Published in final edited form as:
J Am Chem Soc. 2019 February 20; 141(7): 2867–2871. doi:10.1021/jacs.8b12566.

Enantioselective Synthesis of Azamerone

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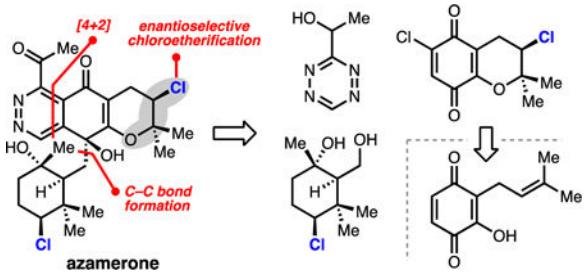
Abstract

A concise and selective synthesis of the dichlorinated meroterpenoid azamerone is described. The paucity of tactics for the synthesis of natural product-relevant chiral organochlorides motivated the development of unique strategies for accessing these motifs in enantioenriched forms. The route features a novel enantioselective chloroetherification reaction, a Pd-catalyzed cross-coupling between a quinone diazide and a boronic hemiester, and a late-stage tetrazine [4+2]-cycloaddition/oxidation cascade.

Graphical Abstract



The napyradiomycins are a diverse class of halogenated meroterpenoids that have been isolated from terrestrial and marine actinomycetes (Figure 1A).[1] Initial isolation efforts were driven by a desire to identify novel antibiotic scaffolds; the napyradiomycins have since demonstrated potent inhibition of gastric (H^+-K^+)-ATPase, nonsteroidal estrogen antagonism, cancer cell cytotoxicities, and activity against Gram-positive bacteria.[1c-f] Of the over 40 members within this class, only napyradiomycin A1 has succumbed to chemical synthesis (**2**, Figure 1A).[2] Syntheses of more highly oxidized members of the napyradiomycins (e.g. **1** and **3**, Figure 1A), which feature densely functionalized, chiral halocycle appendages, remain elusive, representing an exciting arena for synthetic development.

Azamerone is structurally unique among the napyradiomycins. It is the lone example of a phthalazinone-containing natural product.[3] Moore has postulated that this nitrogen–nitrogen

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ASSOCIATED CONTENT

Supporting Information. Experimental procedures, char-acterizations, spectral data, and CIF files. The Supporting Information is available free of charge on the ACS Publica-tions website

No competing financial interests have been declared.

bond-containing heterocycle arises from oxidative rearrangement of SF2415A1 (**5**) via intermediate **6** (Figure 1B).[3a,b] In addition to its unusual hetereocycle, azamerone's highly oxidized structure, diversity of heteroatoms, two stereogenic tertiary alcohols, and two distinct chlorine-bearing stereogenic centers pose significant synthetic challenges. We envisaged that azamerone could be retrosynthetically traced to a chlorobenzopyran, tetrazine, and chlorocyclohexane of general forms **7**, **8**, and **9** (Figure 1C). A challenging enantioselective chloroetherification on prenyl-containing hydroxyquinone **10** (a reaction with no enantioselective variants, Figure 1D), a hindered carbon–carbon bond formation between **9** and **7**, and an electronically mismatched late-stage tetrazine Diels–Alder reaction were thus identified as key challenges for this chemical synthesis.

Our synthetic approach first required the assembly of enantioenriched chlorocycles **7** and **9**. Biosynthetically, the chlorocycle motifs found in **7** and **9** are proposed to derive from chloronium-initiated cyclizations of the prenyl and geranyl fragments within **5** (Figure 1B,C).[4] Neither of these transformations have enantioselective, synthetic parallels (Figure 1D).[5] In fact, the use of enantioselective halogenation in natural product synthesis has been limited thus far to the enantioselective bromochlorination and dichlorination of olefins.[2b,6] Cognizant of these methodological gaps and the challenge of chiral organochloride synthesis in general, we set out to develop a new method for enantioselective chloroetherification to produce a benzochloropyran akin to **7** and to discover a means for resolving the enantiomers of chlorocycle **9**, which was previously made in racemic form (**9**, **X** = OAc, Figure 1C).[9a]

