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Streamlined Catalytic Enantioselective Synthesis of α-Substituted β,γ-Unsaturated Ketones and Either of the Corresponding Tertiary Homoallylic Alcohol Diastereomers

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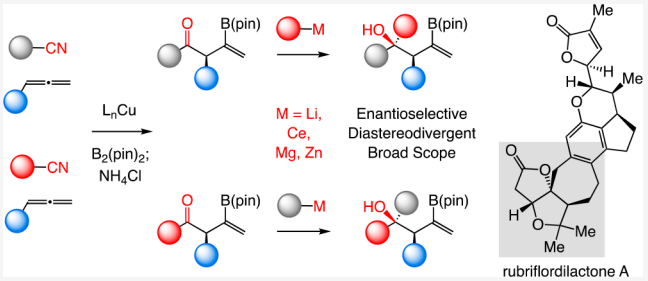
ABSTRACT: A widely applicable, practical, and scalable strategy for efficient and enantioselective synthesis of β,γ-unsaturated ketones that contain an α-stereogenic center is disclosed. Accordingly, aryl, heteroaryl, alkynyl, alkenyl, allyl, or alkyl ketones that contain an α-stereogenic carbon with an alkyl, an aryl, a benzyloxy, or a siloxy moiety can be generated from readily available starting materials and by the use of commercially available chiral ligands in 52−96% yield and 93:7 to >99:1 enantiomeric ratio. To develop the new method, conditions were identified so that high enantioselectivity would be attained and the resulting α-substituted NH-ketimines, wherein there is strong C═N → B(pin) coordination, would not epimerize before conversion to the derived ketone by hydrolysis. It is demonstrated that the ketone products can be converted to an assortment of homoallylic tertiary alcohols in 70−96% yield and 92:8 to >98:2 dr—in either diastereomeric form—by reactions with alkyl-, aryl-, heteroaryl-, allyl-, vinyl-, alkynyl-, or propargyl-metal reagents. The utility of the approach is highlighted through transformations that furnish other desirable derivatives and a concise synthesis route affording more than a gram of a major fragment of anti-HIV agents rubriflordilactones A and B and a specific stereoisomeric analogue.



1. INTRODUCTION

Scores of catalytic methods have been and continue to be developed for enantioselective synthesis of organic compounds, but, typically, no more than a narrow range of products can be accessed, circumventing applicability to preparation of complex molecules. Two notable instances relate to enantioselective synthesis of acyclic ketones containing an α-stereogenic carbon center, a recurring unit in bioactive molecules. Examples of natural products with one or more ketones adjacent to a stereogenic carbon include antibacterial jatrophenone[1] and cebulactam A1[2] (Scheme 1). Catalytic enantioselective protocols for synthesis of acyclic α-substituted ketones have been reported, but several key problems remain "still unconquered", as characterized in a recent review article.[3] The great majority of transformations deliver products where the carbonyl group and/or the stereogenic center are aryl-substituted,[4] a significant restriction considering total synthesis of many bioactive molecules calls for α-substituted aliphatic ketones (see Scheme 1). There are a small number of strategies for enantioselective synthesis of α-alkyl-substituted ketones, but these necessitate a priori generation of an enolate equivalent. There are also other limitations. One method is confined to synthesis of acylsilanes,[5] another produces methyl ketones with an α-quaternary stereogenic center attached to simple alkyl moieties (Me and Et),[6] and a third can be used to access only ketones that contain a methyl and an allyl group.[7] A catalytic enantioselective strategy is available for preparation of ketones masked as *n*-alkyl-substituted silylenol ethers, but the sole option for a C-based substituent at the allylic stereogenic center is a 1,3-diester.[8]

Equally important, it is difficult to convert—with high diastereoselectivity—the aforementioned α-substituted ketone products to their derived tertiary alcohols, which are also commonly occurring in bioactive compounds (e.g., rubriflordilactones A and B,[9−11] Scheme 1). Methods for catalytic enantioselective addition of allyl nucleophiles to ketones are available,[12] but again, most instances involve a nonenolizable ketone (e.g., aryl- or alkynyl-substituted; see the Supporting Information, SI, for extended bibliography);[13,14] in one case reaction with an alkyl ketone led to low diastereomeric ratio (dr),[14b] and in another selectivities were not at useful levels unless the α-substituent was sizable (e.g., a cyclohexyl group).[15] There are reactions that deliver homoallylic tertiary alcohols bearing an *E*-alkenyl−B(pin) moiety but only if the

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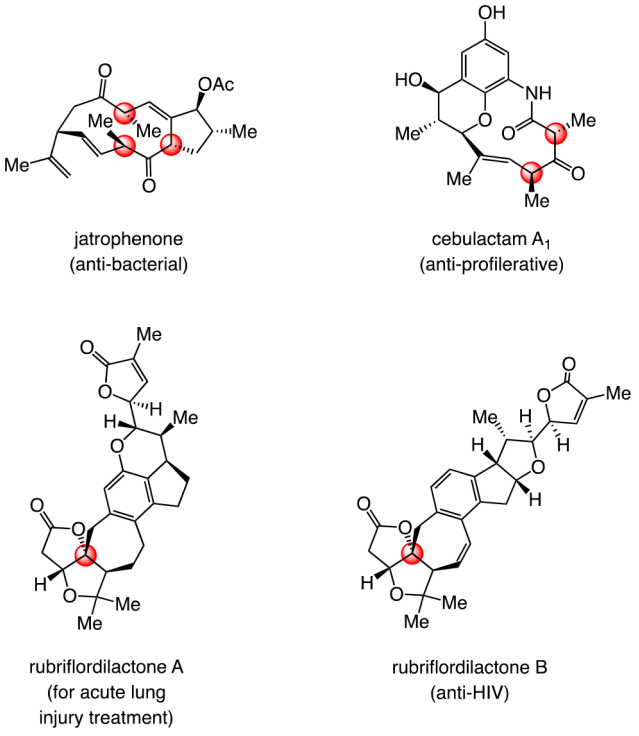
Scheme 1. Bioactive Compounds Containing α-Substituted Ketones or Tertiary Alcohol Derivatives

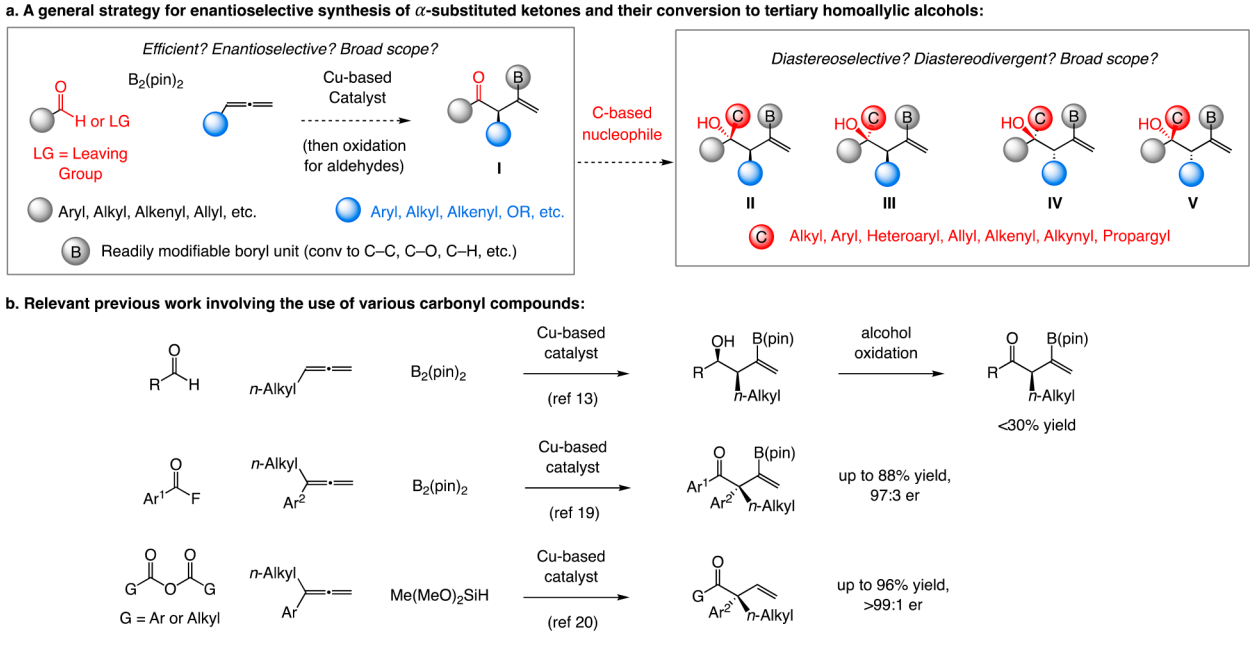


allylic carbon is quaternary (mostly methyl- and *n*-alkyl-substituted).[16] Another limitation is that the above transformations generate one of the possible diastereomers, undermining stereoisomeric analogues synthesis. Apropos, a catalytic diastereodivergent and enantioselective approach for preparation of tertiary homoallylic alcohols was recently introduced; nonetheless, occasional low diastereoselectivities aside, scope limitations were again an issue.[17]

