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Highly Diastereoselective α-Arylation of Cyclic Nitriles

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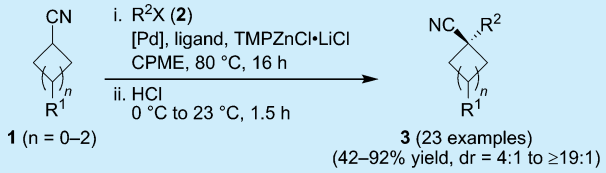
Supporting Information

ABSTRACT: A highly diastereoselective α-arylation of cyclic nitriles has been developed via a Negishi cross-coupling of commercially available aryl, heteroaryl, and alkenyl halides with cyclobutyl nitriles in the presence of tetramethylpiperidinylzinc chloride lithium chloride (TMPZnCl•LiCl) and catalytic XPhos-Pd-G2. A variety of electronically diverse electrophiles were well tolerated, and this chemistry was further advanced with application of both cyclopropyl and cyclopentyl nitriles.



1,1,3,3-Tetrasubstituted cyclobutanes are structural motifs that have garnered significant attention within the synthetic and medicinal chemistry communities in recent years.[1] For example, such motifs have been shown to function as potential TRPV3 agonists[2a] and inhibitors of Akt[2b] (Figure 1).

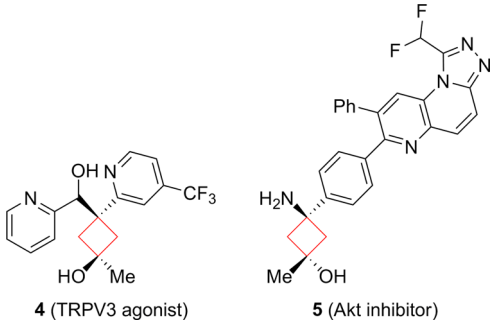
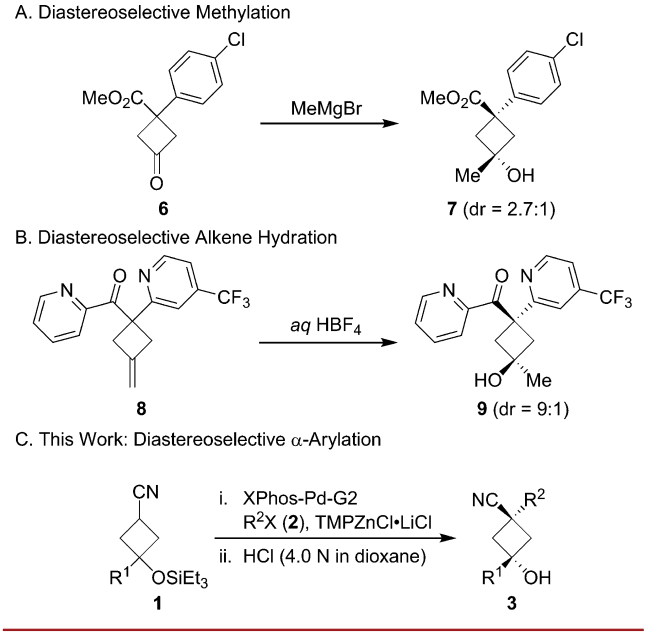


Figure 1. Biologically active 1,1,3,3-tetrasubstituted cyclobutanes.

Recently, there have been various methods developed toward the synthesis of these 1,1,3,3-tetrasubstituted cyclobutane analogues, each invoking a different final disconnection (Scheme 1).[2] For example, a diastereoselective methylmagnesium bromide addition to cyclobutanone **6** was reported in 2012.[2b] However, this process afforded only modest diastereoselectivity toward the desired *trans* diastereomer (i.e., with respect to the spatial relationship between the alkyl and aryl groups; dr = 2.7:1), not to mention the necessity of cryogenic conditions (Scheme 1A). While they were able to dramatically improve the selectivity (dr >20:1) via replacement of the methyl ester group with the much smaller nitrile, our studies have shown this to be highly dependent on the substitution pattern of the arene. In late 2016, a diastereoselective alkene hydration of **8** was demonstrated, although this method favored the *cis* diastereomer (dr = 9:1, Scheme 1B).[2a]