De novo development of an enantioselective chloroetherification required the identification of a substrate that was not only amenable to asymmetric halogenation but also could be parlayed into a synthesis of azamerone. Although considerable advances have been made in the area of intramolecular catalytic, enantioselective chlorolactonization and chloroetherification, high selectivity has been achieved only for styrenyl substrates; use of non-stabilized olefins is accompanied by a precipitous drop in enantioselectivity.[5,7] After extensive investigation of potential substrate structures and chiral catalysts, we discovered that prenylated hydroxyquinone **11** could be chlorocyclized to a benzochloropyran by a TADDOL-ligated titanium complex and *tert*-butyl hypochlorite in modest yield and 10% ee (entry 1, Table 1). Application of other common systems for enantioselective chlorofunctionalization, including cinchona alkaloids, returned racemic product.[7] Unexpectedly, under the conditions of entry 1, *ortho*-quinone **12** was formed as the major product. Significant enol chlorination was observed with formation of a racemic α-chlorinated triketone byproduct. Initial formation of intermediate **13** is proposed, as this is consistent with our hypothesis in a related dihalogenation system that a coordinatively saturated octahedral titanium complex is necessary for high selectivity.[6d] Chloroether **12** likely arises via trapping of the chloronium by the vinylogous carboxylate carbonyl oxygen in **14**; however, titanium is not necessary for such regioselectivity, as the racemic product could be produced in 52% yield solely by the action of *tert*-butyl hypochlorite (see Supporting Information). We anticipated that **12** could be leveraged as a precursor to a *para*-quinone intermediate for the synthesis of azamerone and, therefore, pursued optimization of this chloroetherification.

A survey of chiral ligands afforded optimal TADDOL ligand **B**,[8] which produced chloropyran **11** in increased yield but with similarly low enantioselectivity (entry 2, Table 1). Although comparable to ligand **A** under the conditions of entries 1 and 2, acyclic ligand **B** proved to be more selective and higher yielding across a broader range of conditions and was selected for further optimization efforts. Screening of reaction solvents revealed that 2-methyltetrahydrofuran increased the selectivity of the chloroetherification to 57% ee (entries 3–8, Table 1). Use of other electrophilic chlorine sources led to a reduction in the yield or enantioselectivity of the process (entries 9–11, Table 1). Hypothesizing that adventitious acid could be promoting a racemic background reaction, we found that inclusion of heterocyclic base additives, such as pyridine and quinoline, increased the enantioselectivity of chlorocyclization (entries 12, 13, Table 1); the precise role of these additives is unclear, but they could serve as general bases, activating agents for transfer of electrophilic chlorine, or ligands on titanium. Employing a stoichiometric amount of titanium and chiral ligand delivered only a modest increase in selectivity but a dramatic improvement in yield (entry 14, Table 1). Increasing the amount of *tert*-butyl hypochlorite to 1.3 equivalents provided an improvement in yield when using 25 mol % titanium and ligand (entry 15, Table 1). Gratifyingly, performing the reaction on 4-gram scale under these conditions resulted in an isolated 40% yield (entry 16, Table 1) which was deemed sufficient for completing the synthesis.

With an enantioselective chloroetherification in hand, we commenced our synthesis of azamerone. Prenylquinone **11**, which can be made in two steps from commercially available materials, was cyclized to chloropyran **12** using our optimized conditions (Scheme 1). Treatment of this *ortho*-quinone with aqueous acid induced hydrolysis and isomerization to an intermediate 2-hydroxy-*para*-quinone, which was smoothly converted to its corresponding *ortho*-chloro-*para*-quinone **15** with oxalyl chloride and DMF. Pyranoquinone **15** is embedded within nearly all members of the napyradiomycins (e.g. **1**–**4**, Figure 1).

Our synthesis of the chlorocyclohexane of azamerone focused on first establishing a means to resolve racemic **16** (Scheme 1). In 2010, the Snyder group reported the direct chlorocyclization of geranyl acetate with chlorodiethylsulfonium hexachloroantimonate (see Scheme S2 in Supporting Information).[9a] This reaction provides the primary acetate of diol **16** in racemic form. Important recent work by Gulder,[9b] along with a protocol used here by Snyder[9c] on a mercury-based two-step mimic for halopolyene cyclizations, provided strategies for accessing racemic chlorocycle **16** (Scheme 1). Attempts to catalytically resolve diol **16** by either chemical or enzymatic means were met with limited success. Investigations into resolution by chiral derivatization revealed the *(S)*-α-methoxyphenylacetic ester of diol **16** to be uniquely competent in providing chromatographic resolution of diastereomers on silica gel.[10] This result is noteworthy given the challenges associated with resolving primary alcohols,[11] and we anticipate that access to enantioenriched diol **16** will enable syntheses of other chlorinated natural products. Using this approach, multi-gram quantities of racemic diol **16** can be separated into its constituent enantiomers.

