Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Enantioselective Synthesis of Pyrrolopyrimidine Scaffolds through Cation-Directed Nucleophilic Aromatic Substitution

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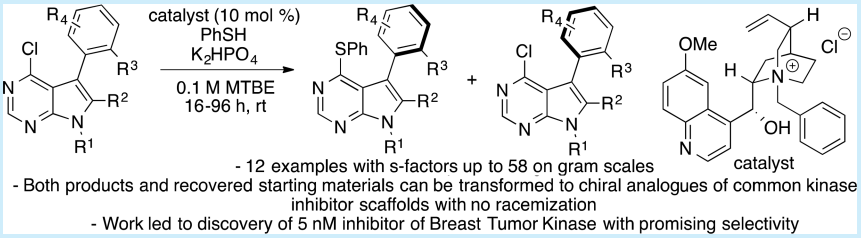
Supporting Information



ABSTRACT: The catalytic enantioselective synthesis of 3-aryl-substituted pyrrolopyrimidines (PPYs), a common motif in drug discovery, is achieved through a kinetic resolution via quaternary ammonium salt-catalyzed nucleophilic aromatic substitution (S_NAr). Both enantioenriched products and starting materials can be functionalized with no observed racemization to give enantiodivergent access to diverse chiral analogues of an important class of kinase inhibitor. One of the compounds was found to be a potent and selective inhibitor of breast tumor kinase.

Atropisomerism[1−3] is a type of chirality that arises from hindered rotation about a bond, and it is common in both natural products[4,5] and small-molecule pharmaceutical scaffolds.[6−8] Atropisomerism differs from other types of chirality in that atropisomers can exist as either stereochemically stable or labile enantiomers depending upon the magnitude of the barrier to rotation about the chiral axis.[9] Stereochemically stable atropisomerism has been largely avoided in modern medicinal chemistry because of complications that arise from dealing with potentially dynamic chirality.[8] Nonetheless, an increasing number of biologically active atropisomeric compounds have appeared in the literature, with the stereochemistry of the chiral axis proving to be a decisive factor for the observed activities.[10,11] Furthermore, the ubiquity of stereochemically unstable atropisomers in drug discovery has been increasing over the past decade. While the chirality of interconverting atropisomers is often overlooked, work by our group and others has demonstrated that this latent chirality can be harnessed to modulate the potency and target selectivity of lead compounds via the synthesis of stereochemically stable analogues.[12−14]

The ability to obtain atropisomerically pure pharmaceutical scaffolds has been a long-standing challenge, with chemists currently relying upon traditional chiral resolutions or HPLC separation on a chiral stationary phase.[15,16] This hinders access to small libraries of atropisomerically pure compounds in early-stage drug discovery and also limits access to larger amounts of lead atropisomeric compounds that may be needed for subsequent studies. A catalytic atroposelective route would facilitate such endeavors, yet there are relatively few[17−22] atroposelective methodologies that yield direct access to relevant atropisomeric pharmaceutical scaffolds. We hypothesized that atroposelective nucleophilic aromatic substitution (S_NAr) could potentially represent a type of enantioselective methodology that would be amenable to diverse atropisomer synthesis problems in drug discovery. For example, our previously reported pyrrolopyrimidine (PPY) kinase inhibitors, a PI4KIIIa inhibitor from GSK,[23] and the FDA-approved urate transport inhibitor lesinurad,[24] are all atropisomerically stable bioactives whose syntheses can potentially involve S_NAr proximal to the chiral axis (Figure 1).

While there are several recent precedents for enantioselective S_NAr,[25−27] we were inspired by the seminal atroposelective S_NAr from the Smith group,[28] who used chiral quaternary ammonium salts to effect the desymmetrization via S_NAr of biaryl pyrimidines (Scheme 1, eq 1). We decided to evaluate whether similar chemistry could be applied to the kinetic

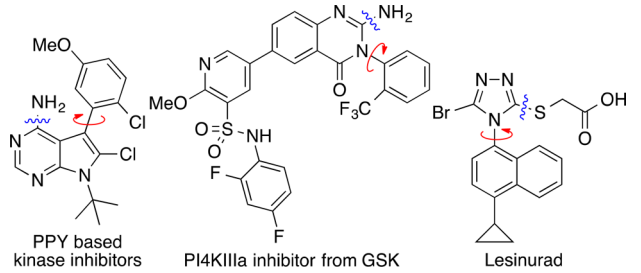


Figure 1. Overview of the potential of atroposelective S_NAr in drug discovery. Atropisomeric axes are designated with curly arrows.