We reasoned that if a wide range of enantiomerically enriched β,γ-unsaturated, β-boryl ketones **I** (Scheme 2a) were to become available, then the size of the β-B(pin) moiety could be exploited toward stereoselective synthesis of every possible tertiary alcohol isomer (**II**–**V**). We first considered accessing **I** through a catalytic enantioselective multicomponent process that might involve a monosubstituted allene, $B_2(pin)_2$, and an aldehyde,[13,18] followed by oxidation of the secondary alcohol. We were however unable to isolate a β,γ-unsaturated ketone in more than 30% yield (Scheme 2b). The major products were a difficult-to-purify mixture of achiral α,β-unsaturated ketones with a B(pin) and a $B(OH)_2$ moiety, the latter of which, containing a smaller boryl unit, is unsuitable for highly diastereoselective additions (**I** → **II**–**V**, Scheme 2a). We surmised that an activated form of a carboxylic acid derivative might be used to prepare a β,γ-unsaturated ketone. In fact, a catalytic enantioselective process involving acyl fluorides and 1,1-disubstituted allenes has been disclosed (Scheme 2b).[19] Then again, substrates were aryl-substituted, and data regarding processes involving monosubstituted allenes, which would yield β,γ-unsaturated ketones prone to loss of enantiomeric purity and/or alkene rearrangement, were not included. In another recent disclosure, related transformations were performed with anhydrides; as before, the method is confined to 1,1-disubstituted allenes that must bear an aryl moiety (Scheme 2b).[20]

The state-of-the-art and the above considerations led us to ponder the possibility of starting with nitriles, a readily accessible set of compounds not used previously for preparation of α-substituted ketones. We have demonstrated that with an appropriate Cu-based catalyst reactions involving a nitrile, a monosubstituted allene, $B_2(pin)_2$, and a silyl hydride (PMHS) can be used to form a large assortment of β,γ-unsaturated NH-ketimines (**III**, Scheme 3a), which are then rapidly reduced in situ to afford the desired boryl-substituted homoallylic amines (**IV**).[21−23] The importance of the envisioned strategy became clearer when we considered possible enantioselective pathways for synthesis of the bicyclic

Scheme 2. Initial Plan and Related Formerly Published Work



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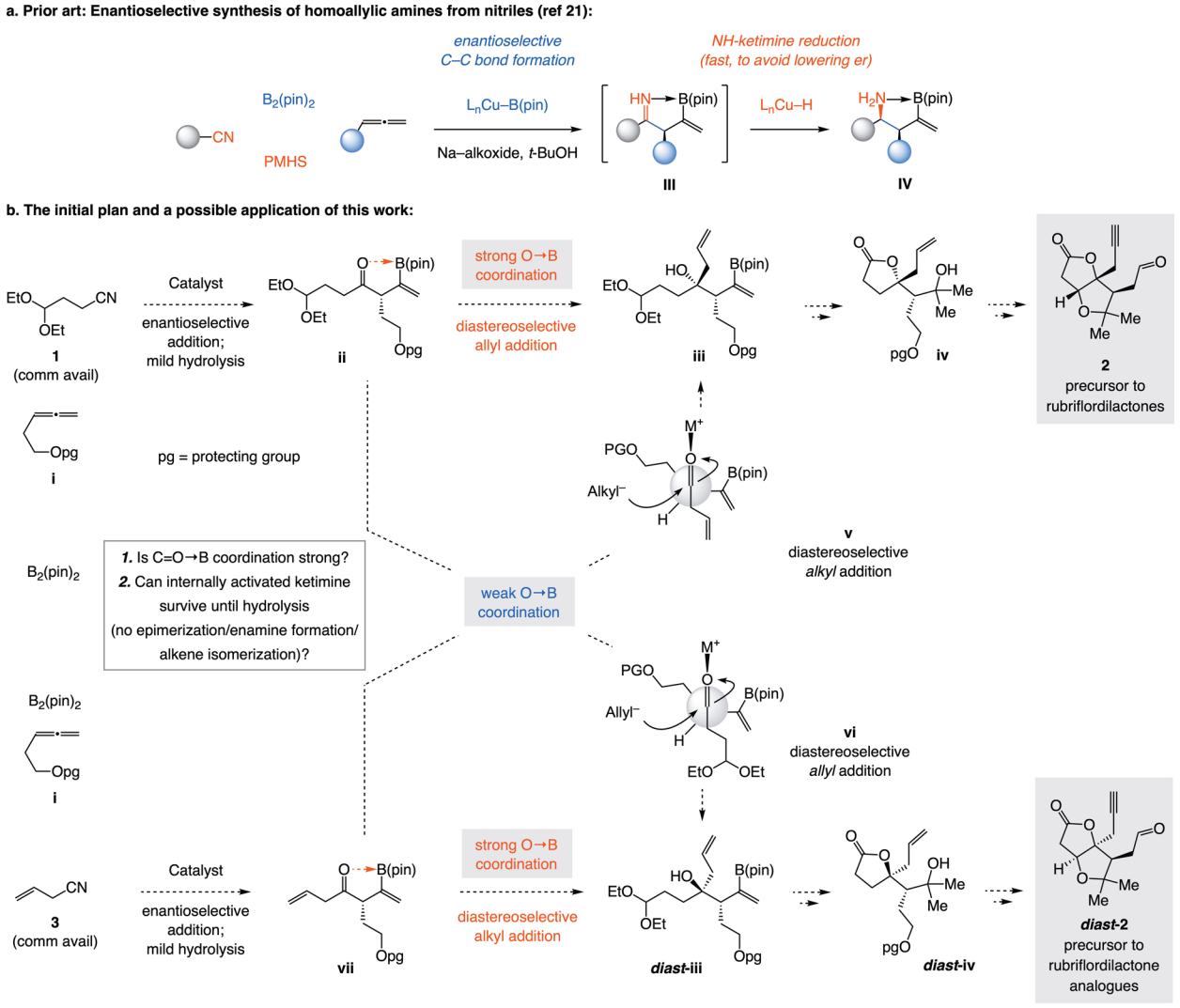
Scheme 3. A Revised and More Flexible Strategy That Involves Nitriles as Substrates



segment and a diastereoisomeric analogue of rubriflordilactones (**2** and *diast*-**2**, Scheme 3b).[24] We imagined a route that could begin with commercially available alkyl nitrile **1**, reaction of which with a monosubstituted allene (**i**) and $B_2(pin)_2$ would afford the corresponding β,γ-unsaturated NH-ketimine enantioselectively. In situ hydrolysis would generate **ii**, a masked and relatively stereochemically robust (less prone to loss of enantiomeric purity) 1,3-diketone that bears differentiated carbonyl groups. Ensuing diastereoselective addition to generate tertiary alcohol **iii**, the alkenylboronate would be oxidized to reveal the second ketone unit followed by lactone generation. Formation of another tertiary alcohol (methyl addition) would furnish **iv**, which would be converted to **2**.

