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Regio- and Enantioselective Synthesis of Azole Hemiaminal Esters by Lewis Base Catalyzed Dynamic Kinetic Resolution

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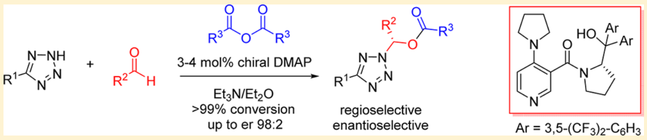
Supporting Information



ABSTRACT: We report a modular three-component dynamic kinetic resolution (DKR) that affords enantiomerically enriched hemiaminal esters derived from azoles and aldehydes. The novel and scalable reaction can be used to synthesize valuable substituted azoles in a regioselective manner by capping (e.g., acylation) of the equilibrating azole-aldehyde adduct. With the use of a prolinol-derived DMAP catalyst as the chiral Lewis base, the products can be obtained in high chemical yield and with high enantiomeric excess. The DKR was performed on a multikilogram scale to produce a tetrazole prodrug fragment for a leading clinical candidate that posed formidable synthesis challenges.

INTRODUCTION

Dynamic kinetic resolutions (DKRs) continue to garner considerable attention as highly efficient means to introduce new stereogenic centers in active pharmaceutical ingredients and in the synthesis of natural products.[1] Enzymatic methods offer a partial solution to this problem, but such transformations remain limited in scope.[2] Noyori's ground-breaking DKR of β-ketoesters by catalytic asymmetric hydrogenation opened the door to a range of transition-metal-catalyzed and organocatalyzed dynamic processes. One such conversion, the nonenzymatic DKR of secondary alcohols, remains a formidable challenge. Recently, Fu developed a dual catalyst system by combining a Ru-based racemization catalyst with a planar-chiral DMAP to achieve the first nonenzymatic DKR of secondary alcohols by acylation.[3] We hypothesized that we could take advantage of the under-exploited dynamic equilibrium between mildly acidic nucleophiles and aldehydes to enantioselectively acylate nonisolable hemiaminal species. Outside of the special cases of aldehydes that form stable hydrates (e.g., formaldehyde, chloral), reports of stable hemiaminal adducts are rare. Nonisolable hemiaminals formed by reversible addition of triazole to aldehydes followed by capping was reported by Smith in 1990.[4] More recently, Banert disclosed the reversible addition of azide to aldehydes followed by azide trapping.[5] Cyclic hemiaminals derived from N-unsubstituted azole aldehydes[6] or imide aldehydes have been reported. Of note, Yamada described the first DKR of a cyclic hemiaminal derived from an imide aldehyde by Lewis base assisted acylation.[7,8] Herein, we describe a new process that takes advantage of a dynamic equilibrium to afford substituted tetrazoles and related azoles in a regio- and enantioselective manner by the use of a sole Lewis base catalyst.[9−12]

Substituted tetrazoles are valuable heterocycles to medicinal chemistry. Most notably, tetrazoles appear in the multibillion dollar angiotensin II receptor antagonist class of blood pressure agents (e.g., losartan and valsartan among others, Figure 1).[13] However, the synthesis of tetrazoles, particularly disubstituted variants, introduces problems of regio- and enantiocontrol.

