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1,2,4-Trifunctionalized Cyclohexane Synthesis via a Diastereoselective Reductive Cope Rearrangement and Functional Group Interconversion Strategy

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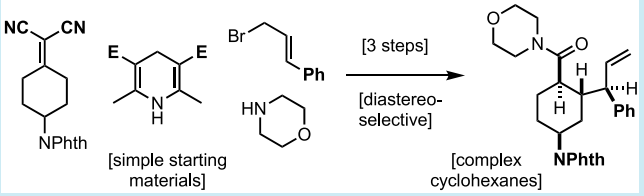
ABSTRACT: Polyfunctionalized cyclohexanes are privileged scaffolds in drug discovery. Reported herein is a method for synthesizing 1,2,4-trifunctionalized cyclohexanes via diastereoselective reductive Cope rearrangement. The scaffolds obtained can be derivatized by orthogonal functional group interconversion to cyclohexanes bearing a 1-amide, 2-branched arylallyl, and variable 4-functional group.



Polysubstituted cyclohexanes bearing pharmaceutical-relevant functionality (e.g., combinations of carboxylic acid derivatives, amines, (hetero)aromatics, aliphatics, etc.) are valuable scaffolds in drug discovery. Desirable qualities include the rigid nature of the ring, locked positioning of the functional groups, and three-dimensionality that the sp^3-rich chairlike structure imparts.[1−4] While the 1,4-disubstitution pattern is extremely common (e.g., Oclacitinib,[5] Nateglinide,[6] Cariprazine,[7] Atovaquone,[8] Velneperit,[9] Balovaptan,[10] Candoxatril,[11] among many others), analogous trisubstituted cyclohexanes are rare (Figure 1A). A potential reason for this is that while the necessary building blocks for constructing 1,4-difunctionalized cyclohexanes are abundantly available, the trifunctionalized variants are comparatively less so. For example, this substitution pattern has been accessed for drug discovery from Hagemann's ester[12] (en route to BMS-986251) and by Diels−Alder cycloaddition[13] (en route to CAS: 1350711-03-3). Other ways to access this and related cyclohexane substitution patterns include arene hydrogenation,[14−22] conjugate addition,[23−25] and C−H functionalization[26−31] (Figure 1B). That said, all of these routes have their own unique challenges and limitations (e.g., stereoselectivity, functional group compatibility).

With an emphasis on pharmaceutical-like functionality, reported herein is the development of a reductive Cope rearrangement-centered route toward 1,2,4-trisubstituted cyclohexanes that bear appropriate functional groups for late-stage divergence into complex and unique drug-like leads. Specifically, it was envisaged that readily available 1,5-dienes **1** (Scheme 1A), while not being thermodynamically favored to undergo Cope rearrangement to **2**, can be driven forward by chemoselective reduction (Scheme 1B). We previously reported the "reductive Cope rearrangement" concept,[32] but herein we address unique stereochemical considerations, expand the scope to ketone-derived (and prochiral)