But our plan presented several challenges. The first originated from the fact C═N → B coordination enhances ketimine electrophilicity, rendering it more susceptible to loss of enantioselectivity than otherwise expected.[21,25] A major concern was not only if it would be possible to avoid enantioselectivity erosion, but also whether enamine formation, or isomerization to the (probably lower energy) α,β-unsaturated isomer could be avoided. For conversion of the same ketimines to the corresponding amines, rapid in situ reduction of the NH-ketimine (see Scheme 3a) circumvented such complications in the case of one set of stereoisomers, and reduction at −78 °C was required for the other. Here, the ketimine would have to remain intact for the duration of the transformation, and without the need for low temperature conditions, because hydrolysis would likely have to be performed at room or near-ambient temperatures. We were concerned that nitriles and/or allenes with an electron-withdrawing substituent would be especially prone to these types of side reactions. The same question extended to ketimine hydrolysis and whether conditions could be found that would be sufficiently mild so that the initial enantioselectivity could be preserved.

Yet another issue was whether C = O → B coordination in **ii** would be strong enough to allow for generation of one diastereomer by allyl addition to a conformationally rigid intermediate (**ii** → **iii**, Scheme 3b). If internal coordination were to prove substantial, then we would have two options for preparing *diast*-**iii**. One would entail, similar to the aforementioned homoallylic amine syntheses (Scheme 3a),[21] disruption of C═O → B coordination with a stronger Lewis acid (vs internal boron, to interact with the carbonyl oxygen).[21] Alternatively, we could begin with allyl nitrile **3** (also commercially available). Subsequent alkyl addition would deliver *diast*-**iii** via **vii**; this would be followed by generation of *diast*-**iv** and then *diast*-**2**, which is the fragment corresponding

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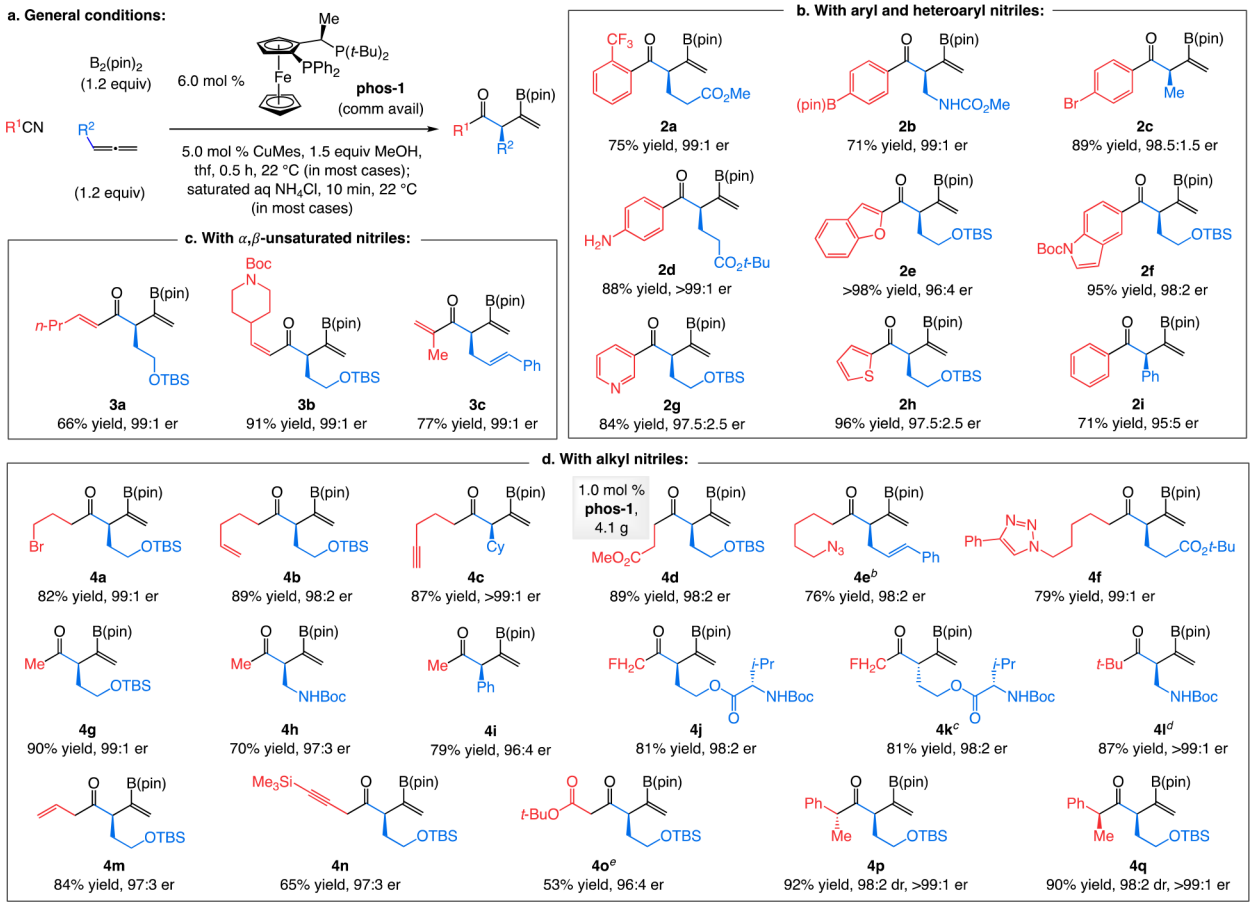
Scheme 4. Enantiomerically Enriched Ketones Bearing an α-Substituted C-Based Tertiary Stereogenic Center[a]



[a]Reactions were performed under N_2 atm. Conversion (nitrile disappearance; > 98% in all cases) was determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). Yields correspond to purified products (±5%). Enantioselectivities were determined by HPLC analysis (±1%). [b]22 °C, 20 min. [c]2.2 mol % ligand (*ent*-**phos-1** for **4k**), 2.0 mol % CuMes, 1.2 equiv nitrile, 8 h. [d]For 16 h, − 25 °C. [e]For 36 h, − 40 °C. See the SI for details.

to 5-*epi*-rubriflordilactone. The stability of **3** under the reaction conditions would be key, as the corresponding allyl aldehyde is more prone to alkene isomerization. If we were to find that C═O → B coordination is indeed weak, then we would transform ketones **ii** and **vii** to tertiary alcohols **iii** and *diast*-**iii** by sterically controlled diastereoselective addition of the appropriate alkyl and allyl moieties via **v** and **vi**, respectively (Scheme 3b). Regardless of the strategy used, the ability to reverse the functional units within the substrate and the nucleophilic agent would be critical, made possible by the ready availability of nitriles. This all hinged on whether additions to ketones would be highly diastereoselective.

2. RESULTS AND DISCUSSION

2.1. Optimal Conditions for Synthesis of α-Substituted Ketones. After extensive screening, we identified conditions for efficient enantioselective conversion of a nitrile, an allene, and $B_2(pin)_2$ to the corresponding β,γ-unsaturated ketone in high yield and enantioselectivity (Scheme 4). As anticipated, reaction temperature (22 or −40 °C), the choice of alcohol (MeOH), and the conditions for NH-ketimine hydrolysis (time and the type of aqueous solution used) were crucial factors (see below for analysis). The chiral catalyst was generated in situ from a bisphosphine ligand (e.g., **phos-1**) and a copper salt (e.g., CuMes (Mes, 2,4,6-trimethylphenyl)), both of which can be purchased (Scheme 4a). The hydrolysis conditions are mild (NH_4Cl, typically for 10 min at 22 °C), likely because, as already noted, of internal ketimine activation by the neighboring Lewis acidic boron atom (see the SI for screening studies).[26]

2.2. Range of α-Substituted Ketone Products. Aryl and heteroaryl nitriles were converted to α-substituted β,γ-unsaturated ketones in 71% to >98% yield and 95:5 to >99:1 enantiomeric ratio (er; Scheme 4b). Transformations with sterically hindered (**2a**), electron-deficient (**2a**-**c**), or electron-rich (**2d**) nitriles were efficient and enantioselective. Heteroaryl nitriles were equally suitable substrates (**2e**-**h**). An aryl boronate (**2b**), an aryl bromide (**2c**), and an unprotected amine (**2d**) were tolerated. Reactions with allenes that contain a carboxylic ester (**2a** and **2d**), a carbamate (**2b**), a methyl (**2c**), or an aryl moiety (**2i**) were similarly effective.