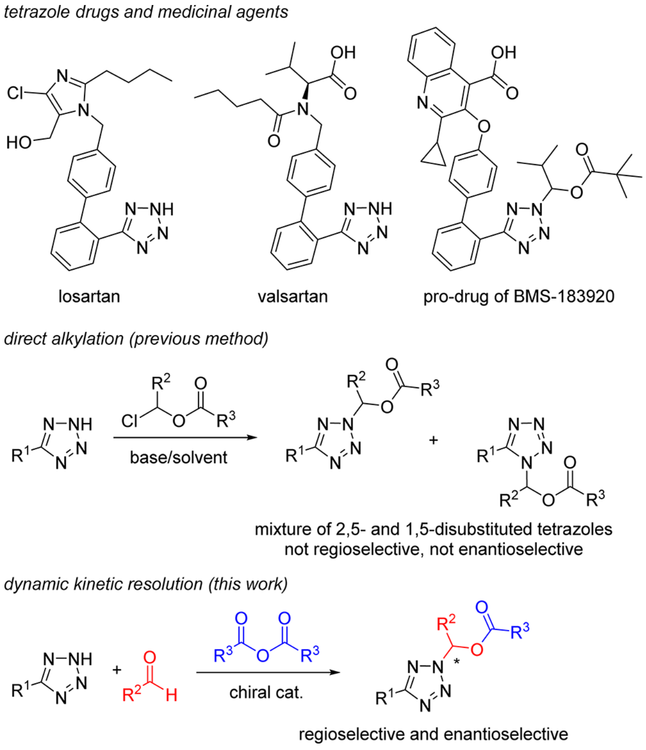


Figure 1. Strategies for alkylation of tetrazoles.

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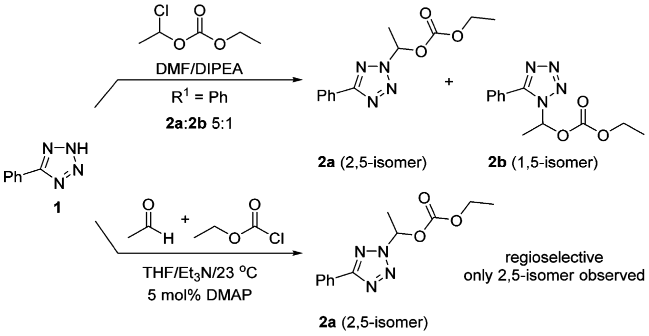
There are several ways to synthesize disubstituted tetrazoles in an unselective manner, but selective methods to access 2,5-disubstituted variants typically employ harsh conditions and are limited in scope.[14,15] Hemiaminal ester substituted tetrazoles have been synthesized by alkylation to afford mixtures of the 1,5- and 2,5-disubstituted products.[16] The use of hemiaminal esters such as methyl substituted pivaloyloxymethyl (MePOM)[11a] results in further complexity by introduction of a new stereogenic center. Methodology to synthesize hemiaminal esters of tetrazoles with the ability to alter the acyl and alkyl groups in a regioselective and enantioselective manner could prove extremely valuable to the development of new biologically active tetrazoles. Furthermore, the ability to control the regiochemistry and stereochemistry of 2,5-disubstituted tetrazoles under mild conditions can expand access to other valuable tetrazole derivatives. Mild methods to address both of these issues do not exist.

RESULTS AND DISCUSSION

Regioselective Synthesis of 2,5-Disubstituted Tetrazoles. Direct alkylation of 5-phenyltetrazole (**1**) with excess 1-chloroethyl ethyl carbonate afforded a mixture of regioisomers **2a** and **2b** favoring the 2,5-disubstituted tetrazole (Scheme 1, top arrow). The assigned structures were confirmed by NOE and X-ray crystallographic studies (see Supporting Information). On the other hand, treatment of 5-phenyltetrazole with acetaldehyde and ethyl chloroformate in the presence of catalytic DMAP showed striking regioselectivity for the 2,5-disubstituted tetrazole (Scheme 1, bottom arrow). NMR analysis of crude reaction material did not show any evidence of 1,5-disubstituted tetrazole formation.

Scheme 1. Synthesis of 1,5- and 2,5-Disubstituted Tetrazoles



Our observations are consistent with previous literature descriptions of DMAP-catalyzed acylations of alcohols[17] and are summarized below. Uncatalyzed reactions formed product in the absence of catalyst after 64−96 h, while DMAP-catalyzed reactions proceed to completion in just 14−16 h. When acetaldehyde-d_4 was employed, full incorporation of deuterium was noted with no evidence of scrambling, lending support to the proposed mechanistic scenario depicted in Figure 2.[18] For reactions conducted for >48 h, no evidence of regioisomeric scrambling of 2,5-isomer **2a** was detected. Furthermore, 1,5-isomer **2b** did not isomerize or decompose in the presence of catalytic DMAP (up to 20 mol %) after long reaction times (>10 d).

