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Selective Formation of Functionalized α-Quaternary Malononitriles toward 5,5-Disubstituted Pyrrolopyrimidinones

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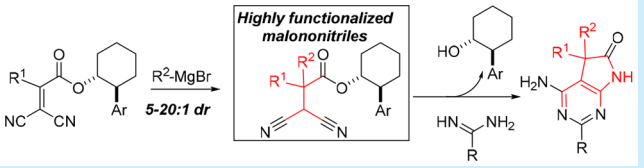
Supporting Information

ABSTRACT: A modular, selective approach to complex α-tertiary substituted malononitriles is reported. The method takes advantage of β-ester-substituted α,α-dinitrile alkenes as highly reactive, chemoselective electrophiles for 1,4-additions with organometallic nucleophiles to produce functionally and sterically dense all-carbon quaternary centers. In the presence of a chiral ester auxiliary bearing an aromatic ring, the 1,4-addition occurs with good to excellent selectivity due to favorable cation−π interactions. The highly functionalized malononitriles represent versatile building blocks and can be applied toward efficient, highly selective syntheses of 5,5-disubstituted pyrrolopyrimidinones.



Pyrrolopyrimidine and -pyrimidinone structural motifs represent a growing class of fused heterocycles of considerable interest in drug development.[1] Compared to closely related indoline or indolinone structural counterparts, substituted pyrrolopyrimidine and -pyrimidinones remain less explored, and general synthetic methods for their preparation and functionalization, while growing, remain limited.[2] Our own efforts to discover a novel class of soluble guanylate cyclase (sGC) stimulators led to the identification of a promising series of 5,5-disubstituted pyrrolopyrimidinones.[3] Leveraging literature precedence first demonstrated for guanidines,[4] pyrrolopyrimidinones of general structure **3** could be assembled in a convergent manner starting from malononitrile **1** and amidine **2** subunits (Figure 1). In this approach, the amidine/guanidine

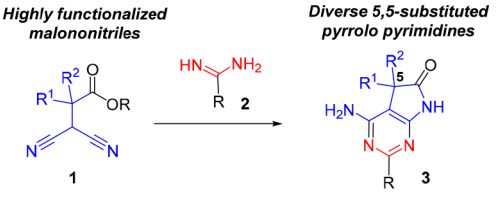


Figure 1. Complex malononitriles in the synthesis of pyrrolopyrimidines.

group condenses with the functionalized malononitrile to form an intermediate aminopyrimidine ring that subsequently reacts with the pendant ester to produce the fused pyrrolidinone ring. While this method enables a convergent approach toward a promising class of 5-substituted pyrrolopyrimidinones, the utility of this method ultimately relies on access to highly functionalized malononitriles.

Complex malononitriles of type **1** represent a significant synthetic challenge due to the requisite reactivity of functional groups and steric congestion at the all-carbon quaternary position.

To address this, we envisioned a modular synthetic strategy to sequentially introduce R^1/R^2 functionalization utilizing 1,4-conjugate addition of carbon nucleophiles to highly activated tetrasubstituted malononitrile alkene **5** (Scheme 1). This

Scheme 1. Strategy To Complex Malononitrile Reagents

approach takes advantage of broadly accessible β-keto esters **4** and commercially available or readily prepared organometallic reagents. Although α,α-dinitrile alkenes are well established partners for 1,4-addition reactions, little has been reported for this reaction with increasingly electron-deficient dinitrile alkenes containing β-ester substitution. While previous examples of reactivity of general structure **5** have largely focused on their use in cycloaddition reactions,[5] an initial report (**5**, $R^1 = CF_3$) disclosed a limited substrate scope for 1,4-addition with unactivated nucleophiles.[6] Based on our interest in this complex malononitrile subunit, we endeavored to explore the reactivity of varied alkenes of type **5** with carbon nucleophiles to generate highly functionalized, sterically dense

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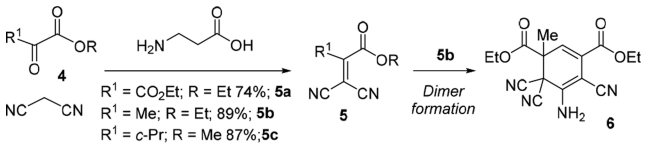
malononitriles affixed to all-carbon quaternary centers. Herein, we report our efforts to access this structural motif, including regioselectivity evaluation, substrate scope, diastereoselective addition mediated by an ester chiral auxiliary, and application toward the synthesis of an enantioenriched 5,5-disubstituted pyrrolopyrimidinone of biological interest.