Transformations of α,β-unsaturated nitriles afforded products in 66−91% yield and 99:1 er (Scheme 4c) without competitive boryl conjugate addition, irrespective of the alkene's substitution pattern or stereochemistry. The case of triene **3c** demonstrates that allenes with an allylic substituent are suitable substrates, and that Cu−B addition to an allene occurs chemoselectively in the presence of a β-substituted aryl olefin, which has been shown to undergo reaction readily with a Cu−B(pin) complex (see also **4e**, Scheme 4d).[27]

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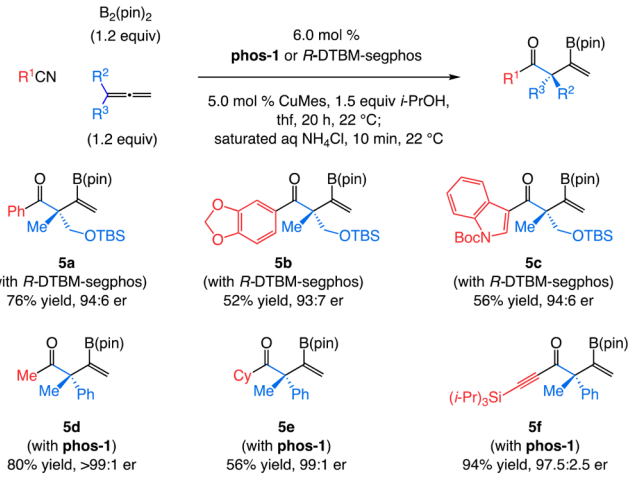
Additions to alkyl nitriles (Scheme 4d), which, as noted above, are particularly important to synthesis of bioactive compounds, were efficient and exceedingly enantioselective. Effective substrates included those bearing an *n*-alkyl substituent (**4a-f**, 76−89% yield, 98:2 to >99:1 er), which may contain a halide (**4a**), an alkene (**4b**), a terminal alkyne (**4c**), a carboxylic ester (**4d**), an azide (**4e**), or a triazole moiety (**4f**). Acetonitrile was transformed to β,γ-unsaturated ketones **4g-i** (70−90% yield and 96:4−99:1 er). Ketone **4d**, precursor to *diast*-**2** (see Scheme 3), was prepared on multigram scale with just 1.0 mol % of the catalyst present. β,γ-Unsaturated ketones **4j** and **4k** were synthesized by the use of **phos-1** and *ent*-**phos-1**, respectively, along with commercially available monofluoroacetonitrile and an enantiomerically pure allene bearing a Boc-protected amino acid residue. (Reactions of CF_2HCN and CF_3CN were not investigated, as these gaseous compounds are significantly more toxic and difficult to use.) The transformation with sterically congested *tert*-butylnitrile delivered **4l** in 87% yield and >99:1 er. β,γ-Unsaturated ketones containing a second allylic moiety (**4m**), a propargylic group (**4n**), or a β-ketoester (**4o**) were formed with similar ease and enantiomeric purity. Preparation of ketones **4p,q**, in which the carbonyl group is flanked by two α-stereogenic centers, illustrate that additions to enantiomercally pure nitriles can be under catalyst control (98:2 diastereomeric ratio (dr), >99:1 er).

1,1-Disubstituted allenes were converted to α,α-disubstituted β,γ-unsaturated ketones (Scheme 5). Thus, aryl- (**5a**),

Scheme 5. Enantiomerically Enriched Ketones Bearing an α-Quaternary Carbon Stereogenic Center[a]

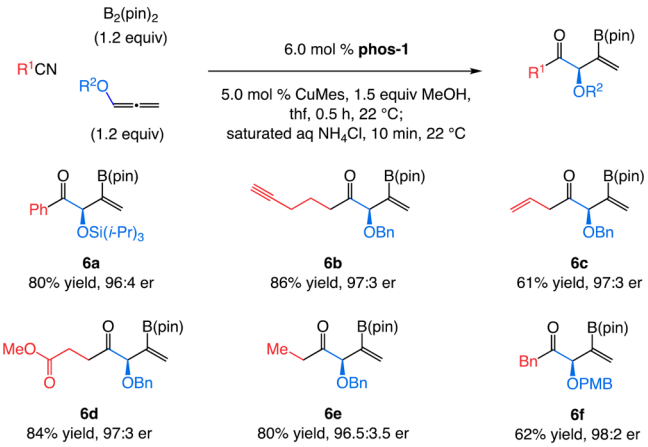


[a]Reactions were performed under N_2 atm. Conversion (nitrile disappearance; >98% in all cases) was determined by analysis of ^1H NMR spectra of unpurified product mixtures (±2%). Yields correspond to purified products (±5%). Enantioselectivities were determined by HPLC analysis (±1%). See the SI for details.

heteroaryl- (**5b,c**), alkyl- (**5d,e**), and alkynyl-substituted (**5f**) products were obtained in 52−94% yield and 93:7 to >99:1 er. For these transformations, the catalyst derived from commercially available (*R*)-(−)-DTBM-segphos afforded superior results in most cases (vs **phos-1**; see the SI for further analysis). It is worth noting that, compared to the aforementioned approach involving acyl fluorides and anhydrides,[19,20] a broader range of products can be accessed.

Oxygen-substituted allenes, accessible in a single step from readily available compounds, are another noteworthy substrate set. Thus, α-siloxy or α-benzyloxy β,γ-unsaturated ketones were synthesized efficiently and in high enantioselectivity (**6a-f**, Scheme 6). There are a limited number of protocols for

Scheme 6. Enantiomerically Enriched Ketones Bearing an α-Substituted O-Based Tertiary Stereogenic Center[a]



[a]Reactions were performed under N_2 atm. Conversion (nitrile disappearance; > 98% in all cases) was determined by analysis of ^1H NMR spectra of unpurified product mixtures (±2%). Yields correspond to purified products (±5%). Enantioselectivities were determined by HPLC analysis (±1%). See the SI for details.

preparation of related compounds,[3,] including one that is diastereodivergent (see the SI for a detailed bibliography).[28] Persisting scope issues and the difficulties associated with product modification notwithstanding, such transformations represent a different bond disconnection (i.e., enolate trapping, aldol additions, or hydroxy-amine additions).

2.3. Other Key Points Regarding α-Substituted Ketone Synthesis.

(1) Enantioselectivities are time-dependent, with epimerization occurring largely at the ketimine stage (see the SI for data). As noted, this is likely because the internal ketimine−boryl coordination increases Cα proton acidity. Alkene isomerization occurs as well with extended reaction times.

(2) Most transformations can be performed and quenched at ambient temperature under mild conditions with little or no loss in enantiomeric purity. In certain cases, it was preferable for reactions to be carried out at −40 °C. These were instances when either the NH-ketimine could displace a leaving group intramolecularly (e.g., **4a**, Scheme 4d), or lowering of er was more of an issue because the product had an aryl-substituted ketone and stereogenic center (e.g., **2i**, Scheme 4b), or the nitrile contained a Lewis basic or more strongly electron-deficient moiety (e.g., **2g**, Scheme 4).