The regioselective synthesis of 2,5-disubstituted tetrazoles was found to be highly modular with respect to the three reacting components. A number of 5-substituted tetrazoles underwent the reaction with aliphatic and aromatic aldehydes and could be capped by various acylating reagents including chloroformates and anhydrides (Table 1). Most ketones were not competent reaction partners presumably because of an unfavorable equilibrium leading to a tetrazole-ketone hemiaminal. However, a hemiaminal ester **8** derived from a strained cyclobutanone could be isolated in good yield.

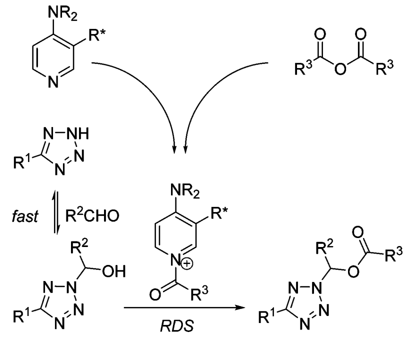
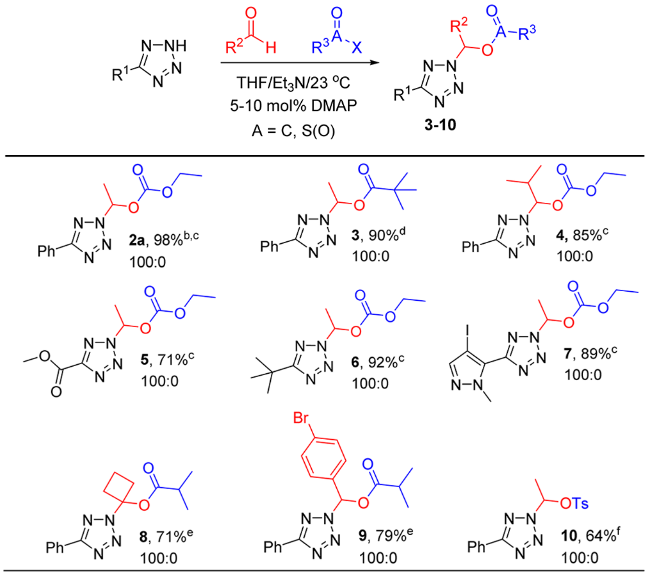


Figure 2. Proposed mechanistic scenario.

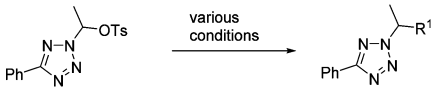
Table 1. Lewis Base Catalyzed Regioselective Synthesis 2,5-Disubstituted Tetrazoles[a]



[a]Reactions conducted at 0.3−0.4 M tetrazole. Isolated yield and ratio of 2,5- to 1,5-tetrazole regioisomers. [b]Reaction was also conducted with 20 mol % PBu_3 and ethyl pyrocarbonate to provide 70% of the 2,5-isomer as the sole product. Acylation reagents: [c]Ethyl chloroformate. [d]Trimethylacetic anhydride. [e]Isobutyric anhydride. [f]*p*-Toluenesulfonyl chloride, the related methanesulfonate was also synthesized, see Supporting Information S-1.