Received: February 16, 2018

DOI: 10.1021/acs.orglett.8b00579
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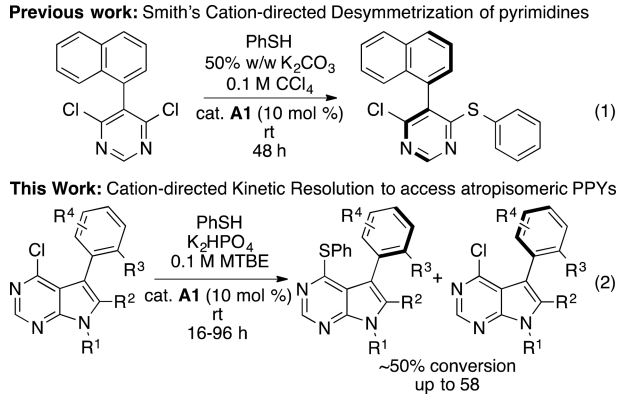
Scheme 1. Overview of Atroposelective S_NAr Methodology



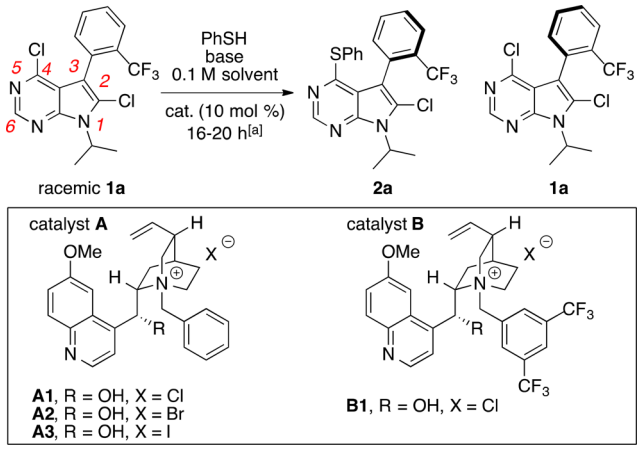
resolutions of the 3-arylated PPY scaffold (Scheme 1, eq 2). We were particularly intrigued by the use of thiophenol as the nucleophile, as the resulting sulfide product could be transformed into an excellent S_NAr leaving group,[29] providing the potential for both the recovered starting material and products to be brought onto the final kinase-inhibiting scaffolds in a stereodivergent manner.

We began our studies by evaluating various catalysts and conditions on racemic PPY **1a**. We chose the trifluoromethyl group adjacent to the axis of chirality for these studies because of its place in the pantheon of medicinal chemistry[30] as well as its bulkiness, which we predicted would prevent any potential racemization. Indeed, the barriers to racemization of **1a** and the product **2a** were determined to be 32.9 and 33.1 kcal/mol, respectively, well above the threshold set by LaPlante for atropisomer stabilities appropriate for drug discovery.[6,7]

Smith's optimal biphasic conditions employing a readily available quinine-based quaternary ammonium salt proved sluggish, however, yielding promising selectivity with an s-factor over 5 (Table 1, entry 1). Removing water (Table 1, entry 2) had little effect on the conversion, but it resulted in a notable increase in s-factor. The choice of solvent proved to be an important factor for both conversion and selectivity (Table 1, entries 2−5), as the s-factor was completely degraded in chloroform, slightly improved in toluene, and significantly improved, at a higher rate, in MTBE. At this point, we evaluated other catalysts (Table 1, entries 5−8) and found that the identity of the catalyst's counteranion and the electronics of the benzyl substitution on the quaternary ammonium were crucial for selectivity. We then evaluated different bases (Table 1, entries 8−12) and found that weaker bases generally performed better, with dibasic potassium phosphate proving optimal, yielding nearly 50% conversion with an s-factor of over 27. Finally, we studied the temperature profile of this reaction (Table 1, entries 13−15) and found that the selectivity was completely degraded at higher temperatures and was surprisingly diminished at lower temperature.