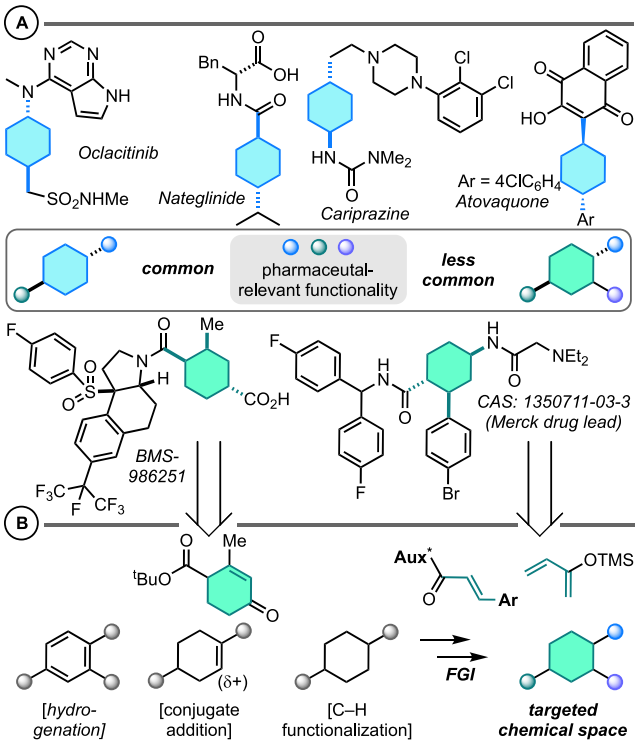


Figure 1. (A) Comparison of 1,4-disubstituted and trisubstituted drug-like space. (B) Methods to access this substitution pattern.

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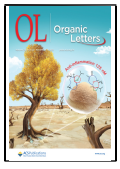

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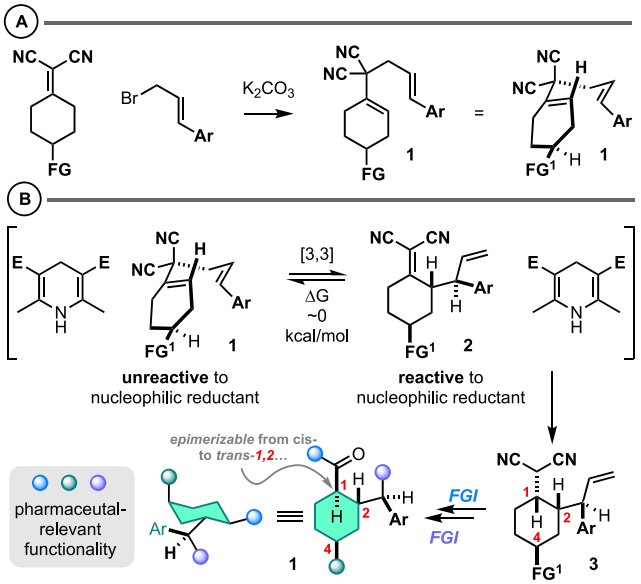
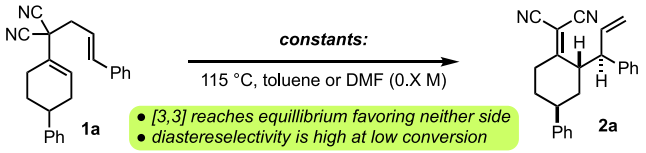
Scheme 1. This Report: Diastereoselective Reductive Cope Rearrangement Yields Trisubstituted Cyclohexanes



alkylidenemalononitriles, and contribute a convergent and divergent route toward challenging trisubstituted cyclohexane drug-like molecules.

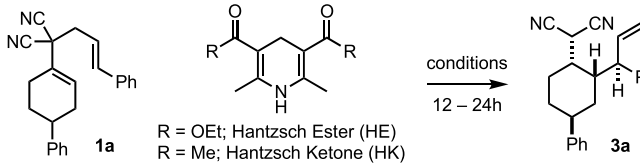
At the outset of our studies, we already appreciated the inherent kinetic, thermodynamic, and stereochemical challenges associated with the Cope rearrangement of 6-functionalized-3,3-dicyano-1,5-dienes. Solutions we have previously reported for achieving Cope rearrangement include the use of "promoting groups"[33,34] and the "reductive Cope rearrangement",[32,35] the latter of which is particularly relevant to this work. Thus, we were not surprised to find that model substrate **1a** yielded [3,3] equilibrium mixtures of **1a** and **2a** with decreasing diastereoselectivity with time (Table 1). That said, we were intrigued by the high diastereoselectivity in the early stages of transformation (20:1 dr after 5 min, Table 1, entry 1, in DMF solvent). Specifically, *we sought conditions that could diastereoselectively reduce the in situ generated alkylidene faster than epimerization*. If found, then complete, stereoselective conversion to tetra-stereogenic, 1,2,4-trifunctionalized cyclohexanes would be possible. Indeed, we were pleased to find after some optimization that the reductive Cope rearrangement proceeded with 100% conversion to the reduced Cope product in 12.4:1.0:0.7 dr (Table 2, entries 4 and 8). While eight diastereomers are possible, the major diastereomer is one of only three diastereomers by crude NMR analysis. As shown in entries 4 and 8, the optimized conditions utilize 20 equiv of a dihydropyridine reductant (Hantzsch ester (HE, entry 4); Hantzsch ketone (HK, entry 8)), in DMF at 100 °C. Changes from these optimal conditions, including temperature, concentration, solvent, and equivalents of reductant, yielded inferior results.