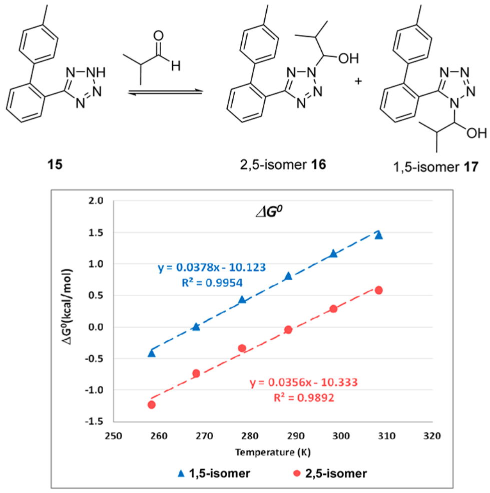
Synthesis of Sulfonate Esters and Further Synthetic Elaboration. The transient hemiaminal species can be trapped not only as esters or carbonates, but also as sulfonate esters (Table 1, **10**).[19] Preliminary results have demonstrated that these racemic sulfonate esters can be displaced with a range of nucleophiles (Table 2). For example, tosylate **10** can react with $LiBEt_3H$ or $AlMe_3$ to afford 2-ethyl-5-phenyl-2*H*-tetrazole (**11**) and 2-isopropyl-5-phenyl-2*H*-tetrazole (**12**), respectively. The combination of the two reactions is formally a completely regioselective alkylation of a tetrazole with primary and secondary alkane electrophiles. Additionally, **10** could be transformed into alkyl fluoride **13** with TBAF or a benzylated tetrazole **14** with $AlPh_3$.

Table 2. Reactions of Sulfonate Esters Derived from Tetrazole Hemiaminals



entry	reagent	R1	yield (%)
1	$LiBEt_3H$	H (**11**)	75
2	$AlMe_3$	Me (**12**)	64
3	TBAF	F (**13**)	59
4	$AlPh_3$	Ph (**14**)	55

Scheme 2. Kinetic Analysis of Tetrazole and Aldehyde



isomer	ΔH^0 (kcal/mol)	ΔS^0 (kcal/mol)
16	-10.3	-0.036
17	-10.1	-0.038

Kinetic Analysis of Hemiaminal Adducts. We were intrigued by the highly regioselective nature of the reaction and wanted to probe whether the 1,5-disubstituted tetrazole isomer of the tetrazole/aldehyde adduct was forming under the reaction conditions. Variable temperature NMR spectroscopic studies in acetonitrile-d_3 in which a 5-phenyltetrazole was treated with an aldehyde under pseudo-first-order conditions (ca. 20 equiv. aldehyde) showed a preponderance of the 2,5-adduct.[20] There was no evidence of formation of any 1,5-adduct for 5-phenyltetrazole and acetaldehyde (see Supporting Information). However, for the more sterically demanding 5-(biphenyl-2-yl)tetrazole **15** and isobutyraldehyde, the 2,5-adduct **16** was present in an approximately 4.5:1 ratio along with the 1,5-adduct **17** (Scheme 2). Kinetic analysis of the two isomers showed that formation of the 2,5-adduct is favored by approximately 0.8 kcal/mol at 25 °C. The reaction showed negligible temperature dependence within the temperature window (−15 to 35 °C) of the experiment. In this latter case, the greater steric demand of the ortho-substituted phenyl may twist it out of conjugation with the tetrazole making the 1-position more accessible (see Supporting Information for more detail). In a separate acylation experiment with **15**, isobutyraldehyde, and isobutyric anhydride (vide infra, Table 4), 2,5-disubstituted product **26** was obtained as the sole product. Given these results, we surmised that it is the rate of acylation of the products of the dynamic aldehyde-azole equilibrium that ultimately produces the high regioselectivity.

Enantioselective Synthesis of 2,5-Disubstituted Tetrazoles via Dynamic Kinetic Resolution. With a good understanding of the regioselective formation of 2,5-disubstituted tetrazoles in hand, we turned our attention toward the formation of the hemiaminal stereogenic center in an enantioselective fashion. It is now widely accepted that the rate-determining step in the kinetic resolution of secondary alcohols with chiral Lewis base catalysts is the addition of the alcohol to acylated catalyst. The difference in energy between diastereomeric transition states gives rise to reaction selectivity.[21,22] In the case of a tetrazole hemiaminal, selective acylation has additional challenges, because it requires fast reaction of only one of the four possible isomers to ensure a successful selective outcome (Figure 3).