With the optimal reaction conditions (Table 1, entry 12) in hand, we next set out to define the substrate scope of this reaction. As our goal was to develop an enantioselective methodology that would be amenable to a medicinal chemistry campaign, we focused on substrates with diverse substitutions at the positions that would likely be modified during the structural optimization of a PPY kinase inhibitor. We first studied the effect of changing the substitution on N-1 (R^1 in Scheme 2), which in kinase inhibitors is typically substituted with aliphatic side chains that mimic the ribose of ATP.[31] With

Table 1. S_NAr Reaction Optimization



entry	cat.	solvent	base	temp.	conv. (%)[b,c]	s-factor[b,c]
1	**A1**	CCl_4	K_2CO_3(aq)	rt	22.2	5.64
2	**A1**	CCl_4	K_2CO_3	rt	25.8	9.48
3	**A1**	$CDCl_3$	K_2CO_3	rt	30.7	1.64
4	**A1**	$CH_3C_6H_5$	K_2CO_3	rt	20.7	11.2
5	**A1**	MTBE	K_2CO_3	rt	55.9	23.7
6	**A2**	MTBE	K_2CO_3	rt	38.0	12.0
7	**A3**	MTBE	K_2CO_3	rt	34.0	6.00
8	**B1**	MTBE	K_2CO_3	rt	28.0	3.00
9	**A1**	MTBE	Cs_2CO_3	rt	14.5	2.93
10	**A1**	MTBE	K_3PO_4	rt	7.77	1.51
11	**A1**	MTBE	$KHCO_3$	rt	48.2	16.3
12	**A1**	MTBE	K_2HPO_4	rt	50.7	27.9
13	**A1**	MTBE	K_2HPO_4	95 °C	81.7	1.02
14	**A1**	MTBE	K_2HPO_4	60 °C	62.8	1.09
15	**A1**	MTBE	K_2HPO_4	4 °C	16.4	5.99

[a]Reactions were performed on a 0.0267 mmol scale of **1a** with 7.5 equiv of thiophenol and 12 equiv of base. [b]Conversions and s-factors were determined using HPLC. [c]Results are reported as averages of at least three trials. See the Supporting Information (SI) for more details.

this in mind, we focused on diverse aliphatic substitutions (**1a**−**e**) and found that our optimal conditions gave excellent selectivities (s-factors ranging from ∼15 to 40) regardless of the steric nature of the aliphatic substitution, suggesting that this chemistry is quite amenable to the types of substitutions a medicinal chemist is likely to employ at that position.

We next studied the effect of changing the C-3 aryl group, which is known in kinase inhibitors to engage the "gatekeeper" region of the kinase and is commonly exploited to modulate kinase inhibitor selectivity (Scheme 2).[32] Changing this position resulted in some loss of selectivity; the optimal conditions still yielded synthetically useful selectivities with s-factors over 10 for most substrates, with the only exception being **1g**, which yielded an s-factor of only 6. PPY **1i**, which underwent the kinetic resolution with an s-factor of almost 13, is particularly notable, as it represents an atropisomerically stable analogue of the canonical chemical probe NA-PP1.[33]

We finally evaluated the effects of changing the substitution on C-2 of the PPY (Scheme 2). This position needs to be substituted to impart stereochemical stability to the system and can be exploited to impart greater selectivity by engaging nonconserved residues.[34] Substitution here can also modulate the electronics of the pyrimidine ring, which forms crucial hydrogen-bonding interactions with the hinge region of the

DOI: 10.1021/acs.orglett.8b00579
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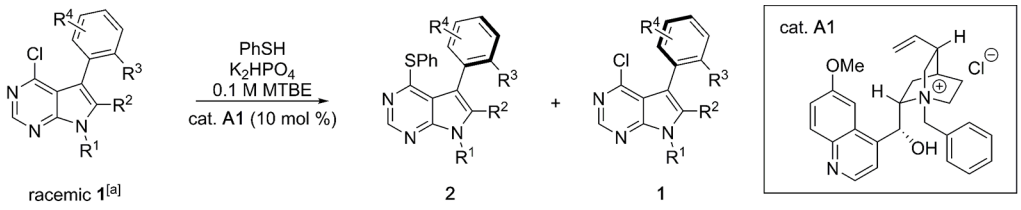
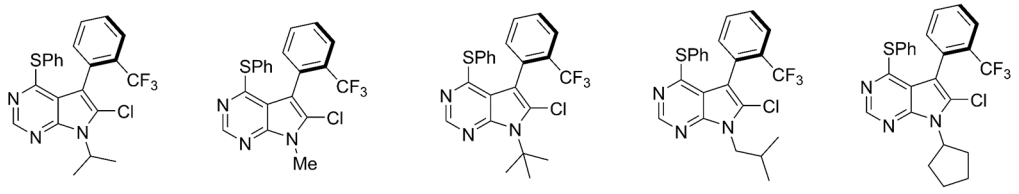
Scheme 2. Substrate Scope of PPYs