Substrates **5a** and **5b** were assembled via Knoevenagel condensation and isolated via distillation (Scheme 2).[7] The

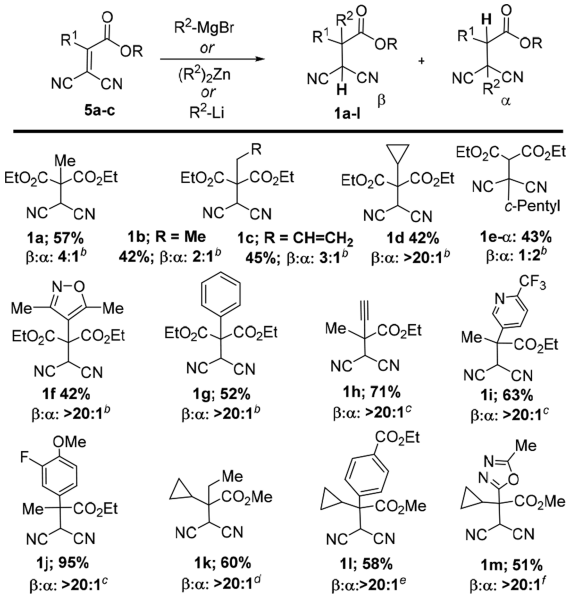
Scheme 2. Synthesis of Alkenes 5a−c



stability of **5b** proved challenging, and care was necessary during isolation to avoid formation of dimerized substrate **6**.[8] In comparison, the *c*-Pr analogue **5c** could be readily isolated as a crystalline, bench-stable solid that did not undergo dimerization.

With the alkenes in hand, the substrate scope and regioselectivity for the 1,4-addition reaction were explored (Scheme 3). Starting with **5a**, the alkene bearing β,β-diester and

Scheme 3. Regioselectivity and Substrate Scope of 1,4-Addition Reaction with Carbon Nucleophiles[a]

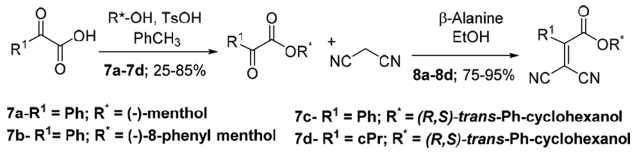


[a]Regioselectivity was determined by crude ^{1}H NMR. Standard conditions utilized commercially available or in situ derived Grignards at 0 to −30 °C in THF unless otherwise noted. [b]Starting material **5a**. [c]Starting material **5b**. [d]From treatment of **5c** with Et_2Zn at −78 °C warming to −40 °C. [e]Starting material **5c**. [f]Treatment of **5c** with in situ derived organolithiate.

dinitrile substitution demonstrated a preference for addition at the position β to the malononitrile.[9] Some trends could be seen, with aliphatic Grignards providing lower levels of regioselectivity, the most drastic example being *c*-pentyl-MgBr that afforded **1e-α** as the major isomer (examples **1a−c,e**). The one exception to this trend was *c*-PrMgBr, which gave high selectivity for the desired isomer. In contrast, sp^2-type nucleophiles proceeded with high selectivity at the β position with **5a**. In the case of Ph-MgBr (**1g**), the high selectivity for the β regioisomer (>20:1) could be reversed via addition of stoichiometric copper to preferentially afford the α-regioisomer.[10] The analogues **5b** and **5c** were similarly reactive and demonstrated consistently high levels of regioselectivity with a range of organometallic reagents including aryl (**1j,l**), heteroaryl (**1i,m**) and even alkyl nucleophiles (**1k**). Impressively, even given the additional steric bulk of the cPr substituent of **5c**, highly steric congested quaternary carbon centers were readily accessed through this method. The exceptional reactivity of these alkenes is further evident in **1k** that can be formed with $ZnEt_2$ at cryogenic temperatures.