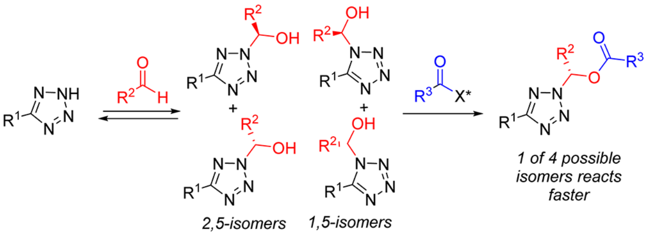
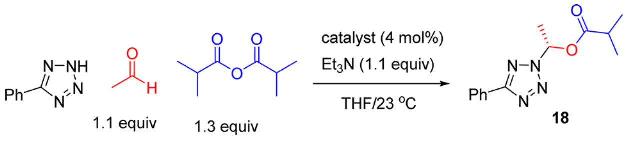
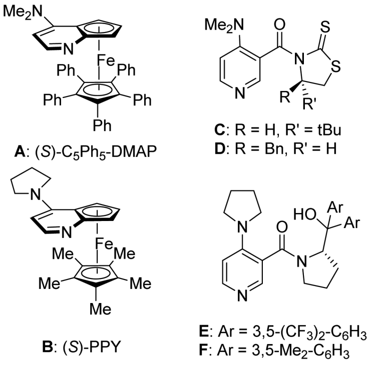


Figure 3. General dynamic kinetic resolution of tetrazoles (regio- and enantioselective).

As DMAP was a competent catalyst in the achiral reaction variant, we surveyed known chiral DMAP catalysts from Fu (**A**, **B**),[23] Yamada (**C**, **D**),[24] and Connon (**E**, **F**)[25] for enantioinduction (Table 3).[26,27] For the preliminary investigation, 5-phenyltetrazole, acetaldehyde, and isobutyric anhydride were chosen as the reaction components. Although all chiral DMAP catalysts evaluated yielded product, enantioselectivity varied. We found that catalyst **E** performed best with our model system, affording product with an enantiomeric ratio (er) of 90:10.

Table 3. Survey of Chiral DMAP Derivatives



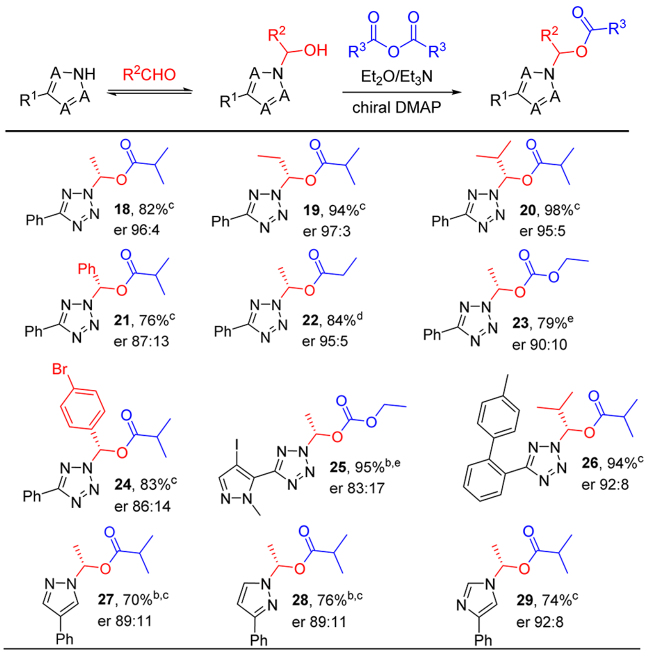


cat	yield	er
A	84	50:50
B	82	51:49
C	82	64:36
D	90	62:38
E	82	90:10
F	88	49:51

We were able to further optimize the reaction conditions using catalyst **E**. Enantioselectivity increased most dramatically when the solvent was changed from THF to less polar solvents such as diethyl ether or toluene. Altering the base did not improve the reaction. As expected, lowering the temperature of the reaction did increase the enantioselectivity, but not significantly. Consequently, ambient conditions were chosen to explore the scope of the dynamic kinetic resolution (see Supporting Information for additional optimization details).