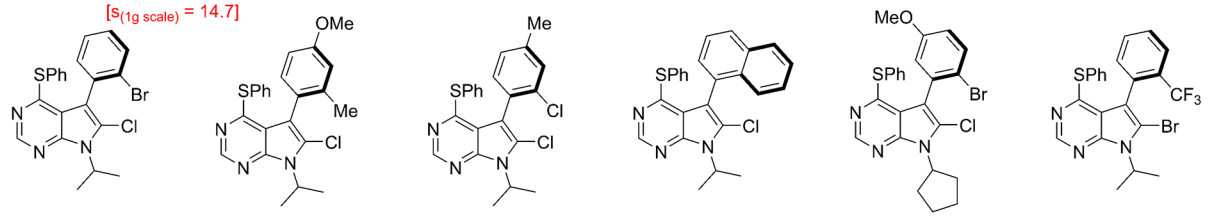
1a (41%,[d] er[b] = 7:94)
2a (42%,[d] er[b] = 8:92)
conversion[c,d] = 51.2%
s[c,d] = 28.3
[$s_{(1g\ scale)}$ = 14.7]

1b (38%, er = 10:90 er)
2b (46%, er = 87:17)
conversion = 46.2%
s = 14.9

1c (30%, er = 18:82)
2c (43%, er = 6:94)
conversion = 48.8%
s = 29.1

1d (46%, er = 5:95)
2d (48%, er = 83:17)
conversion = 53.7%
s = 36.9

1e (43%, er = 6:94)
2e (34%, er = 9:91)
conversion = 52.0%
s = 39.8



1f (31%, er = 2:98)
2f (48%, er = 13:87)
conversion = 54.2%
s = 36.4

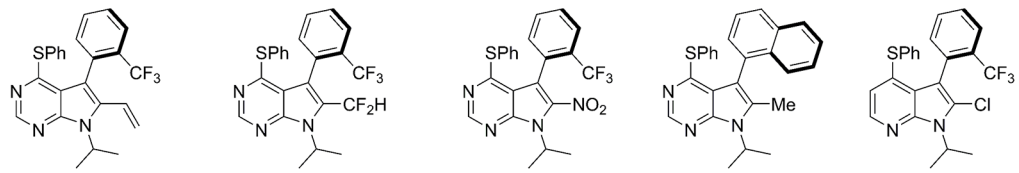
1g (30%, er = 1:99)
2g (48%, er = 27:73)
conversion = 65.4%
s = 6.06

1h (29%, er = 4:96)
2h (50%, er = 17:83)
conversion = 63.2%
s = 13.9

1i (40%, er = 8:92)
2i (46%, er = 24:76)
conversion = 51.2%
s = 12.7
[$s_{(1g\ scale)}$ = 15.0]

1j (34%, er = 94:6)
2j (47%, er = 88:11)
conversion = 54.1%
s = 17.1

1k (41%, er = 11:90)
2k (42%, er = 7:93)
conversion = 47.1%
s = 15.5
[$s_{(3g\ scale)}$ = 58.0]



1l (23%, er = 22:80)
2l (24%, er = 72:28)
conversion = 39.5%
s = 8.74

1m (30%), **3m** (er[e] = 0.3:99.7)
2m (68%, er = 17:83)
conversion = 69.8%
s = 11.5 (from **3m**)

1n (44%, er = 36:64)
2n (41%, er = 72:28)
conversion = 40.8%
s = 2.02

1o (not determined)
2o (not determined)
conversion = >5%
s = not determined

1p (not determined)
2p (not determined)
conversion = >5%
s = not determined

[a]Reactions were performed on a 25 mg scale of **1**. [b]Reported er was determined for one trial of the S_NAr of each substrate and its product. [c]Conversions and s-factors were determined using HPLC. [d]Results are reported as an average of at least three trials. [e]The er and s-factor were determined from the aminated substrate. See the SI for more details.