Table 1. Cope Rearrangement Has No Thermodynamic Preference for One Side of the Equilibrium or the Other and Epimerization Occurs



entry	time	Toluene		DMF	
		conv. (%)	d.r.	conv. (%)	d.r.
1	5 min	3.8	20:01	9.1	20:01
2	10 min	10.7	20:01	15.3	9.1:1
3	30 min	16.7	10:01	29.6	5.9:1
4	1 hr	25.9	8.5:1	38.3	3.1:1
5	2 hr	27.8	7:01	44.4	2.4:1
6	3 hr	32.3	3.3:1	45.5	2.2:1
7	4 hr	29.5	3.1:1	46	1.8:1
8	5 hr	28.4	2.6:1	47.4	1.9:1
9	6 hr	32.7	2.1:1	47.9	1.8:1

Table 2. Reductive Cope Rearrangement Can Promote the [3,3] Step with Stereochemical Fidelity



Entry	Reductant	Solvent	Conc. (M)	Temp. (°C)	d.r.
1	5 equiv. HE	DMF	0.2	100	5.8:1.0:0.5
2	5 equiv. HE	DMF	0.1	115	6.0:1.0:0.3
3	10 equiv. HE	DMF	0.1	100	7.7:1.0:0.5
4	20 equiv. HE	DMF	0.1	100	12.4:1.0:0.7
5	5 equiv. HE	tol	0.1	115	2.7:1.0:0.3
6	5 equiv. HE	EtOH	0.1	100	4.9:1.0:1.0
7	10 equiv. HK	DMF	0.1	100	8.3:1.0:0.6
8	20 equiv. HK	DMF	0.1	100	12.3:1.0:0.2

With conditions in hand for achieving diastereoselective reductive Cope rearrangement, we turned to the scope of the reaction (Scheme 2). Notably, the necessary starting materials **1** are readily available for 4-substituted-cyclohexylidene malononitriles and cinnamyl bromides (see Scheme 1A). We opted to report a two-step procedure capped with an oxidative amidation[36] reaction as the reduced Cope products often could not be separated from the reductant and/or its byproduct pyridine, which complicated isolation and characterization. We found that, within the scope examined, trifunctionalized cyclohexanes **4a**–**4o**, could be prepared with a range of yields and diastereoselectivity. While the reductive Cope rearrangement produced three diastereomers (major and two minors), following oxidative amidation only two diastereomers were observed, suggesting epimeric convergence for two of the diastereomers. Further, when synthesizing Weinreb amides, in many cases, the diastereomeric ratio had a notable improvement. This is likely due to the epimeric convergence, but also improved chromatographic separation of the amide diastereomers. The mild reductant (Hantzch ester (**HE**) or Hantzsch ketone (**HK**)) was tolerant to various 4-functional groups including phenyl, aliphatics, esters, amides, and phthalimides. There was also a decrease in diastereoselectivity for both