The three-component modularity of the DKR is shown in Table 4. Aliphatic aldehydes provided the highest er, but aromatic aldehydes were also suitable reaction partners. The acylation reagent could be varied away from isobutyric anhydride to propionic anhydride and diethylpyrocarbonate with only a slight to moderate drop in er. The chemistry could also be applied to other azoles such as pyrazoles and an imidazole to afford (regioselectively) the corresponding hemiaminal esters in high yield and good er. Most interestingly, for product **26**, catalyst **E** was able to predominantly acylate a single regioisomeric and enantiomeric hemiaminal from the observed mixture in the NMR study (vide supra). Finally, we were able to assign the stereochemistry of the products by analogy after the absolute configuration of enantiopure **25** was obtained by X-ray crystallography. The stereochemistry of aromatic aldehyde derived **21** and **24** was assigned in a similar manner based on the absolute configuration of **S-2** (see Supporting Information).

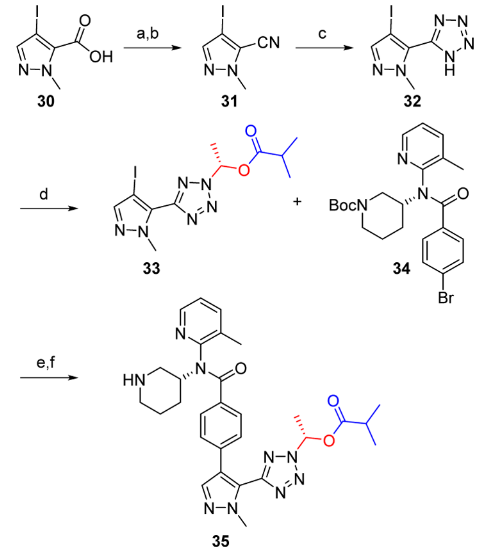
Table 4. Chiral DMAP Catalyzed DKR of Tetrazole-Derived Hemiaminal Esters and Carbonates[a]



[a]Reactions conducted at 0.1 M azole. [b]Reaction conducted in toluene. Acylation reagents. [c]Isobutyric anhydride. [d]Propionic anhydride. [e]Diethylpyrocarbonate.

In contrast to the facile chiral DMAP catalyzed acylations, sulfonylation reactions using catalytic amounts of a number of chiral Lewis bases furnished racemic products in modest yield. A reaction conducted with a stoichiometric amount of catalyst **E** produced sulfonate **10** in low yield and low but quantifiable enantioenrichment (see Supporting Information).[28]

Scheme 3. Large-Scale Application of the Tetrazole-Based DKR[a]



[a]Reagents and conditions: (a) CDI 1.05 equiv, CH_2Cl_2, then NH_4Cl 3 equiv, Et_3N 3 equiv, 75%; (b) TFAA 2 equiv, 2,6-lutidine 3 equiv, CH_2Cl_2, 0 °C, 95%; (c) NaN_3 3 equiv, NH_4Cl 3 equiv, 2.3:1 DMF/H_2O, 100 °C, 16 h, 90%; (d) CH_3CHO 2 equiv, 3 mol % catalyst **E**, Et_3N 1.5 equiv, isobutyric anhydride 1.5 equiv, MTBE [0.07 M tetrazole], 0 °C. 100%, 97:3 er; (e) (i) *i*PrMgCl 1.3 equiv, [2.0 M in THF], THF, −49 °C, 35 min; (ii) $ZnCl_2$, 0.69 equiv [1.9 M in 2-MeTHF], −49 °C to RT; (iii) **34**, Pd-117 0.66 mol %, THF, 50 °C, 78%; (f) HCl 7 equiv [2.0 M in Et_2O], CH_3CN, 1.5 h, 25 °C, 89%.