(3) Reactions were faster when MeOH was used, delivering products in higher er compared to when a larger alcohol was utilized (see the SI for the relevant data). The increased rate with the smaller alcohol likely results from more efficient protonolysis of the bisphosphine−Cu−ketimine complex, leading to faster catalyst regeneration; there was only ∼10% conversion with *t*-BuOH. Diminished enantioselectivity with *i*-PrOH is probably

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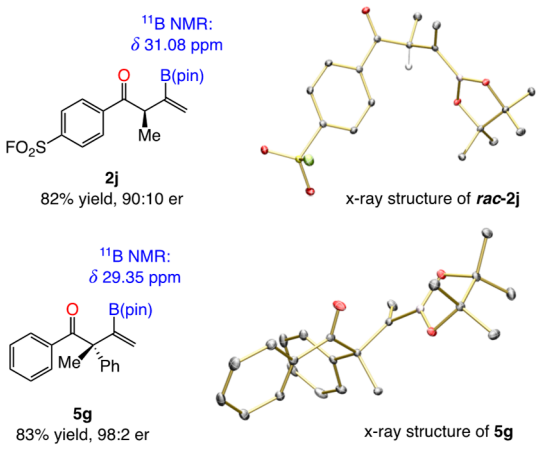
due to slower protonolysis of the copper−ketimine intermediate (i.e., less facile C = N−CuL_n + ROH → C = NH + $ROCuL_n$), and, as already mentioned, the longer reaction time allows for more extensive enantioselectivity erosion prior to ketimine hydrolysis. Because C−C bond formation is slower for products containing a quaternary carbon (Scheme 5), protonolysis of the copper−allyl intermediate becomes more competitive (see the SI for further analysis). Use of a bulkier ligand and/or proton source (epimerization no longer an issue) thus proved to be advantageous, and the transformations with 1,1-disubstituted allenes were higher yielding with *i*-PrOH and/or DTBM-segphos (see the SI for additional data).

(4) Reactions are easy to perform. The chiral ligands are purchasable; **phos-1** belongs to a family of ligands used on industrial scale.[29,30] The majority of the nitriles are commercially available and others can be synthesized in one to two steps (see the SI for details). Many stereochemically defined alkenyl nitriles (Scheme 4c) can be prepared stereoselectively by catalytic cross-metathesis.[31] Most allenes can be obtained in one to two steps (see the SI for details). Methylallene is a feedstock compound used as fuel additive. A small excess of an allene and $B_2(pin)_2$ suffices.

2.4. Diastereoselective Conversion to Tertiary Homoallylic Alcohols. Owing to variations in reactivity and size between nucleophiles and difficult-to-predict impact of enthalpic and/or entropic factors,[32] we surmised that different sets of conditions and optimal reagents would be needed to transform the above *β*,*γ*-unsaturated ketone products to various corresponding tertiary homoallylic alcohols.

The first issue was whether there is significant internal C=O → B coordination within the ketone products. Spectroscopic studies and X-ray structures of *β*,*γ*-unsaturated ketones **2j** and **5g** (Scheme 7) revealed that—unlike NH-ketimines[21]—the boron atoms are tricoordinate. That is, as noted before (see Scheme 3), to access either diastereomer with high selectivity, we would need to manipulate the identity of the nitrile and the

Scheme 7. X-ray Structures Show No Carbonyl to Oxygen Coordination[a]



[a]See the SI for details.

nucleophile, having to rely solely on steric factors (vs C=O → B(pin) coordination and its disruption).

Addition of MeLi to phenyl ketone **2k** (−78 °C, thf) afforded ***R*,*R*-7a** in 91:9 dr, and with MeMgBr, the reaction was inefficient and minimally diastereoselective (17% conv, 68:32 dr). We reasoned that in a process largely controlled by steric factors, a more sizable nucleophile should be more diastereoselective, and thus investigated additions of organocerium compounds.[33,34] This led us to find that by combining MeLi or MeMgCl and $CeCl_3$·2LiCl,[34] a salt that facilitates Li or Mg/Ce ligand exchange,[35] ***R*,*R*-7a** can be isolated in 77% yield and 97:3 dr (Scheme 8). Under the same conditions, we obtained doubly homoallylic tertiary alcohol **7b** in 93:7 dr. Synthesis of *tert*-butyl-substituted alcohol **7c** and monoprotected 1,2-diol **7d** did not require a Ce-based reagent, presumably because *t*-BuLi is sufficiently large and the benzyloxy unit can accommodate a chelate structure to ensure high diastereoselectivity.[36] As the neighboring hydroxy group engenders partial hydrolysis of the pinacolato moiety, products were isolated, after $NaIO_4$/NH_4OAc workup, as robust and easily isolable boronic acids (see the SI for details). Analytical data indicate that there is no adventitious loss of enantiomeric purity during nucleophilic addition (e.g., 97:3 and 98:2 er for **7b** and **7d**, namely, the identical enantiomeric purity recorded for the corresponding *α*-substituted ketone precursors; see the SI for additional details).

Additions of aryllithium and heteroaryllithium compounds were equally efficient and diastereoselective (Scheme 9). Products ***S*,*R*-7a**, complementary to the aforementioned ***R*,*R*-7a** (Scheme 9), doubly homoallylic alcohol ***S*,*R*-8a**, and pyridyl-, and thienyl-substituted **8b** and **8c** were isolated in 63−81% yield and 92:8 to >98:2 dr. Diastereoselective formation of aryl,aryl-substituted tertiary alcohols ***S*,*R*-8d** and ***R*,*R*-8d**, preparation of which by alternative strategies would be challenging, underscores the versatility of the approach. As before, analysis of the enantiomeric purity of the tertiary alcohols indicated that there was no epimerization occurring during nucleophilic addition (see ***S*,*R*-8d** and ***R*,*R*-8d**, Scheme 9).

We then examined additions of different allylmetal compounds to *α*-substituted *β*,*γ*-unsaturated ketones. This included Ce-, Cu-, and Ti-based reagents generated in situ from reaction of an allylmagnesium chloride or allylzinc bromide (see the SI for details). Reaction with a blend of allylmagnesium chloride and $CeCl_3$ in thf resulted in conversion of **2k** to ***R*,*R*-8a** [for ***S*,*R*-8a**, see Scheme 9] in 80% yield and 91:9 dr after 10 min at room temperature. A more generally effective protocol entailed the use of a mixture of allylmagnesium chloride and manganese pivalate[37] [prepared from inexpensive $Mn(OAc)_2$]. After 1 h at −78 °C, doubly homoallylic tertiary alcohols ***R*,*R*-8a** and **9a-c** were isolated in 70−89% yield and 92:8 to >98:2 dr (Scheme 10). These selectivity trends may be attributed to varying sizes of the anionic ligand, a hypothesis supported by the observation that when $MnCl_2$ and $MnBr_2$ were used, diastereoselectivities were lower (e.g., ***R*,*R*-8a** in 85:15 and 86:14 dr, respectively). *α*-*p*-Methoxybenzyl-substituted ketone **9d** (Scheme 10) was obtained in 76% yield and 97:3 dr when allylmagnesium bromide was used (no Mn salt), likely due to chelation control. Similar to diastereoselective alkyl and aryl additions, we did not observe any loss of enantiomeric purity in a diastereoselective allyl addition processes (see **9c-d**, Scheme 10).

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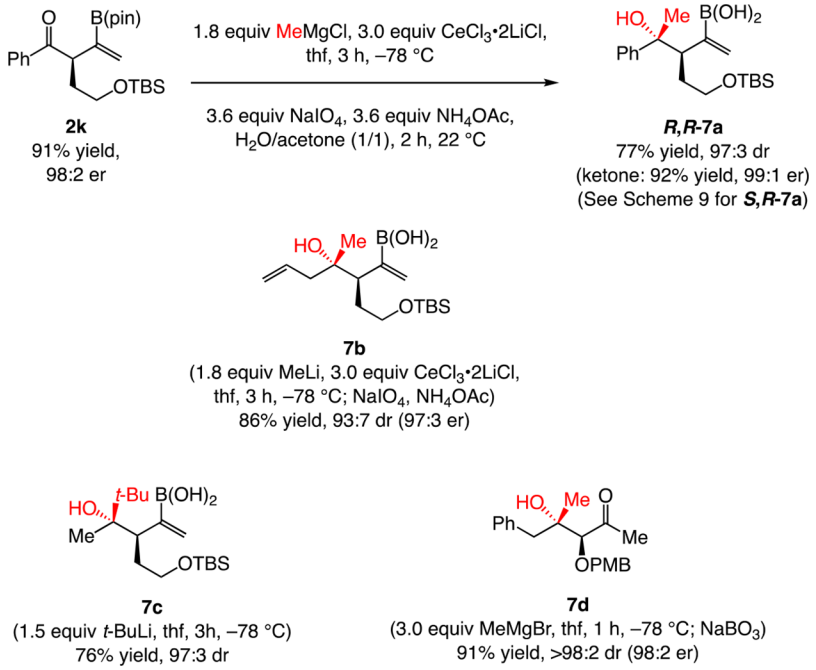
Scheme 8. Diastereoselective Synthesis of Tertiary Homoallylic Alcohols Through Addition of an Alkyl Group[a]



[a]Reactions were performed under N_2 atm. Conversion (nitrile disappearance; >98% in all cases) was determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). Yields correspond to purified products (±5%). Enantioselectivities were determined by HPLC analysis (±1%). See the SI for details.