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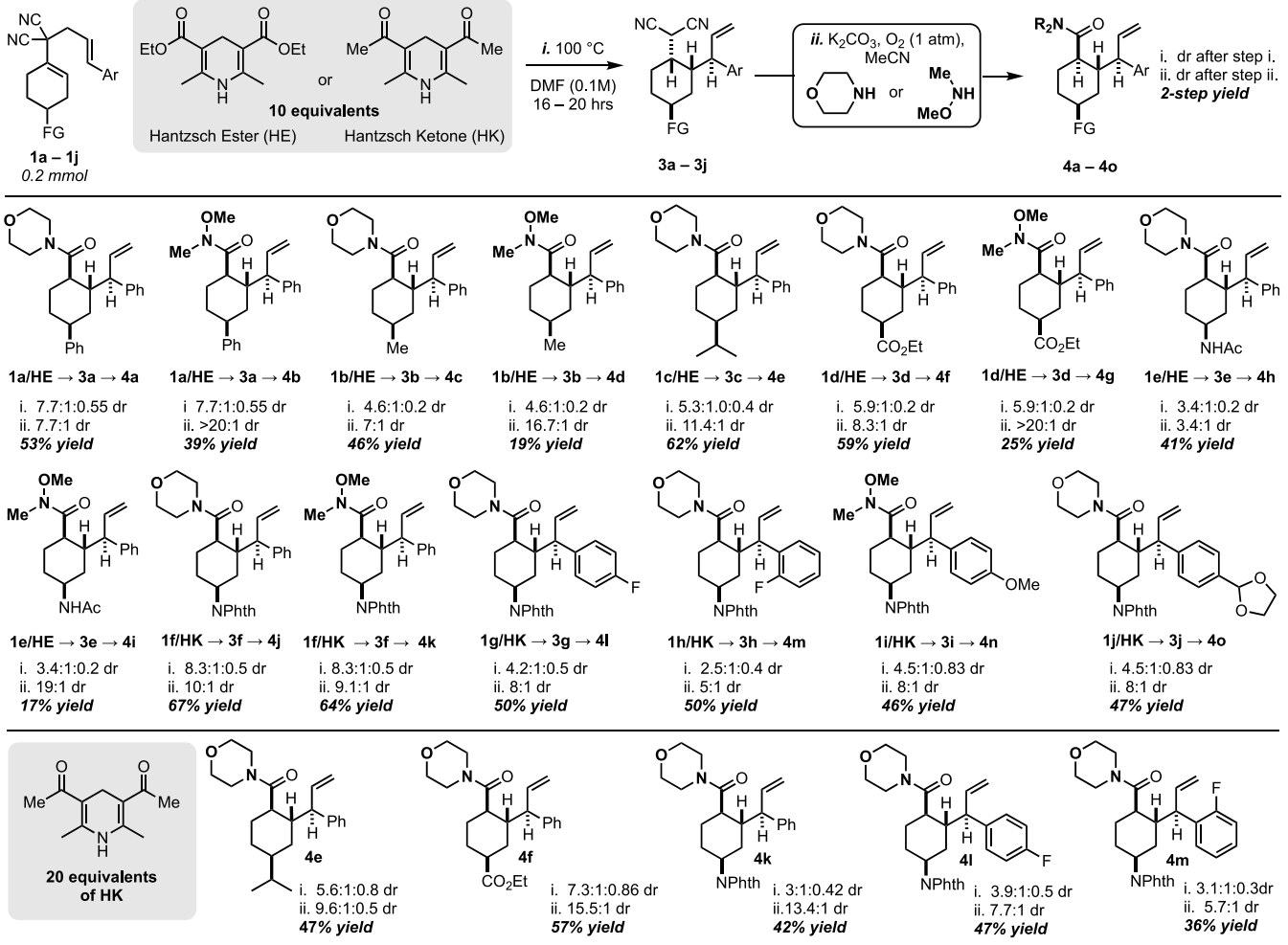
Scheme 2. Scope of the Reductive Cope Rearrangement/Oxidative Amidation Sequence