Multikilogram Synthesis of a Tetrazole Prodrug Fragment via Dynamic Kinetic Resolution. As noted previously, tetrazoles are valuable heterocycles in drug discovery and can serve as carboxylic acid isosteres.[29,30] However, the physical properties of tetrazoles can lead to molecules with low permeability and consequently low oral bioavailability.[31] One way to overcome this limitation is to mask the tetrazole as a prodrug. While prodrugs of carboxylic acids are well-known,[32] tetrazole prodrugs are significantly less common.[16] Although a regio- and enantiomeric mixture of prodrugs will ultimately be cleaved *in vivo* to the same parent compound, the relative rates of enzymatic cleavage of the isomers will differ.[33] Dosing a single isomer is therefore preferred. Furthermore, the inability to control regio- and stereochemistry of the prodrug can hinder the identification and scalability of a compound with suitable biopharmaceutical properties as well as the crystalline solid form.[34]

We were interested in fine-tuning the properties of a small molecule tetrazole prodrug for a medicinal chemistry program. The prodrug would, by design, be enzymatically cleaved *in vivo* to provide the parent tetrazole as the active drug species. The modularity of this DKR allowed us to probe the substitution pattern and properties of the enzymatically labile prodrug moiety. Ultimately, tetrazole prodrug **35**, derived from acetaldehyde and isobutyric anhydride, possessed the desired properties and was selected for advanced *in vivo* and toxicology studies. Multigram quantities of the prodrug **35** was required. Conversion of commercially available acid **30** by a two-step amidation/dehydration sequence provided nitrile **31** in 71% yield. With due caution, cycloaddition of nitrile **31** with hydrazoic acid, formed *in situ*, gave tetrazole **32**.[35] On a 2.5 kg scale, tetrazole **32** was converted into **33** in a regioselective and enantioselective manner using catalyst **E** (189 g, 3 mol %) and slightly modified conditions compared to Table 4. The solvent was changed to methyl *tert*-butyl ether, and the equivalents of aldehyde were increased to drive the reaction to completion. The prodrug fragment **33** was obtained in quantitative yield and er 97:3 before subsequent processing. After removal of the minor enantiomer by chiral preparative chromatography, **33** was treated with iPrMgCl to effect magnesiation at −40 °C followed by transmetalation with $ZnCl_2$. Negishi coupling with 4-bromobenzamide **34** and deprotection provided multigram quantities of **35** (Scheme 3).[36]

■ CONCLUSIONS

A modular, operationally simple and mild method for the regioselective formation of 2,5-disubstituted tetrazole hemiaminal esters was developed. The chemistry was extended to sulfonate esters, which upon reaction with nucleophiles, provided a formal, regioselective alkylation of a tetrazole with primary and secondary alkane electrophiles. An azole/aldehyde dynamic equilibrium was exploited to resolve a transient hemiaminal via a chiral DMAP-catalyzed enantioselective acylation. This new methodology was applied on multikilogram scale to facilitate the synthesis of a compound for a medicinal chemistry program. Extension of this DKR to sulfonate and phosphate esters, additional heterocycles, and other classes of Lewis base catalysts is underway.

■ ASSOCIATED CONTENT

Supporting Information

. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b00207.

Experimental details and characterization data (PDF)
X-ray crystal structure of compound **S-2** (CIF)
X-ray crystal structure of compound **2b** (CIF)
X-ray crystal structure of compound **25** (CIF)

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Notes

The authors declare the following competing financial interest(s): All authors were employed by Pfizer, Inc. at the time this work was done.

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