The combination of vinylmagnesium bromide or an alkynyllithium compound and $CeCl_3$·2LiCl was used to synthesize tertiary allylic and propargylic alcohols **10** and **11** (Scheme 11; in 88% and 85% yield and 96:4 and 97:3 dr, respectively). We confirmed that alkynyl additions proceed without any competitive epimerization of the α-substituted ketone substrate (see **11**). Homopropargylic tertiary alcohol **12a** was prepared by treatment of ketone **2l** with an organozinc halide, formed in situ from the commercially available bromide. Conversion of ester-substituted ketone **4d** to butyrolactone **12b** was performed on multigram scale (78% yield, >98:2 dr).

2.5. Functionalization of α-Substituted Ketones and Tertiary Homoallylic Alcohols. Ketones and tertiary alcohol products prepared through the strategies detailed above can be efficiently, chemoselectively, and/or diastereoselectively modified to generate other desirable entities (Scheme 12; see the SI for more examples). For instance, α-substituted ketone **4d** was transformed in two steps to trisubstituted alkenyl boronate **13** in 70% overall yield and 92:8 dr. Again, we did not detect any loss of enantiomeric purity (**13** in 97:3 er; see the SI for details). Spirocyclic butyrolactones are recurring motifs in naturally occurring bioactive compounds (e.g., anti-inflammatory curcumalactones[38,39]). A different type of lactone was prepared by catalytic conversion[40] of ***S,R*-8d** to α,β-unsaturated butyrolactone **14** in 71% yield (98:2 er, no loss of enantiomeric purity), providing access to another building block regularly found within bioactive compounds (e.g., antimalarial arteannuin[41]). Syntheses of homoallylic alcohols **15a,b**, isolated in 93% and 91% yield after NHC−Cu-catalyzed C−B to C−H transformation, are equally important derivatives. Regarding **15a**, the necessary alkyl-substituted ketones cannot be easily prepared by alternative methods (e.g., catalytic multicomponent CuH-catalyzed approaches)[14b,15] and enantioselective synthesis of **15b** would be most challenging through addition to a virtually symmetric ketone. Analysis of the enantiomeric purity of **15b** indicated that there was no loss in er during the pathway starting from the corresponding α-substituted ketone (98:2 er). The *p*-methoxybenzyl group in **6f** was removed to give α-hydroxy ketone **16** in 85% yield (Scheme 12) with a slight loss of enantiomeric purity (98:2 vs 95.5:4.5 er). Compounds such as **16** have been used for enantioselective preparation of rare sugars and the corresponding bioactive molecules.[42]

2.6. Application to Synthesis of Rubriflordilactones A and B Fragment 2. The functional groups in an α-substituted β,γ-unsaturated ketone may be modified chemoselectively, as underscored by enantio- and diastereoselective synthesis of a fragment of rubriflordilactones A and B (**2**; Scheme 13). The same moieties can be found in other anti-HIV compounds, such as members of the schisandraceae family of natural triterpenoids.[43]

By using 2.0 mol % of the Cu complex derived from *ent*-**phos-1**, we synthesized multigram quantities of ketone ***S*-4m** in 83% yield and 96:4 er. The reaction was performed with air-stable $Cu(PPh_3)_3F$·2EtOH[44] (vs CuMes) and without rigorous exclusion of air and moisture. Diastereoselective addition of an organocerium species, generated in situ by treatment of commercially available chloride **17** and lithium 4,4-di-*tert*-butylbiphenylide (LiDBB; to generate the alkyl−Li reagent) and $CeCl_3$, was followed by alkenyl boronate oxidation, furnishing **18** in 99% yield and 96:4 dr, again without any diminution in enantiomeric purity (96:4 er). The tertiary alcohol was accordingly generated and the second ketone moiety was unmasked by a single-vessel operation. One-step acetal removal/cyclization and oxidation[45] delivered lactone **19** (~3.1 g). Chemoselective methyl addition to the ketone (vs cyclic ester) by treatment of **19** with $CeCl_3$ (22 °C) and then

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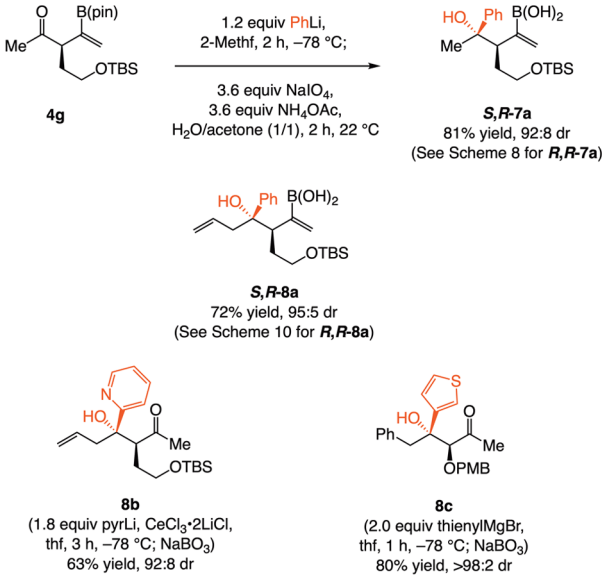
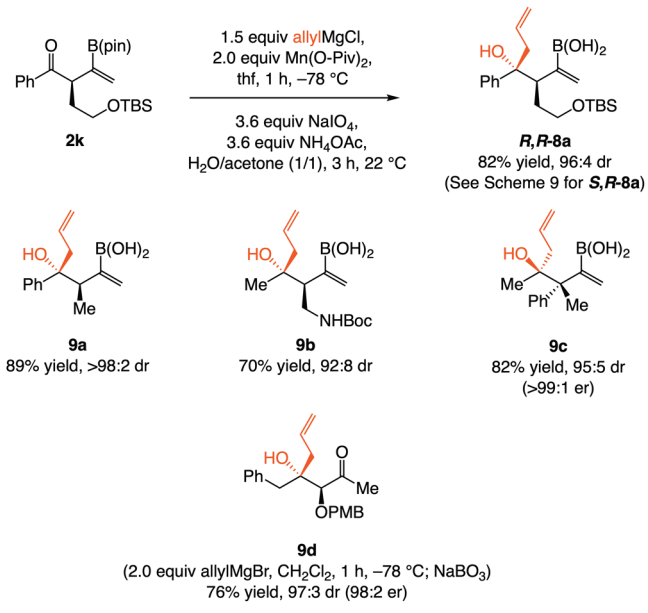
Scheme 9. Diastereoselective Synthesis of Tertiary Homoallylic Alcohols Through Addition of an Aryl Moiety[a]



[a]Reactions were performed under N_2 atm. Conversion (nitrile disappearance; > 98% in all cases) was determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). Yields correspond to purified products (±5%). Enantioselectivities were determined by HPLC analysis (±1%). See the SI for details.

Scheme 10. Diastereoselective Synthesis of Tertiary Homoallylic Alcohols Through Addition of an Allyl Group[a]



[a]Reactions were performed under N_2 atm. Conversion (nitrile disappearance; > 98% in all cases) was determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). Yields correspond to purified products (±5%). Enantioselectivities were determined by HPLC analysis (±1%). See the SI for details.

MeMgCl (−78 °C),[46] delivered tertiary alcohol **20** (85% yield; ~4.0 g). The corresponding α,β-unsaturated lactone was subsequently prepared,[47] leading to concomitant intramolecular conjugate addition to generate bicyclic lactone **21** (55% yield; 68% yield, based on recovered **20**). Simultaneous removal of the silyl groups and oxidation of the primary alcohol afforded **2** (89% yield, 2 steps). Thus, the 11-step route afforded the desired fragment in 22% overall yield (10 steps and 27% overall yield if the alcohol precursor to the allene is purchased vs 16% overall yield and 16 steps previously[24]). We were able to synthesize ketone ***S*-4m** and tertiary alcohol **18** on multigram scale easily, efficiently, and in high er and dr, respectively (Scheme 13), allowing us to secure 1.06 g of **2**. The X-ray structure of **2** confirmed its assigned stereochemical identity.