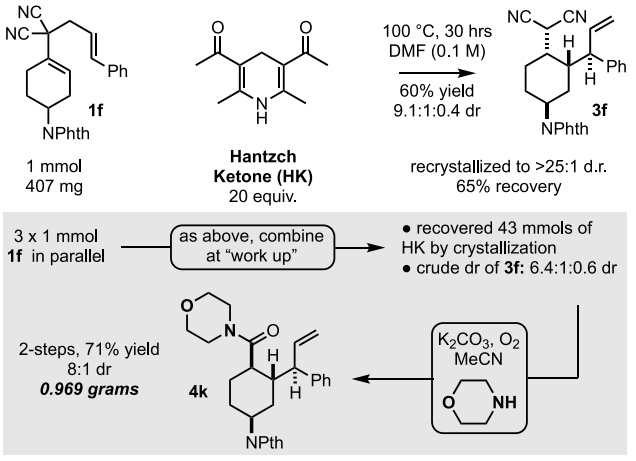


electron-rich and -poor arenes (**3g**–**3j**); however, good yields and increased diastereoselectivity were observed post-amidation (**4l**–**4o**), again, likely a result of epimeric convergence and chromatographic separation. Ultimately, the process can yield many combinations of trifunctionalized cyclohexanes with practical yields and diastereoselectivity in many of the cases from the scope study.

To be most valuable, it was deemed necessary to showcase that gram amounts of material could be prepared for divergent synthesis. In this regard, attempted scale up procedures (5 and 10 mmol) were unsatisfactory providing decreased diastereoselectivity as well as challenges associated with removal of the excess reductant and byproduct pyridine. For batch chemistry, the optimized conditions were only reproducible up to 1 mmol scale (Scheme 3A). Thus, we opted to run 3 × 1 mmol scale reactions in parallel, which yielded a near-gram quantity of **4k** (71% yield, 8:1 dr) by the standard procedure (Scheme 3B). Notably, in these scale-up studies, we also were able to confirm that the excess Hantzsch ketone could be collected in high purity via crystallization (43 mmol (theoretical = 57 mmol); 75% recovery) and recycled.

With a method in hand for producing gram quantities of the reduced Cope products (Scheme 3), the next goal was to demonstrate how these scaffolds can be rapidly diverted to trifunctionalized drug-like cyclohexanes (Scheme 4). In Scheme 4A, we utilized a diastereomerically pure substrate

Scheme 3. Scalability of the Sequence



3f, whereas, in Scheme 4B, substrate **3f** with 11.9:1 dr was examined. First, oxidative amidation[36] of the diastereomerically pure **3f** with a representative 2°-amine (morpholine) resulted in good yields and, surprisingly, epimerization of the α-amide stereocenter on **4j** (Scheme 4A). **3f** obtained as an 11.9:1 diastereomeric mixture also converges to a single amide **4j** (Scheme 4B). We propose that epimerization occurs via enolization of either intermediate acyl cyanide or the resulting