kinase. PPY **1k**, in which the chlorine in **1a** is replaced with bromine, proved to be an excellent substrate, yielding an s-factor of 16. Notably, **1k** performed substantially better when used on a multigram scale, yielding an s-factor of almost 60. Substrates with vinyl (**1l**) and difluoromethyl (**1m**) also proved quite amenable to this chemistry, yielding s-factors near or at 10, respectively. PPY **1n** possessing a nitro group at this position yielded poor selectivity, largely due to a significantly increased background reaction in the absence of catalyst. On the other hand, more electron-rich substrates, such as PPY **1o**, which possesses a methyl group, and azaindole **1p**, proved unreactive. These later substrates underscore the expected importance of electronics for the rate and selectivity of S_NAr.

We next sought to determine whether both the recovered starting materials and products from this kinetic resolution could be brought forward to the final kinase-inhibiting PPY scaffold (with NH_2 at C-4) without losing enantiopurity. Typical conditions to accomplish this require heating at 140 °C with ammonium hydroxide in a sealed tube, which would almost certainly result in complete racemization. While evaluating other options, we found that stirring recovered starting material PPYs (Scheme 3, eq 1) in neat 2,4-dimethoxybenzylamine resulted in quantitative aminated product in 24−48 h. Subsequent treatment of the isolated 2,4-dimethoxybenzyl-substituted aniline with trifluoroacetic acid (TFA) over the course of an hour then yielded the known kinase-inhibiting scaffold with no observable degradation in enantiopurity for any of the cases evaluated.

We also found that we could oxidize the product sulfide to a sulfone using *m*CPBA (Scheme 3, eq 2), which could then be transformed to **3** using the route described above with no observable degradation in enantiopurity. Notably, we did not observe any oxidation at the C2−C3 double bond or oxidation of either of the pyrimidine nitrogens (N-5 and N-7), most likely because of the greater nucleophilicity of the sulfide compared with the PPY system. It should also be noted that in

DOI: 10.1021/acs.orglett.8b00579
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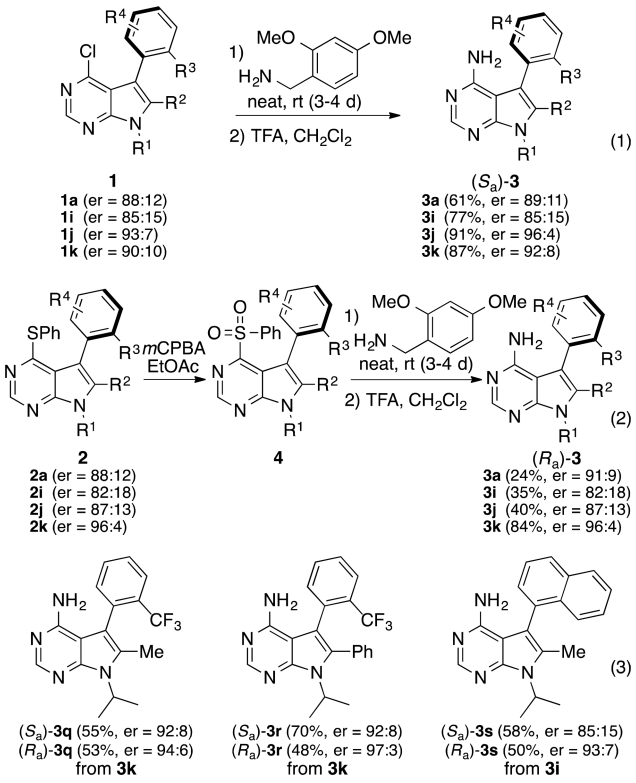
Scheme 3. Transformation of Enantioenriched (eq 1) Starting Materials and (eq 2) Products into C-4-Aminated Kinase Inhibitors and (eq 3) Modification of C-2 (See the SI for More Details)



many cases we observed an increase in er, most likely because the final products were often isolated via trituration. Notably, one of the evaluated substrates was **1j**, which gave either enantiomer of **3j**, a PPY of which we previously obtained a small-molecule crystal structure of enantiopure material,[12] allowing us to assign the stereoinduction of this reaction, with the product of the kinetic resolution being the R_a atropisomer.