We next investigated the coupling of quinone **15** and an appropriate derivative of chlorocyclohexane **(–)-16**. Initial studies attempted to unite these pieces through a 1,2-addition of generalized organometallic **9** (**X** = metal, Figure 1C) into the more electrophilic

carbonyl of **15**. These efforts were hampered due to Grob-type fragmentation of organometallic **9**, which occurs at temperatures above –78 ˚C, and due to preferential reduction of the quinone by organometallic reagents. Owing to these obstacles, a cross-coupling approach was adopted for the union of these fragments (Scheme 1). Chemoselective dehydration of the primary alcohol in **16** with triflic anhydride and DBU provided olefin **17**, which was hydroborated to form boronic hemiester **18** in good yield and diastereoselectivity. Boronic hemiester **18** is stable to column chromatography, allowing for facile removal of a minor diastereomer; X-ray crystallographic analysis of racemic **18** unambiguously verified its relative configuration. This cross-coupling partner has precedent in the synthesis of sclareolide derivatives and was chosen to attenuate Grob-type fragmentation.[12]

Quinone **15** was joined with boronic hemiester **18** through a quinone diazide-based coupling strategy (Scheme 1). Chemoselective condensation of tosyl hydrazide with quinone **15** followed by treatment with base provided intermediate quinone diazide **19**, which was directly used as a cross-coupling electrophile without purification. Screening of conditions revealed that SPhos-ligated palladium was able to catalyze $C_{sp}{}^3$–$C_{sp}{}^2$ bond formation between sterically hindered boronic hemiester **18** and quinone diazide **19**, providing phenol **20** in 46% overall yield from **15**. Quinone diazide **19** was completely consumed in this reaction, and no elimination of either alkly chloride was observed. The structure and relative configuration of phenol **20** was confirmed via X-ray crystallography of its acetate. Small amounts of another diastereomer were produced due to the presence of minor enantiomers of each substrate. Limited precedent exists for Suzuki reactions with quinone diazides, and to the best of our knowledge, this represents the first example of this reaction type with a $C_{sp}{}^3$ nucleophile.[13]

Subsequent dechlorination, silylation, and hypervalent iodine-mediated *para* oxidation[14] of phenol **20** provided the desired stereoisomer of *para*-quinol **21** as the major product in 42% yield (Scheme 1). Protection of the tertiary alcohol of **21** was necessary to prevent two undesired pathways: (1) the unprotected tertiary alcohol in **21** acting as a nucleophile during arene oxidation to exclusively form a diastereomeric mixture of spirocycles; (2) in oxidized quinol structures such as **21**, free tertiary alcohols are prone to oxa-Michael additions into the proximal enone (see Schemes S11, S15, S16 in Supporting Information). Two diastereomeric products from the latter of these undesired pathways were verified via X-ray crystallography (see Supporting Information), enabling relative stereochemical assignments.

Inspired by Boger, we envisioned that quinol **21** could be expediently translated to azamerone through a [4+2]-cycloaddition with an appropriately functionalized tetrazine.[15] Although it is a direct means for phthalazinone construction, we recognized that electron-deficient enone **21** was ill-matched to participate in this inverse electron-demand cycloaddition. After discovering that acyltetrazine **8** (Figure 1C) had limited stability, we chose its reduced variant **22** for further study (Scheme 2). Unfortunately, initial attempts to thermally induce reactivity between **21** and tetrazine **22** were unsuccessful. During our studies, Wegner and coworkers reported that bisboron complex **23** is able to catalyze the cycloaddition of tetrazines with naphthoquinones.[16] Encouraged by their auspicious results,

we applied complex **23** to our system and were delighted to observe formation of silyl-azamerone **1-TBS**. This reaction was surprisingly regioselective, and the alternate constitutional isomer was not observed. This cascade is presumed to occur through initial [4+2]-cycloaddition, subsequent expulsion of dinitrogen via [4+2]-retrocycloaddition (to provide dihydropyridazine **24**), and both in situ oxidative aromatization and benzyl alcohol oxidation to **1-TBS**. The alcohol oxidation occurred to a varying extent in some experiments but could also be accomplished with Dess–Martin periodinane (see Supporting Information). Treatment with hydrochloric acid affected desilylation and provided azamerone **1**[17] in 34% overall yield from **21**.