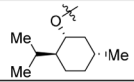
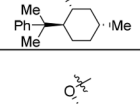
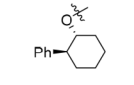
Having established the utility and regioselectivity of the method to access diverse prochiral and racemic malononitriles, we turned our focus to the asymmetric synthesis of the 1,4-adducts. Given the high reactivity of the alkenes with organometallic reagents, we focused on a chiral auxiliary approach to access diastereomerically enriched malononitriles. Starting with commercially available chiral alcohols, alkenes bearing the ester auxiliaries were readily prepared via acid-catalyzed esterification of α-ketoacids followed by Knoevenagel condensation with malononitrile to provide moderate to good yields of **8a−d** (Scheme 4).

Scheme 4. Synthesis of Alkenes Bearing Ester Auxiliary



Initial attempts at diastereoselective addition with menthol ester **8a** proved disappointing in which a near 1:1 mixture of diastereomers was observed for methyl and aryl Grignard reagents (Table 1, entry 1 and 2). Phenyl-substituted menthol analogue **8b** failed to improve diastereoselectivity with methyl Grignard (entry 3) and unexpectedly proved unreactive with

Table 1. Stereoselectivity with Chiral Ester Auxiliaries[a]

entry	OR*	R1	R2	ex	dr
1[b]		Ph-**8a**	Me	**9a**	1.2:1
2[c]		Ph-**8a**	2-MeOPhMgBr	**9b**	1.2:1
3[b]		Ph-**8b**	Me	**9c**	1:1
4[c]		Ph-**8b**	2-MeOPhMgBr	**9d**	NR
5[b,g]		Ph-**8c**	Me	**9e**	6:1
6[d,g]		Ph-**8c**	*c*-Pr	**9f**	>20:1
7[b]		*c*-Pr-**8d**	Me	**9g**	1.5:1
8[e]		*c*-Pr-**8d**	2-MeOPhMgBr	**9h**	>20:1
9[f]		*c*-Pr-**8d**	Ethyne	**9i**	>20:1

[a]Diastereomeric ratio (dr) was determined by crude ^{1}H NMR or chiral supercritical fluid chromatography (SFC). Standard conditions utilize commercially available or in situ derived Grignards in THF; see the Supporting Information for details. [b]MeMgCl, −78 °C. [c]2-MeOPhMgBr, −78 °C. [d]*c*-PrMgBr, −40 °C. [e]2-MeOPhMgBr, −40 °C. [f]EthynylMgBr, 0 °C. [g]Absolute stereochemistry of **8c** was confirmed by vibrational circular dichroism (VCD); see the SI.

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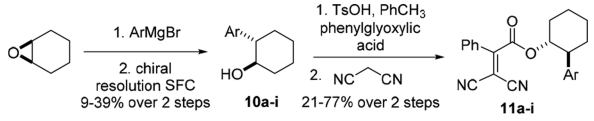
larger nucleophiles (entry 4). Moving to ester auxiliary **8c**, we reasoned that closer proximity of the phenyl ring of the chiral ester appendage to the site of 1,4-addition may improve facial selectivity through improved conformational bias resulting from potential π-stacking interactions with the alkene.[11] Gratifyingly, treatment of **8c** with Me-MgCl provided a modest 6:1 diastereomeric ratio (dr) (**9e**). Furthermore, excellent diastereoselectivity was observed for larger alkyl nucleophiles leading to **9f** in >20:1 diastereoselectivity. When R = *c*-Pr (entries 7−9), diastereoselectivity was significantly reduced for methyl Grignard addition (**9g**) but showed similarly high selectivities for aryl (**9h**) and ethynyl (**9i**) nucleophiles.