In order to support an internal drug research and development program in our laboratories, we sought to develop a highly diastereoselective method to synthesize the *trans* diastereomer of cyclobutanol **3** for structure–activity relationship (SAR) studies. Since initial studies centered on organometallic addition to the cyclobutanone precursor proved unsuccessful for our target molecule of interest (dr ≤3:1), we envisioned α-arylation of the cyclobutyl nitrile as an alternate disconnection, with the potential to invoke both substrate and catalyst control on the diastereoselectivity (Scheme 1C).[3] While the α-arylation of nitriles has had limited focus due to their decreased acidity relative to the analogous ketones,[4]

Scheme 1. Diastereoselective Strategies toward 1,1,3,3-Tetrasubstituted Cyclobutanes



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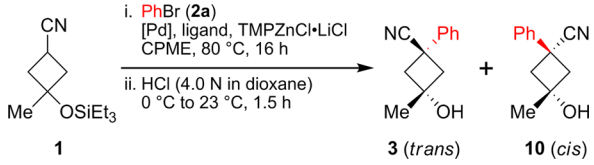
recent work has showcased its application toward the synthesis of 1,1-disubstituted cyclopropyl nitriles.[5] Herein, we now describe the first highly *trans* selective synthesis of 1,1,3,3-tetrasubstituted cyclobutyl nitriles **3** via α-arylation of **1** with aryl, heteroaryl, and alkenyl halides **2**.

We initiated our studies by examining the α-arylation reaction between 3-methyl-3-((triethylsilyl)oxy)cyclobutane-1-carbonitrile (**1**) and bromobenzene (**2a**) to form both *trans* (**3**) and *cis* (**10**) diastereomers of 3-hydroxy-3-methyl-1-phenylcyclobutane-1-carbonitrile (Table 1). Initial use of literature

Table 1. Optimization of α-Arylation[a,b]



1 | 3 (*trans*) | 10 (*cis*)

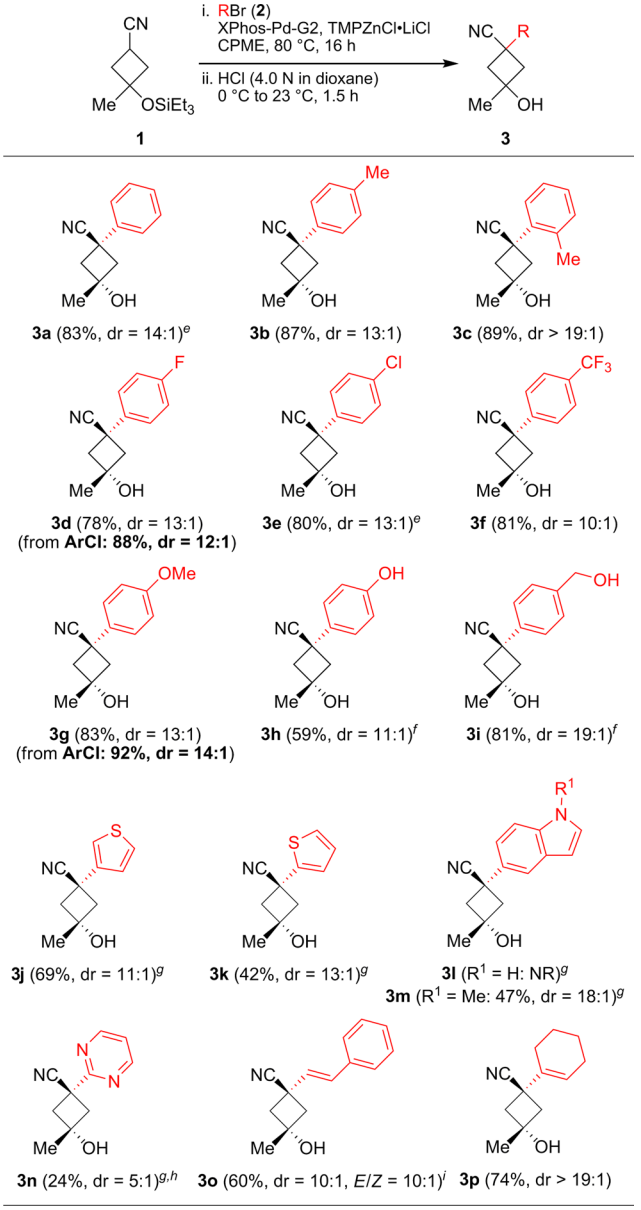
entry	[Pd] (mol %)	ligand (mol %)	yield[c] (%)	dr[d] (3/10)
1[e,f]	Pd_2dba_3 (5)	BINAP (10)	74	3:1
2[f]	Pd_2dba_3 (5)	BINAP (10)	57	6:1
3[f]	Pd_2dba_3 (5)	XantPhos (10)	69	10:1
4	Pd_2dba_3 (5)	XantPhos (10)	85	11:1
5	Pd_2dba_3 (5)	XPhos (10)	80	12:1
6	Pd_2dba_3 (5)	RuPhos (10)	63	10:1
7	XPhos-Pd-G2 (10)		76	14:1
8	XPhos-Pd-G2 (2.5)		86 (83)[g]	14:1