The first synthesis of azamerone has been reported. Our successful route relied on development of an enantioselective chloroetherification with a substrate suitable for elaboration into the target. Identification of a scalable resolution process provided access to an enantioenriched chlorocyclohexane that had been made previously in racemic form. A convergent cross-coupling between a quinone diazide and a hindered boronic hemiester, followed by a late-stage arene oxidation and bisboron-mediated tetrazine [4+2]-annulation installed the fully-oxidized framework of azamerone. We anticipate that this sequence and the strategies leveraged herein will find use in syntheses of other members of the napyradiomycin meroterpenoids.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

This work is dedicated to Prof. Dale Boger on the occasion of his 65th birthday. We are grateful to Dr. A. Oliver (Notre Dame) and Dr. N. Settineri (UC Berkeley) for X-ray crystallographic analysis, Dr. S. Lynch (Stanford University) for assistance with NMR spectroscopy, Prof. B. Moore (Scripps Institute for Oceanography) for providing an authentic sample of **1**, Prof. Dr. H. Wegner (Justus Liebig University Giessen) for providing an initial amount of bisboron complex **23**, Sajan Patel (Stanford University) for the synthesis of additional **23**, and Prof. Y. Xia (Stanford University) for assistance with LCMS.

Funding Sources

This work was supported by Stanford University, the National Institutes of Health (R01 GM114061), the National Science Foundation (DGE-114747 GRF to MLL), and the Center for Molecular Analysis and Design at Stanford (GRF to GMM).

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(17). Synthetic 1: $[\alpha]D^{23} = -7$ (c = 0.1, MeOH); ref. 3a: [α]D = –8.8 (c = 0.0025, MeOH).

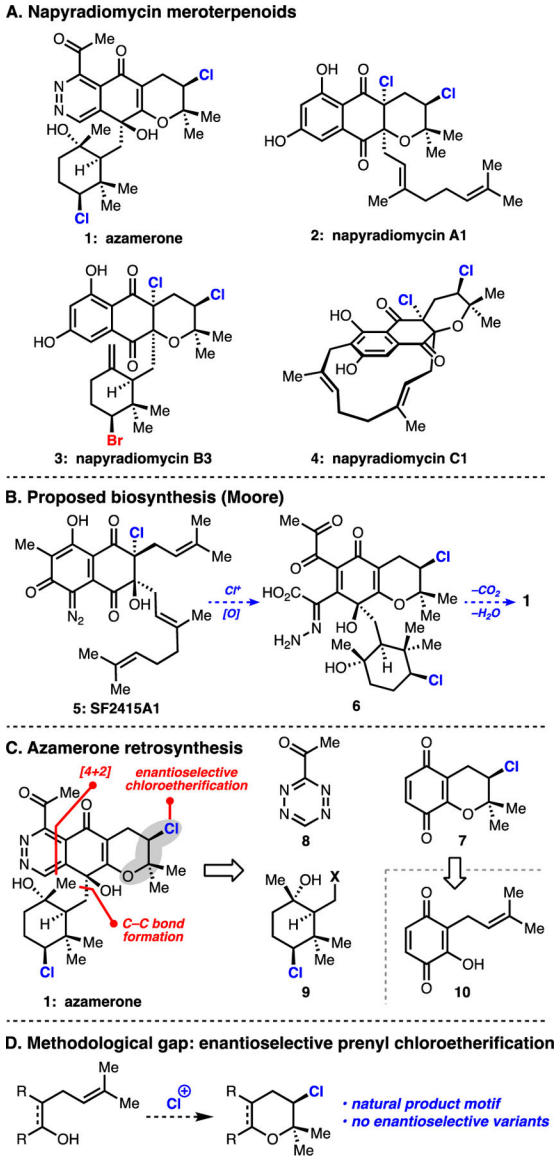
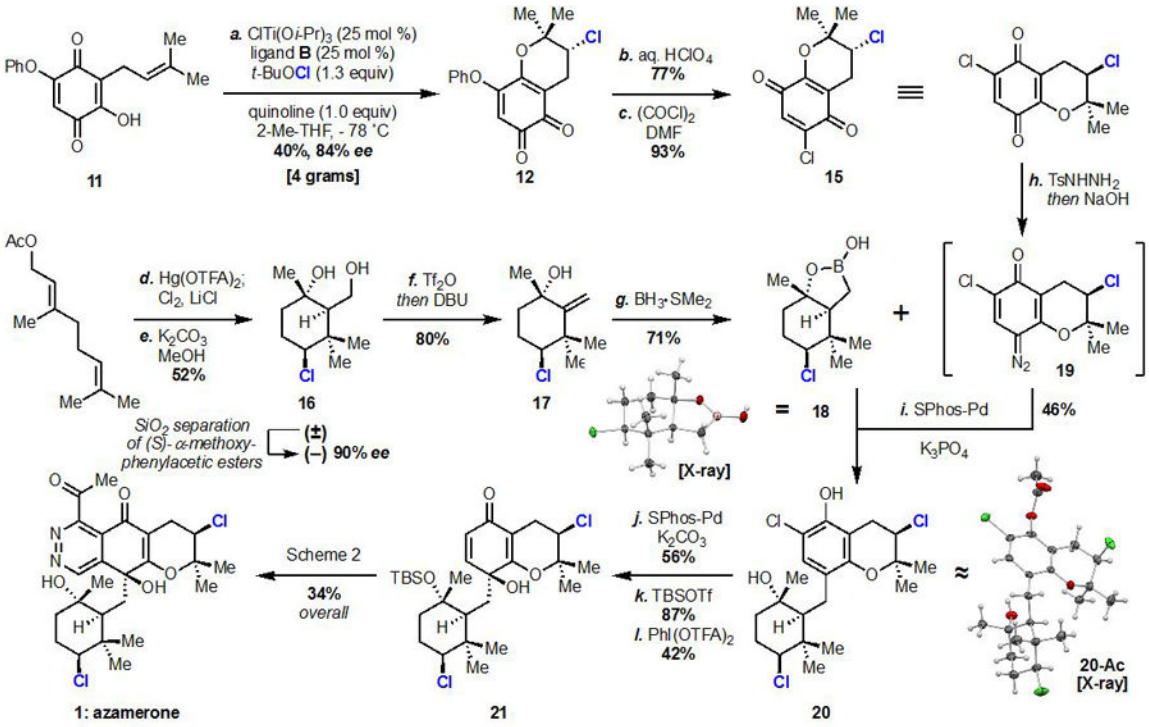