As C-2 was perhaps the most limited position in terms of scope, we next sought out to determine whether it could be diversified after kinetic resolution (Scheme 3, eq 3). We focused on further functionalization of the final C-4-aminated products (**3**), as the same chemistry could be used on both enantiomers. We performed these studies on **3i** and **3k**, which possess a chlorine and bromine at C-2, respectively. To avoid complications arising from the C-4 aniline, we Boc-protected this functionality (see the SI) in both cases. Protected **3k** could be readily functionalized to C-2-methylated **3q** using cutting-edge chemistry reported by Schoenebeck[35] and C-2-arylated **3r** using conditions reported by Buchwald,[36] each in good yield over two steps with no observed racemization. Protected **3i** can also be transformed to the C-2-methylated analogue **3s** using Organ's PEPPSI-ipent catalyst[37] with no observed degradation in er. Furthermore, the enantiomeric purity of each enantiomer could be improved via trituration with hexanes/isopropanol. It should be noted that as **3i** has a lower barrier to rotation (27.9 kcal/mol) than **3k** (32.7 kcal/mol), it was not amenable to the incorporation of smaller sp^2 substitutions. Nonetheless, **3k** and **3s** possess barriers to rotation that would be appropriate for chemical probes.

We finally tested each atropisomer of **3q** and **3s** for inhibitory activity across the kinases Src and breast tumor kinase (Brk). Src is a prototypical kinase that is often studied in chemical biology and has been implicated in several resistant cancers.[38] Brk inhibitors have recently received interest for targeting of breast cancer.[39,40] The R_a atropisomer of **3q** displayed modest activity (IC_{50} of 2434 nM) toward Brk, whereas both atropisomers displayed no activity against Src (Figure 2). Enantioenriched **3s** proved interesting, as the

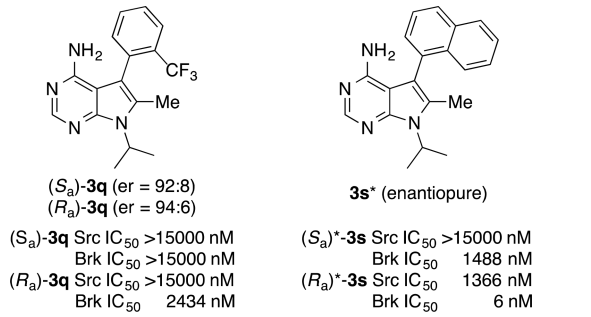


Figure 2. Evaluation of enantioenriched PPYs across Src and Brk kinases. IC_{50} values were determined using Promega's ATP Glo Kinase Inhibition Assay in duplicate. See the SI for more details.

putative R_a atropisomer displayed low-nanomolar activity toward Brk with a 35-fold preference for Brk over Src. As both enantioenriched samples of **3s** possessed relatively significant amounts of the other enantiomer (7% or 15%, as shown in Scheme 3, eq 3), we next sought to obtain enantiopure samples. While we could modulate the reaction conversion to obain improved er values, for simplicity we chose to further purify an aliquot of each enantioenriched sample of **3s** by HPLC on a chiral stationary phase. Perhaps unsurprisngly, the observed trends for enantioenriched **3s** were amplified with the enantiopure sample, as **3s** (R_a)* inhibited Brk with an IC_{50} of 6 nM and Src with an IC_{50} of 1366 nM. The >225-fold preference for Brk over Src is striking and suggests that the R_a atropisomer of **3s** is an intriguing lead toward a selective Brk inhibitor. More in-depth studies are currently underway.

In conclusion, we have developed an S_NAr approach to the kinetic resolution of an important class of kinase inhibitors. The chemistry proved quite robust and has allowed us to access several new enantioenriched PPY analogues. Overall, we have shown that this chemistry should be quite amenable to furnishing libraries and gram quantities of atropisomer-enriched PPYs. We hope that these studies will serve as a springboard toward employing atroposelective S_NAr to other pharmaceutically relevant atropisomeric scaffolds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00579.

Experimental procedures and compound characterization data (PDF)

DOI: 10.1021/acs.orglett.8b00579
Org. Lett. XXXX, XXX, XXX−XXX

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Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Primary support for this project came from the National Institute of General Medical Sciences of the National Institutes of Health (R35GM124637). M.M.C. is thankful for support from CalVet Veteran Services. S.T.T. is thankful for a fellowship from the SDSU Research Foundation.

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DOI: 10.1021/acs.orglett.8b00579
Org. Lett. XXXX, XXX, XXX−XXX