2.7. Synthesis of a Stereochemical Analogue of Rubriflordilactones A and B Fragment. To synthesize the fragment corresponding to 5-*epi*-rubriflordilactone (*diast*-**2**), we began with **12c**, a compound that carries the requisite alkynyl moiety. This is unlike the route leading to **2** (Scheme 13) where an alkene-to-alkyne approach strategy was adopted. The difference in strategy arises because for the earlier sequence the necessary propargylic substrate, unlike most other nitriles, was not sufficiently stable for us to obtain reproducible results. We first investigated the addition of several methyl anion equivalents to lactone **12b** (see Scheme 8), but were unable to isolate **23** in more than 20−30% yield. Spectroscopic analysis indicated competitive addition to the lactone carbonyl group. Identifying an alternative route was not challenging because of the variety of nitriles that can be easily accessed and the different nucleophilic compounds that may be used to convert a β-boryl ketone to the desired tertiary alcohol.

We chose to retain the alkenyl boronate in **12c** and use it to generate 1,1-disubstituted alkene by catalytic cross-coupling (Scheme 14).[48] Regioselective synthesis of the tertiary alcohol **23** was accomplished by the use of a Co-based complex[49] (61% overall yield for three steps from **4d**, >98:2 dr). However, attempts to prepare the derived α,β-unsaturated lactone, under the conditions used to generate **21**, were ineffective (mixture of byproducts). We attributed this to adventitious influence of the lithium alkoxide, likely formed under the basic conditions. To address this problem, we prepared the corresponding tertiary silyl ether prior to α,β-unsaturated lactone formation.[50] The desired bicylic lactone was obtained cleanly by addition of a fluoride salt, unmasking the tertiary and primary alcohols (one-pot operation). Oxidation of the primary alcohol furnished *diast*-**2** in 76% yield (three steps from **23**) and >98:2 dr (Scheme 14). The nine-step route (seven steps, longest linear sequence) afforded the desired product in 32% overall yield (including synthesis of the allene in two steps and 78% yield). In comparison, the same fragment has been formerly prepared in eight steps (six steps, longest linear sequence) and 19% overall yield.[51] Neither of the reported strategies for diastereo- and enantioselective synthesis of **2** or *diast*-**2** are easily amenable to preparation of the alternative diastereomer.

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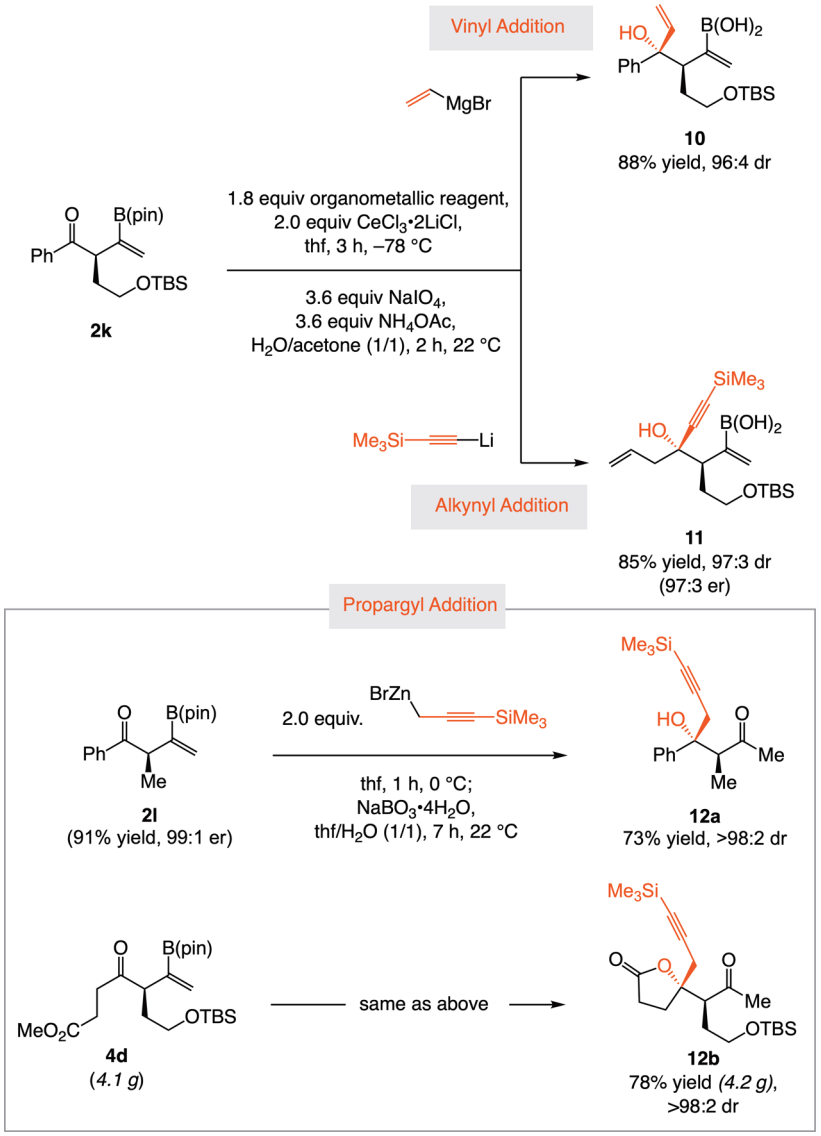
Scheme 11. Diastereoselective Synthesis of Tertiary Homoallylic Alcohols Through Addition of a Vinyl, an Alkynyl, or a Propargyl Group[a]



[a]Reactions were performed under N_2 atm. Conversion (nitrile disappearance; > 98% in all cases) was determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). Yields correspond to purified products (±5%). Enantioselectivities were determined by HPLC analysis (±1%). See the SI for details.

3. CONCLUSIONS

In brief, we offer practical and generally applicable solutions to two longstanding problems in the synthesis of bioactive compounds and their different analogues: streamlined methods for enantioselective preparation of easily modifiable α-substituted ketones and their diastereoselective conversion to tertiary homoallylic alcohols, which may be accessed in either diastereomeric form. Substrates, ligands, and the Cu salt are commercially available or can be prepared easily. A large excess of any of the starting materials partners or a glovebox is not needed. The transformations are scalable.

One key challenge was finding a way to synthesize α-substituted β,γ-unsaturated ketones that contain a B(pin) moiety at Cβ in high enantioselectivity and avoiding subsequent erosion of enantiomeric purity or isomerization. This required identifying conditions under which the ketimine intermediate, which is particularly prone to epimer formation owing to internal coordination between the ketimine N and the neighboring Lewis acidic B, would be able to retain its enantiomeric purity for the duration of the transformation at ambient or near-ambient temperatures. The presence of a B(pin) moiety also had its advantages. The possibility of generating useful derivatives (e.g., cross-coupling) aside, the size of the boryl moiety made it possible for different nucleophilic additions to the neighboring ketone to be exceptionally diastereoselective.