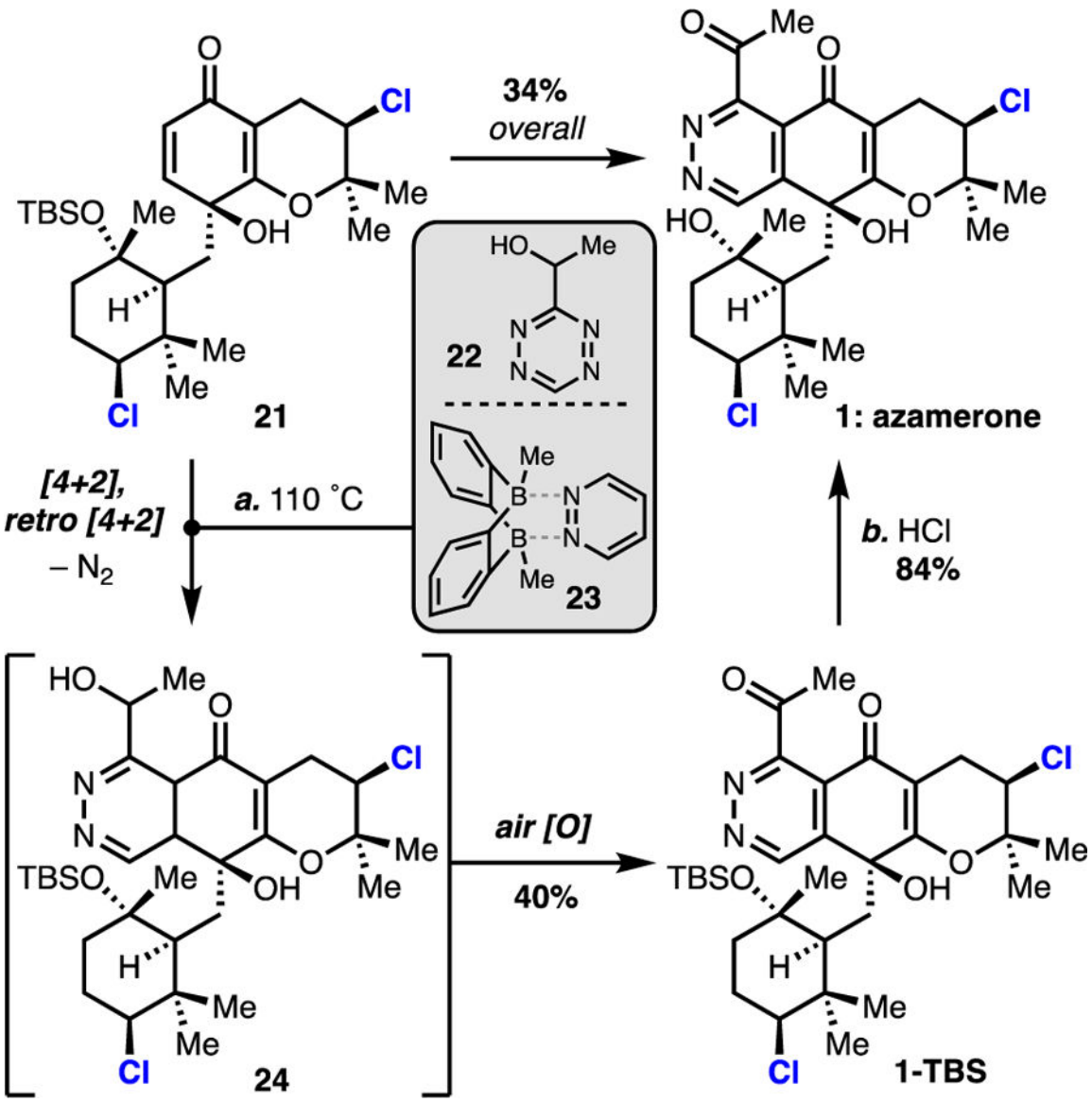
Figure 1.