[a]Reactions were performed in duplicate on a 1.5 mmol scale. [b]Reaction conditions: **1** (1.8 mmol, 1.2 equiv), **2** (1.5 mmol, 1.0 equiv), [Pd], ligand, TMPZnCl•LiCl (1.8 mmol, 1.2 equiv, 0.65 M in THF), CPME (4.2 mL, 0.37 M), 80 °C, 16 h in sealed vials under N_2 atmosphere, followed by HCl (4.0 N in dioxane, 1.9 mL, 5.0 equiv), 0 °C to 23 °C, 1.5 h. [c]Yield was determined by HPLC analysis using anisole as standard. [d]dr was determined by HPLC. [e]LiHMDS (1.8 mmol, 1.2 equiv, 1.0 M in THF) was used instead of TMPZnCl•LiCl. [f]THF (4.2 mL, 0.37 M) was used instead of CPME. [g]Number in parentheses is an isolated yield.

conditions with LiHMDS as base provided efficient reaction (74% yield),[5] albeit in only modest diastereoselectivity (dr = 3:1; entry 1). Hypothesizing that this poor diastereoselectivity could be explained by either the hard nucleophilic character of the resulting metalated nitrile or the $(Me_3Si)_2NH$ byproduct inhibiting the Pd-catalyzed coupling reaction,[6] we envisioned that switching to a zinc−amide base could improve the diastereoselectivity and functional group compatibility. Gratifyingly, use of TMPZnCl•LiCl[7] with Pd_2dba_3 as precatalyst and BINAP as ligand was immediately met with success (57% yield and dr = 6:1; entry 2). Use of XantPhos as ligand, with a larger bite angle than BINAP (108° vs 87°),[8] further improved diastereoselectivity (dr = 10−11:1), and the yield could be further increased to 85% by switching to CPME as solvent (entries 3 and 4). Switching to monodentate phosphine ligands revealed that the sterically encumbered XPhos further improved the diastereoselectivity to 12:1 while maintaining high yield (80% yield; entry 5), while RuPhos resulted in lower yield and diastereoselectivity (63% yield and dr = 10:1; entry 6). Use of the precatalyst XPhos-Pd-G2 (10 mol %) was found to further increase the diastereoselectivity to 14:1, and decreasing the catalyst loading to 2.5 mol % had a negligible effect on both the reaction efficiency and diastereoselectivity (85% yield and dr = 14:1; Table 1, entries 7 and 8).