Given the initial success with the *trans*-phenylcyclohexanol-based ester **8c**, we rationalized that substitution on the phenyl ring of phenylcyclohexanol could further improve diastereoselectivities by affording a greater conformational bias. A focused set of analogues to test this hypothesis were synthesized and evaluated with our most challenging nucleophile, methyl Grignard (Scheme 5). To enable rapid evaluation of varied

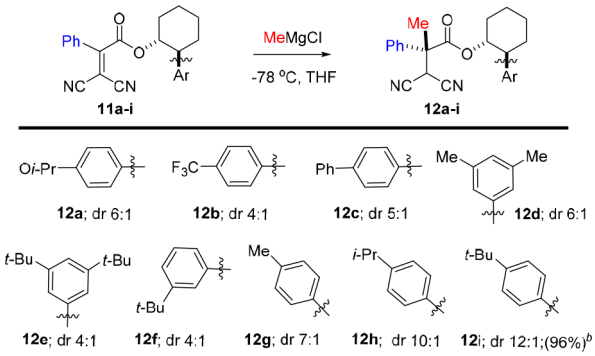
Scheme 5. *trans*-Phenylcyclohexanol Analogue Synthesis



auxiliaries, a simple high-throughput route to the custom chiral alcohols was leveraged, starting with addition of an aryl Grignard to cyclohexene oxide. The racemic *trans*-alcohols were then readily separated via supercritical fluid chromatography (SFC),[12] reacted with phenylglyoxylic acid, and condensed with malononitrile to provide single enantiomer alkenes **11a−i**.

With substituted aryl *trans*-cyclohexanoate auxiliaries in hand, stereoselectivity for 1,4-conjugate addition with methyl Grignard was explored (Scheme 6). Substrate scope included

Scheme 6. Stereoselectivity for 1,4-Addition with 2-Hydroxyphenyl-Substituted Auxiliary Analogues[a]



[a]All diastereoselectivities were determined by chiral SFC. [b]Isolated yield.

electron-donating and electron-withdrawing substituents and compounds with varying patterns of steric bulk at the 3−5 position of the aryl ring. A clear trend was observed with increasing alkyl steric bulk at the 4-position as Me (**11g**) → *i*-Pr (**11h**) → *t*-Bu (**11i**) provided incremental improvements in selectivity affording up to a 12:1 selectivity with the *tert*-butyl substituent. Interestingly, this same selectivity was not observed with the 4-substituted Ph (**11c**), CF_3 (**11b**), and O-*i*-Pr (**11a**) substrates. Similarly, substitution of Me/*t*-Bu at the 3- and 3,5-positions appeared to afford no improvement in selectivity.[13] In general, yields were high for the 1,4-addition reaction of methyl Grignard with **11i** affording both good diastereoselectivity (12:1) and high yield (96%) in the formation of **12i**.

Structural models for select transition states were studied by DFT computations to investigate factors governing the selectivity of the aryl-containing chiral auxiliaries. Exploring several conditions,[14] proper selectivity ratios were only obtained when dimeric Me-MgCl was included, as depicted in Figure 2. Several density functionals were investigated, and it

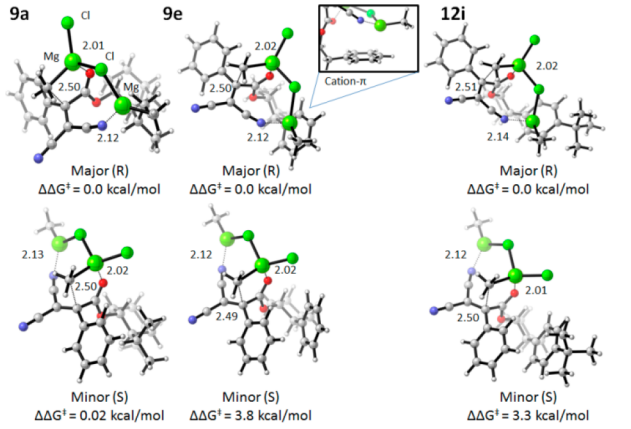


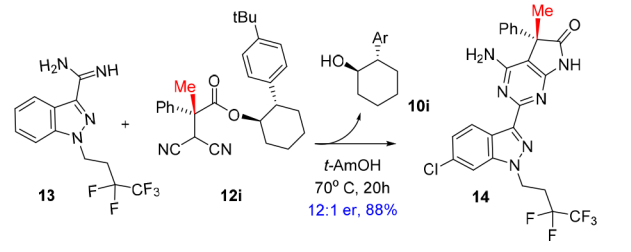
Figure 2. Transition-state structures calculated at the M06-2X/6-31G** level with SMD implicit THF. Bond distances are for dashed lines.