(**A**) Representative napyradiomycin meroterpenoids. (**B**) Proposed biosynthesis of azamerone. (**C**) Retrosynthetic analysis of azamerone. (**D**) Methodological gap.



Scheme 1.

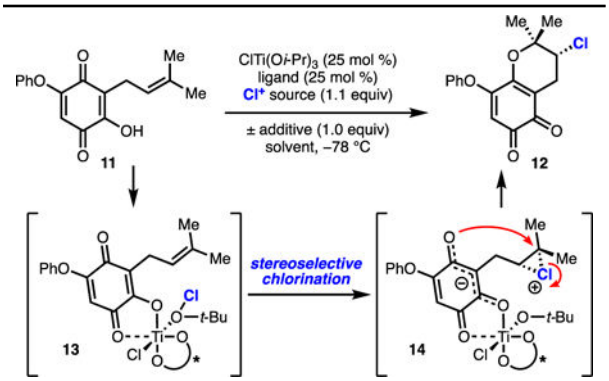
Short enantioselective synthesis of azamerone.[a]



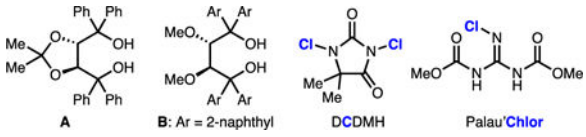
Scheme 2.
Tetrazine cycloaddition sequence.[a]

Table 1.

Enantioselective chloroetherification optimization



entry[a]	conditions	yield (%)	ee (%)
1	**A**, *t*-BuO**Cl**, DCM	29	10
2	**B**, *t*-BuO**Cl**, DCM	39	7
3	**B**, *t*-BuO**Cl**, hexanes	11	<1
4	**B**, *t*-BuO**Cl**, PhMe	38	16
5	**B**, *t*-BuO**Cl**, Et_20	36	14
6	**B**, *t*-BuO**Cl**, *t*-BuOMe	25	16
7	**B**, *t*-BuO**Cl**, THF	18	22
8	**B**, *t*-BuO**Cl**, 2-Me-THF	33	57
9	**B**, N**C**S, 2-Me-THF	<5	-
10	**B**, D**C**DMH, 2-Me-THF	42	33
11	**B**, Palau'**Chlor**, 2-Me-THF	28	29
12	**B**, *t*-BuO**Cl**, 2-Me-THF, pyridine	20	78
13	**B**, *t*-BuO**Cl**, 2-Me-THF, quinoline	24	81
14[b]	**B**, *t*-BuO**Cl**, 2-Me-THF, quinoline	68	84
15[c]	**B**, *t*-BuO**Cl**, 2-Me-THF, quinoline	45	79
16[c,d]	**B**, *t*-BuO**Cl**, 2-Me-THF, quinoline	40[e]	84



[a] Reactions were conducted on 0.035–0.176 mmol scale, and ^{1}H-NMR yields are reported based on 1,4-dinitrobenzene as internal standard;

[b] 100 mol % ClTi(O*i*-Pr)3, 100 mol % **B**

[c] 1.3 equiv *t*-BuOCl

[d] reaction conducted on 4.0 grams **11**

[e] isolated yield.