With optimized conditions in hand, we set out to explore the scope of this Negishi cross-coupling reaction through the reaction of 3-methyl-3-((triethylsilyl)oxy)cyclobutane-1-carbonitrile (**1**) with a variety of aryl bromides. Many substrates showed good reactivity under standard reaction conditions (Scheme 2, entries **3a**−**l**). Electronically neutral toluene-based aryl bromides **2b,c** were well tolerated, with high yields and

Scheme 2. Electrophilic Scope of α-Arylation Reaction[a−i]



[a]Reactions were performed in duplicate on a 1.5 mmol scale. [b]Reaction conditions: **1** (1.8 mmol, 1.2 equiv), **2** (1.5 mmol, 1.0 equiv), XPhos-Pd-G2 (2.5 mol %), TMPZnCl•LiCl (1.8 mmol, 1.2 equiv, 0.65 M in THF), CPME (4.2 mL, 0.37 M), 80 °C, 16 h in sealed vials under N_2 atmosphere, followed by HCl (4.0 N in dioxane, 1.9 mL, 5.0 equiv), 0 °C to 23 °C, 1.5 h. [c]Isolated yields. [d]The structure of the major diastereomer is shown, with the dr of the crude reaction mixture being determined by HPLC. [e]Major diastereomer was confirmed by single-crystal X-ray crystallographic analysis. [f]2.2 equiv of TMPZnCl•LiCl was used. [g]10 mol % of XPhos-Pd-G2 was used. [h]dr as determined by ^{1}H NMR analysis of the crude reaction mixture. [i]*E*/*Z* ratio determined by HPLC analysis of crude reaction mixture.

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Org. Lett. XXXX, XXX, XXX−XXX

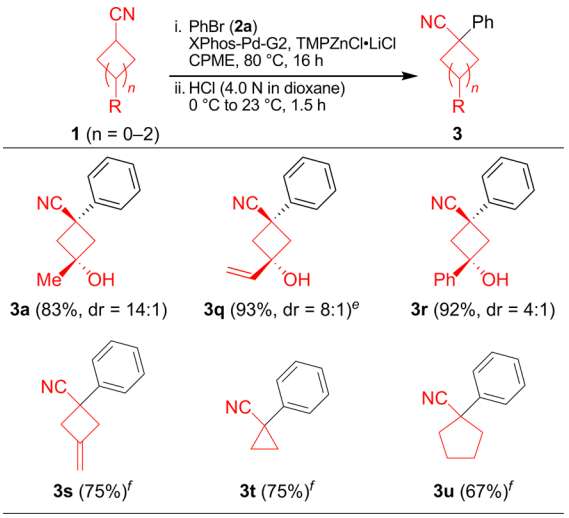
diastereoselectivity obtained despite steric hindrance imposed by the 2-Me group (87−89% yield, dr ≥13:1; Scheme 2, **3b**,**c**). Furthermore, aryl bromides containing both electron-donating and electron-withdrawing groups underwent successful α-arylation, providing moderate to high yields (59−83%) and diastereoselectivity (dr ≥10:1) of coupled products (Scheme 2, **3d**−**h**). The product **3e** formed via reaction with 1-bromo-4-chlorobenzene **2e** provided selective coupling with the bromide, thus allowing the chloride to be a useful handle for further derivatization. Interestingly, although aryl chlorides are often challenging coupling partners due to their slow oxidative addition to the active catalyst,[9] we were pleased to find that both 1-chloro-4-fluorobenzene and 4-chloroanisole were suitable coupling partners under standard reaction conditions, providing both **3d** and **3g** in comparable yields (88−92% vs 78−83%) and diastereoselectivity (dr ≥12:1 vs dr = 13:1). As the previous work using LiHMDS showed incompatibility of 4-bromophenol **2h** in their α-arylation reaction,[5] we were pleased to find both **2h** and 4-bromobenzyl alcohol **2i** were well tolerated in this Negishi coupling reaction. Both **3h** and **3i** were afforded in moderate to high yield (59−81%) and diastereoselectivity (dr ≥11:1), although an extra equivalent of TMPZnCl•LiCl was required to convert the phenol to the corresponding zinc phenoxide.