was determined that quasiharmonic corrected free energies[15] calculated with M06-2X/6-31G** with SMD implicit THF agreed best with experimental data.[16]

Example **9a**, containing a chiral auxiliary with an isopropyl group *trans* to the ester substituent provided no diastereoselectivity following 1,4-addition consistent with calculations, which showed the relative free energy difference in the two transition states to be 0.0 kcal/mol. Alternatively, auxiliaries which have an aryl group *trans* to the ester (such as **9e** and **12i**) enable a favorable cation−π interaction between the second Me-MgCl of the dimer and the auxiliary (Figure 2). The estimated preference for the (*R*) configuration shifts from 0.0 to 3.3 or 3.8 kcal/mol. The energy differences overpredict the observed selectivity potentially due to other active forms of the nucleophile that were found to be nonselective in our model.

With diastereomerically enriched **12i**[17] in hand, application of the reagents toward the synthesis of 5,5-disubstituted pyrrolopyrimidine sGC stimulator **14** was investigated (Scheme 7). Coupling **12i** with amidine **13** under mild conditions afforded the desired substrate in high yield and with an

Scheme 7. Enantioenriched Synthesis of an sGC Stimulator



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enantiomeric ratio (er) of 12:1 consistent with the selectivity of **12i**. In the process of the transformation, the ester auxiliary **10i** is cleaved and can be recovered during purification.[18] The method enables access to substrates of type **14** without any additional linear steps and represents a significant improvement in overall yield of **14**.[19]

In summary, regioselective 1,4-conjugate addition with organometallic reagents to highly activated, tetrasubsituted α,α-dinitrile alkenes affords a general, flexible approach to highly functionalized, sterically congested malononitrile building blocks. Good to excellent stereoselectivity was achieved with ester-based chiral auxiliaries, affording up to >20:1 diastereomeric ratios for a variety of nucleophiles. The high selectivity observed with aryl-containing auxiliaries is attributed to cation$-\pi$ interactions between the Grignard dimer and the auxiliary. While these synthons should be of broad synthetic utility, they bear strong application in the preparation of 5,5-disubstituted pyrrolopyrimidines and -pyrimidinones, a class of bioactive molecules of considerable interest as exemplified by **14**.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01930.

X-ray data for compound **14** (CIF)

Experimental details, characterization data, and NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(8) (a) Formation of dimer of **5b** was reported, but a structure was not proposed; see ref 7. (b) Formation of byproduct **6** was accelerated when stored neat or at room temperature for prolonged periods of time. Compound **5b** was stored as a 1 M solution in benzene at −4 to −20 °C.

(9) This selectivity trend is in line with previous reports of reactions with substrate **5a** in which the position β to the dinitrile appears to react preferentially. See ref 5a,b.

(10) 5:1 α/β selectivity was observed; see the SI.

(11) For an example of phenylcyclohexanol as a chiral ester appendage on a kilogram scale, see: Song, J. J.; Tan, Z.; Xu, J.; Reeves, J. T.; Yee, N. K.; Ramdas, R.; Gallou, F.; Kuznich, K.; DeLattre, L.; Lee, H.; Feng, X.; Senanyake, C. H. *J. Org. Chem.* **2007**, *72*, 292.

(12) SFC separation was used to prepare enantiomerically pure auxiliaries, but chiral syntheses have been reported.

(13) 2-Substituted aryl analogues were prone to elimination during ester formation step with the alcohol and phenylglyoxylic acid.

(14) See the SI.

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(17) The absolute stereochemistry of **12i** was assigned according to the known stereochemistry of **8c** and **14**. Both **12i** and **8c**→**9e** led to the same enantiomer of **14**.

(18) See the SI for details.

(19) The absolute configuration of **14** was determined by X-ray crystallography, and the enantiomer formed was evaluated by SFC chiral chromatography; see the SI.

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