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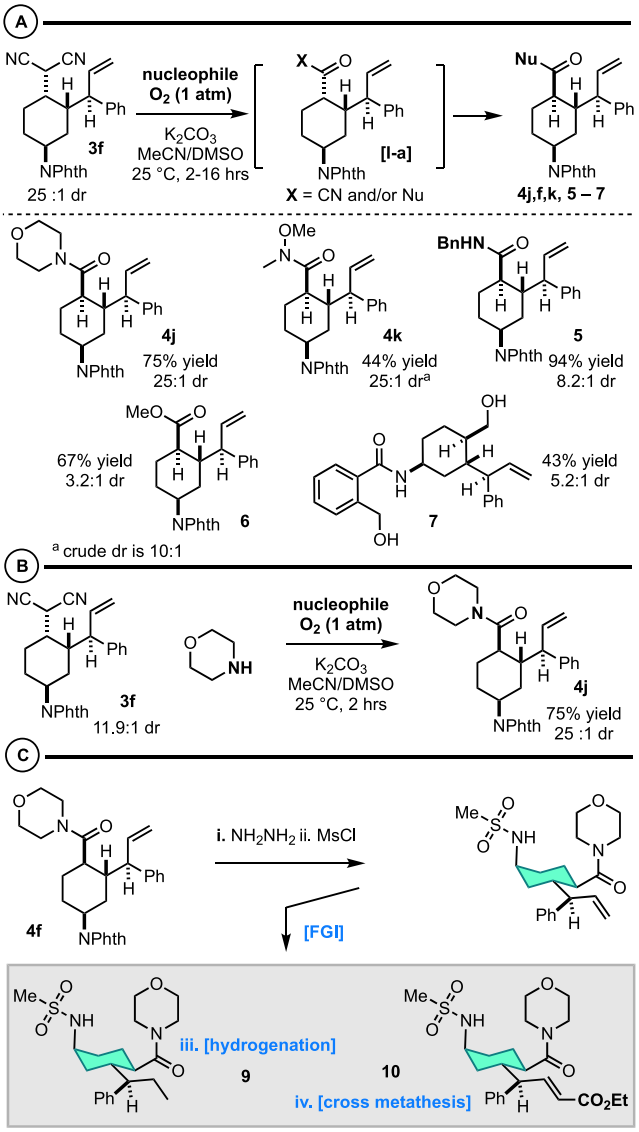
Scheme 4. Divergent Functional Group Interconversion of the Malononitrile, Alkene, and Phthalimide Functional Groups: (A) Oxidative Amidation, Oxidative Esterification, and Redox Interconversion of Malononitriles; (B) Diastereomeric Mixtures of Malononitriles Can Converge via Oxidative Amidation; (C) Complete Functional Group Interconversion to Functionally Dense Drug-like Cyclohexanes



i. 5 equiv. $NH_2NH_2 \bullet H_2O$, MeOH (0.05M), 70 °C, 1.5h, ii. 2 equiv. MsCl, 4 equiv. Et_3N, CH_2Cl_2 (0.1M), 0 °C - rt, 2h, ***73% yield (2 steps)*** iii. 10% Pd/C, H_2 (1 atm), MeOH (0.05M), rt, 4h, ***82% yield***. iv. 4 equiv. ethyl acrylate, 15 mol% HG-II, tol (0.2M), 80 °C, 16h, ***42% yield***.

amide. In terms of scope, we were also able to produce a Weinreb amide **4k** with high diastereoselectivity. Primary amines and alcohols[37] were less diastereoselective en route to **5** and **6**, respectively. Redox interconversion[38] of **3f** to the primary alcohol **7** was also achieved with moderate diastereoselectivity. Notably, under these conditions, $NaBH_4$ also partially reduced the phthalimide.[39] Next, we aimed to demonstrate that the *other* functional groups can be manipulated in sequence resulting in a divergent route to novel, functionally dense, drug-like cyclohexanes (Scheme 4C). In this regard, we examined model substrate **4f**. The phthalimide can be deprotected and refunctionalized (e.g., sulfonylation) yielding **8**. The alkene functionality can be manipulated in various ways including hydrogenation (**9**) and cross metathesis[40,41] (**10**). This results in the synthesis of cyclohexanes with a dense array of functionality.

In conclusion, described herein is a straightforward sequence toward densely functionalized trisubstituted cyclohexanes whereby a key diastereoselective reductive Cope rearrangement yields cyclohexane building blocks decorated with a 1-malononitrile, 2-branched arylallyl moiety, and variable 4-functional group. Straightforward iterative functional group interconversion can yield unique and complex drug-like scaffolds. We envisage this chemistry to be useful in generating new leads in drug discovery campaigns. In future studies, we aim to further increase the scope, diastereoselectivity, and enantioselectivity of the overall process.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c03310.

Experimental procedures and characterization data (^{1}H NMR, ^{13}C NMR, HRMS, X-ray) (PDF)

Accession Codes

CCDC 2112743 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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