Gratifyingly, this reaction was not limited simply to aryl bromides, with both heteroaryl and alkenyl bromides also proving to be compatible with these conditions (Scheme 2, entries **3j**−**p**). Both 2- and 3-bromothiophene afforded the desired compounds **3j**,**k** in high diastereselectivity (dr ≥11:1), albeit only moderate yield (42−69%). Additionally, while the free N−H of 5-bromoindole **2l** seemed to shut down the reaction, use of 5-bromo-1-methylindole **2m** provided **3m** in moderate yield (47%) and excellent diastereoselectivity (dr = 18:1). We were pleased to find that 2-bromopyrimidine **2n** was also tolerated in this Negishi cross-coupling reaction, albeit in only modest yield (24%) and diastereoselectivity (dr = 5:1). Furthermore, both β-bromostyrene **2o** and 1-bromocyclohexene **2p** underwent successful reaction, affording the desired products **3o**,**p** in moderate yield (60−74%) and diastereoselectivity (dr ≥10:1).

Given our interest in utilizing this methodology to synthesize a variety of compounds for SAR studies, we set out to test our reaction conditions with alternately substituted cyclic nitriles (Scheme 3). We were pleased to find that both 3-((triethylsilyl)oxy)-3-vinylcyclobutane-1-carbonitrile (**1b**) and 3-phenyl-3-((triethylsilyl)oxy)cyclobutane-1-carbonitrile (**1c**) afforded the desired α-arylated products **3q** and **3r** in high yield (92−93%), albeit with only modest diastereoselectivity (dr ≥4:1). Given the versatility of a vinyl group and exocyclic methylenes, products **3q** and **3s** provide useful synthetic handles for further functionalization. Furthermore, bromobenzene could be effectively coupled with both cyclopropyl nitrile (**1e**) and cyclopentyl nitrile (**1f**) to provide the desired α-arylated products **3t** and **3u** in high yields (67−75%).

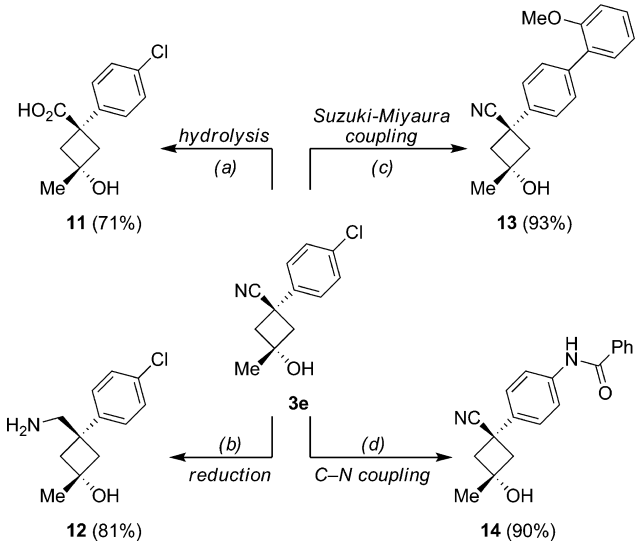
We demonstrated the inherent utility of these products, which can be readily converted to a number of important derivatives in an expedient manner, in Scheme 4. For instance, hydrolysis of the nitrile **3e** furnished the corresponding carboxylic acid **11** in 71% yield. Similarly, reduction of the nitrile to the primary amine **12** was accomplished in 81% yield with lithium aluminum hydride. Finally, the Suzuki−Miyaura coupling[10] and C−N coupling[11] of **3e** furnished biaryl **13** and

Scheme 3. Nucleophile Scope of α-Arylation Reaction[a−f]



