ee and >20:1 dr (**11k** to **11s**). As we expected, this dynamic kinetic asymmetric vinylation strategy is also suitable for α-aryl ketones, giving rise to many chiral tertiary allylic alcohols in 74 to 95% ee with all >20:1 dr (**12a** to **12h**).

### Further applications

Probably because of the formidable difficulty in simultaneously achieving facile racemization and stereocontrol, α,α-dialkyl ketones are particularly challenging substrates with lower acidity and have not been used in the DyKAT addition chemistry. Encouraged by the racemization reactivity and the excellent levels of stereocontrol in our protocol, we thought that this strategy would also be applicable to these most challenging substrates. We found that a wide range of commercially available cyclic or acyclic α,α-dialkyl ketones (with benzyl, allyl, linear alkyl, and branched alkyl substituents) successfully participated in the DyKAT delivery of tertiary alcohol products with high yield and stereoselectivities [**13a** to **13h**, 58 to 95% ee, >20:1 dr (Fig. 5A)], further highlighting the generality of our method. To demonstrate the scalability of the reaction, we performed gram-scale reactions (Fig. 5B). Arylation of α-aryl ketone 1a (5.5 mmol) or alkenylation of α-amino ketone **5a** (4.0 mmol) in the presence of lower loading of catalyst (1 or 4 mol %) provided the corresponding tertiary alcohols in high yield (>1 g obtained) with similar levels of enantio- and diastereoselectivity as before. Moreover, our use of an air-stable Ni(0)-precatalyst allowed us to perform the reaction under glovebox-free conditions [using Schlenk techniques (supplementary materials)]. Considering the sterically encumbered nature of the tertiary alcohol installed in the arylation reaction, we considered whether this functionality could be applied in downstream transformations. The enantioconvergent arylation of a racemic γ-ketoester and the subsequent lactonization occurred in a single operation providing access to a γ-butyrolactone derivative (**14**) featuring two adjacent stereocenters in 91% yield with 93% ee and >20:1 dr (Fig. 5C). This result prompted us to explore more general transformations. By using Watson's stereoretentive nickel-catalyzed Suzuki-Miyaura coupling protocol (*41*), we successfully converted the acylated tertiary alcohol to the complex molecule **16**, which contained two contiguous chiral centers with an acyclic all-carbon quaternary center in high efficiency (Fig. 5D). Furthermore, Pd-catalyzed hydrogenation of amino allylic alcohol **11a** gave the corresponding alkylated amino alcohol **17** in 93% yield (Fig. 5E). Therefore, the combination of vinylation and reduction provides a formal DyKAT alkylation of racemic ketones. Another hydrogenation reaction through Pd catalysis afforded debenzylated product **18**, a tertiary amino alcohol isomer of sympathomimetic amine ephedrine (Fig. 5F). In addition, **18** is

the key precursor for synthesizing privileged chiral Pybox ligand (*42*). To further showcase the applicability of the DyKAT strategy in drug modification, we converted the commonly used, nonsteroidal, and anti-inflammatory medicines ibuprofen, naproxen, and ketoprofen to their ketone derivatives, which can all undergo the enantioconvergent arylation with excellent diastereo- and enantiocontrol regardless of whether racemic or enantiopure precursors were used (Fig. 5G). Drug mimics **19** and **20** were obtained in high yields (93 to 94%), whereas the ketoprofen mimic **21** was prepared in a lower yield because of the competitive reaction of two ketone groups in the substrate. The arylation products (**13g** and **13h**) were subjected to esterification conditions to give an opioid analgesic, prodine (**22**), and the precursor to μ-opioid receptor antagonist alvimopan (**23**) (*43*), respectively, further demonstrating the utility of the current protocol (Fig. 5H).

## Mechanistic studies

We next conducted several control experiments to gain insight into the DyKAT process. First, we separated the two enantiomers of α-branched ketone (*R*)-**1b** and (*S*)-**1b** by using preparative high-performance liquid chromatography (HPLC) and subjected them and racemic-**1b** to the standard reaction conditions, respectively (Fig. 6A). Both enantiomers and racemate were transformed to product **3v** in 97% ee with the same absolute and relative configuration, which indicates a complete catalyst-controlled process. When we used (*R*)-**1b**, the product **3v** was obtained with 59% yield in 1 hour (with 40% **1b** recovered) and with 99% yield in 3.5 hours. However, when we used (*S*)-**1b** as substrate, only 36% **3v** was obtained in 3.5 hours (with 65% **1b** recovered). The reaction with racemic **1b** gave a middle yield of 75% in 3.5 hours (with 22% **1b** recovered). These results reveal that (*R*)-**1b** is the stereochemically matched substrate with the Ni-**L1** catalyst, giving a faster reaction than that of (*S*)-**1b**. The recovered substrates were all racemic, which suggests that racemization is far more rapid than the arylation step, which is a requirement for a DyKAT to occur. Moreover, when we used the enantiomer of **L1**/HCl [(*S*,*S*,*S*,*S*)-ANIPE/HCl] instead of **L1**/HCl, enantiomers of **3v** and **6a** were generated efficiently, again indicating the excellent catalyst-controlled course (Fig. 6B).

The reaction performed well under base-free conditions. We then subjected free NHC (**L1**) to the DyKAT arylation and vinylation reactions of α-amino ketone **5a** (Fig. 6C). These reactions also proceeded effectively, giving the corresponding products in similar levels of yield, enantio-, and diastereoselectivity with the in situ NHC generation method. We also observed fast racemization of the less acidic α,α-dialkyl ketones [(*R*)-**1c** and (*S*)-**1c**] under base-free conditions (Fig. 6D). We next performed several control experiments to rule out other possible racemization pathways. The reactions with free carbene and $Ni(cod)_2$, respectively, did not promote ketone racemization (Fig. 6E). In another experiment, we found that the combination of base and boronic ester (5 mol % of base and 1.5 equiv of PhBneo for mimicking the reaction conditions) also did not racemize the ketone. These results suggest that both the racemization and C–C bond-forming processes occur in the absence of a base, and that the ketone racemization may not happen through a traditional base-deprotonating enolate-formation process. Thus, on the basis of our observations and previous reports (*30*, *31*), we propose a catalytic cycle (Fig. 6F). A chiral **L1**-Ni(0) complex and the matched ketone substrate [(*R*)-**1b**] undergo oxidative cyclization to afford an oxanickelacycle. The oxanickelacycle can be opened by PhBneo through transmetalation to form an aryl-alkyl nickel species, which undergoes reductive elimination to give product and regenerate nickel catalyst. The rapid racemization under the Ni-NHC complex through a reversible β-H elimination and reinsertion efficiently converts (*S*)-**1b** to (*R*)-**1b**, allowing complete consumption of ketone substrate.

Beyond the immediate utility of this method, we anticipate that the Ni-NHC–enabled enantioconvergent strategy will spur the development of other DyKAT processes for the rapid synthesis of valuable complex targets.

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## SUPPLEMENTARY MATERIALS

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Materials and Methods
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