The considerable scope of the approach is mostly because of three factors: (1) countless nitriles can be purchased or prepared easily, (2) various allenes are readily accessible, (3) many useful C-based moieties can be added to the ketone products in high yield and dr, and (4) key substrates, such as allyl nitrile, are sufficiently robust to allow them to be used in efficient and highly enantioselective transformations that generate ketones and would be more difficult to prepare by

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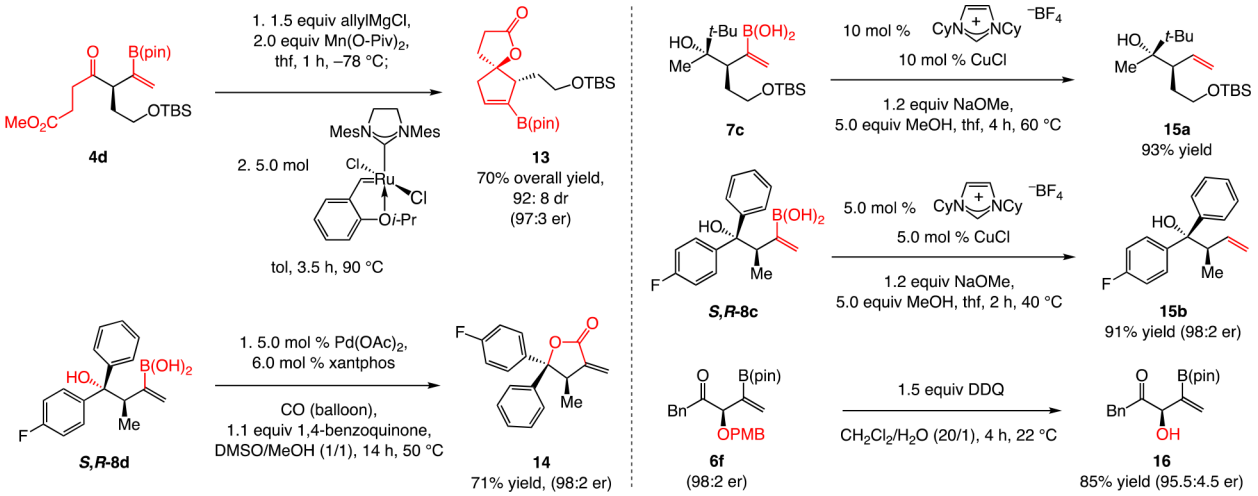
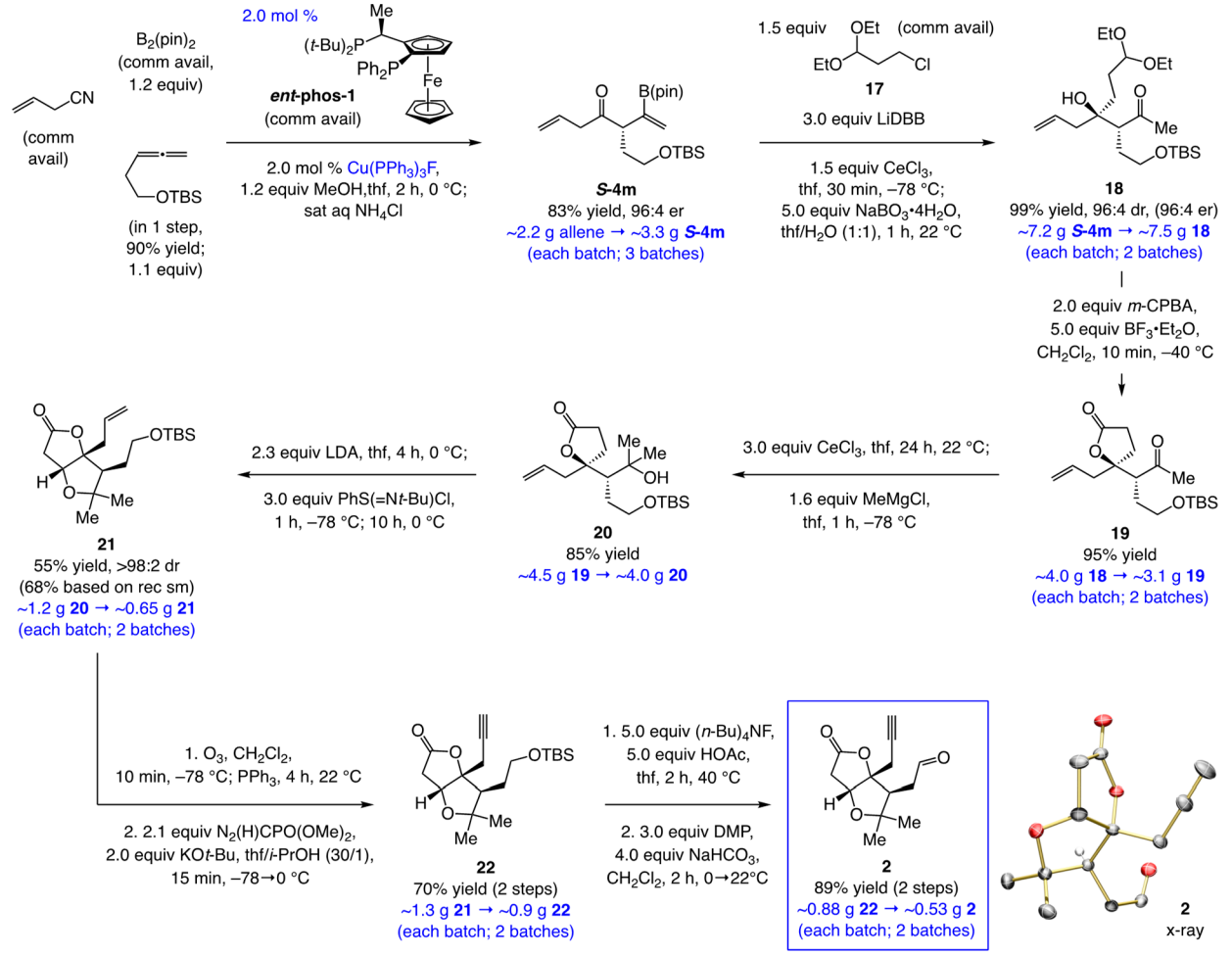
Scheme 12. Representative Modifications of α-Substituted Ketones and Tertiary Homoallylic Alcohol Products[a]



[a]Reactions were performed under N_2 atm. Conversion (nitrile disappearance; >98% in all cases) was determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). Yields correspond to purified products (±5%). Enantioselectivities were determined by HPLC analysis (±1%). See the SI for details.

Scheme 13. Enantio- and Diastereoselective Gram Scale Synthesis of a Fragment of Rubriflordilactones A and B[a]



[a]Reactions were performed under N_2 atm. Conversion (nitrile disappearance; > 98% in all cases) was determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). Yields correspond to isolated and purified products (±5%). Enantioselectivities were determined by HPLC analysis (±1%). See the SI for details.

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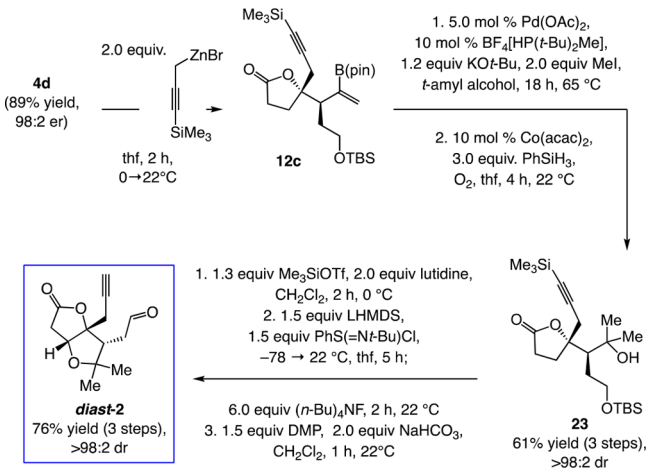
Scheme 14. Enantio- and Diastereoselective Synthesis of a Fragment of 5-*epi*-Rubriflordilactone A and B′′[a]



[a]Reactions were performed under N_2 atm. Conversion (nitrile disappearance; >98% in all cases) was determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). Yields correspond to isolated and purified products (±5%). Enantioselectivities were determined by HPLC analysis (±1%). See the SI for details.

the use of an aldehyde, an ester, or an anhydride. By managing the identity of the nitrile substituent and the organometallic entity that serves as the nucleophile, a sizable assortment of tertiary homoallylic alcohols can be prepared efficiently and in high enantio- and diastereomeric purity in every possible stereoisomeric form. The application to a fragment of rubriflordilactones A and B and a stereoisomeric derivative supports our claim.

The strategies described in this report are likely to impact the way many medicinally relevant organic molecules are synthesized.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c08732.

Experimental details for all reactions and analytic details for all products (PDF)
NMR spectral details (PDF)
Crystallographic data (CIF)
Crystallographic data (CIF)
Crystallographic data (CIF)
Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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