[a]Reactions were performed in duplicate on 1.5 mmol scale. [b]Reaction conditions: **1** (1.8 mmol, 1.2 equiv), **2** (1.5 mmol, 1.0 equiv), XPhos-Pd-G2 (2.5 mol %), TMPZnCl•LiCl (1.8 mmol, 1.2 equiv, 0.65 M in THF), CPME (4.2 mL, 0.37 M), 80 °C, 16 h in sealed vials under N_2 atmosphere, followed by HCl (4.0 N in dioxane, 1.9 mL, 5.0 equiv), 0 °C to 23 °C, 1.5 h. [c]Isolated yields. [d]When applicable, the structure of the major diastereomer is shown, with the dr of the crude reaction mixture being determined by HPLC analysis. [e]dr was determined by ^{1}H NMR analysis of the crude reaction mixture. [f]Step ii was not carried out.

Scheme 4. Further Derivatization of 3e[a,b]



[a]Reaction conditions: (a) **3e** (0.43 mmol), KOH (15 equiv), *n*-BuOH/H_2O (5:3, 0.40 M), 100 °C, 18 h; (b) **3e** (0.47 mmol), $LiAlH_4$ (1.5 equiv), THF (0.4 M), 0 °C to 23 °C, 1 h; (c) **3e** (0.50 mmol), 2-methoxyphenylboronic acid (1.5 equiv), $Pd(OAc)_2$ (5 mol %), SPhos (10 mol %), K_2CO_3 (3.0 equiv), MeCN/H_2O (3:2, 0.4 M), 100 °C, 3 h; (d) **3e** (0.50 mmol), benzamide (1.05 equiv), *t*-BuBrettPhos-Pd-G3 (5 mol %), K_3PO_4 (1.4 equiv), *t*-BuOH (0.5 M), 110 °C, 3 h. [b]Yields in parentheses are isolated yields.

secondary amide **14** in 93% and 90% yields, respectively, further demonstrating the synthetic utility of the aryl chloride.

In a preliminary mechanistic proposal, the high diastereoselectivity can be rationalized by comparing the pseudoe-

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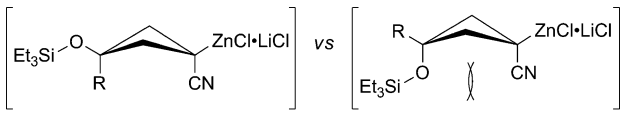
Org. Lett. XXXX, XXX, XXX−XXX

quatorial (**15**) and pseudoaxial (**16**) organozinc intermediates[12] resulting from deprotonation of nitrile **1** with TMPZnCl•LiCl (Figure 2). Previous work found that acetonitrile zinc anion



15 (*pseudoequatorial*) (*towards trans*) **16** (*pseudoaxial*) (*towards cis*)

Figure 2. Rationale for the observed diastereoselectivity by comparison of the pseudoequatorial and pseudoaxial intermediates.

shows coordination of the metal to the nucleophilic carbon.[13] Based on these data, we propose this diastereoselectivity to be driven predominantly by sterics, with the (triethylsilyl)oxy group preferentially being in the pseudoequatorial conformation (**15**), decreasing the unfavorable 1,3-diaxial interactions with the nitrile group (see **16**). The decreased diastereoselectivity observed when R = Ph (dr = 4:1; compared to dr = 14:1 when R = Me) further supports this hypothesis, with poorer size discrimination between the phenyl and (triethylsilyl)oxy groups.

In conclusion, we have developed the direct and highly diastereoselective α-arylation reaction of substituted cyclobutyl nitriles (**1**) with various aryl, heteroaryl, and alkenyl halides (**2**). To the best of our knowledge, this process provides the first example of α-arylation of a cyclobutyl nitrile, allowing the *trans* diastereomer **3** to be preferentially formed, and proved to be general. Lastly, we expanded the utility of the aryl cyclobutyl nitriles via functional group interconversion to a number of important motifs.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01421.

General experimental procedures, characterization of new compounds, and ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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