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Development of a Chiral DMAP Catalyst for the Dynamic Kinetic Resolution of Azole Hemiaminals

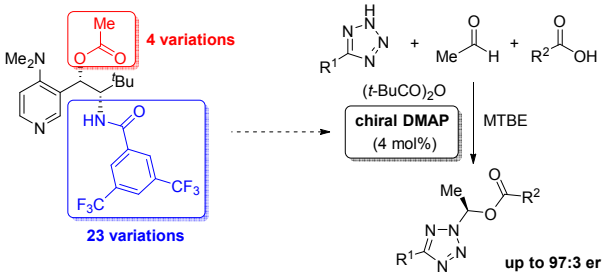
Artis Kinens,[†] Marcis Sejejs,[†§] Adam S. Kamlet,[‡] David W. Piotrowski,*[‡] Edwin Vedejs[†] and Edgars Suna*[†§]

[†] Latvian Institute of Organic Synthesis, Aizkraukles 21, LV-1006, Riga, Latvia

[§] University of Latvia, Department of Chemistry, Jelgavas 1, LV-1004, Riga, Latvia

[‡] Worldwide Medicinal Chemistry, Pfizer, Inc., Eastern Point Road, Groton, CT 06340, USA

edgars@osi.lv, david.w.piotrowski@pfizer.com



Abstract: A new catalyst for the dynamic kinetic resolution of azole hemiaminals has been developed using late-stage structural modifications of the *tert*-leucinol-derived chiral subunit of DMAP species.

Keywords: dimethylamino pyridine, nucleophilic catalysis, dynamic kinetic resolution, hemiaminal, acylation

Introduction

Chiral *N*,*N*-dimethylaminopyridine (DMAP) catalysts have found wide application in asymmetric synthesis.[1,2] Following seminal contributions by Vedejs[3] and Fu,[4,5] a variety of chiral DMAP derivatives have been developed for a range of enantioselective acyl transfer reactions.[6–15] The development of new chiral DMAP catalysts often has relied on an empirical approach involving the preparation and testing of a large number of structural analogues. For example, the development of a catalyst for the enantioselective Steglich rearrangement of oxindoles has required the synthesis of a small library of chiral DMAP analogues using the multicomponent Ugi reaction.[16,17] A complementary approach to the *de novo* synthesis of chiral pyridines is structural modification of already established DMAP catalysts to enable new synthetic applications.[18] This strategy requires the pyridine core to possess a chiral subunit amenable to late-stage modifications, preferably by simple synthetic transformations. Among a variety of chiral DMAP derivatives, the chiral subunit in AcOLeDMAP catalyst (*S*,*S*)–**1a** is especially suitable for the late-stage structural variations of the amide and the ester moieties (Figure 1). The AcOLeDMAP was developed for the enantioselective Steglich rearrangement of indolyl acetates and carbonates,[19] and subsequently it was also successfully employed in the kinetic resolution of secondary alcohols.[20] However, attempts to use the catalyst (*S*,*S*)–**1a** in other asymmetric acyl transfer reactions (*vide infra*) resulted in poor enantiocontrol. Herein we report that relatively simple structural modifications of the AcOLeDMAP (*S*,*S*)–**1a** allowed for remarkable improvement of enantioselectivity in the dynamic kinetic resolution (DKR) of azole-derived hemiaminals (Figure 1).

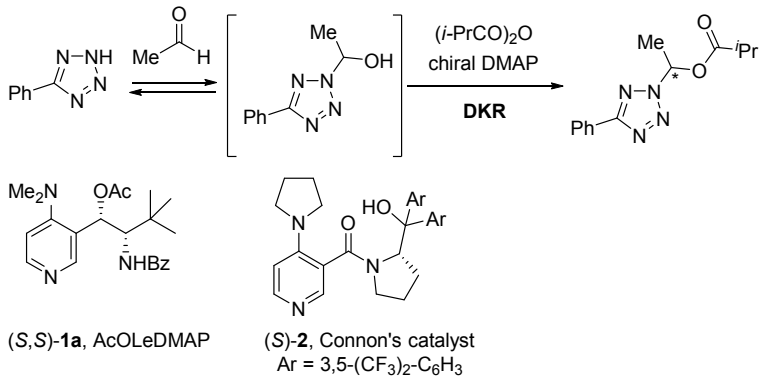


Figure 1. DKR of azole-derived hemiaminals.

Chiral hemiaminals are frequently encountered structural motifs in natural products and pharmaceuticals. For example, a chiral *N*-acyl hemiaminal subunit was shown to contribute to the cytotoxic properties of pederin/mycalamide family of natural products.[21,22] In addition, tetrazole-derived *O*-acyl hemiaminals (Figure 1) have recently found increasing application as pro-drugs of tetrazoles.[23–26] Notwithstanding the presence of a stereogenic center in most of the above-mentioned hemiaminals, the majority of available synthetic methods provide access only to racemic material.[27–30] Only recently, a highly stereoselective method for the synthesis of enantiomerically enriched (up to 98:2 er) tetrazole-derived *O*-acyl hemiaminals has been developed based on the DKR of equilibrating hemiaminals using Connon's catalyst (*S*)–**2** (Figure 1).[31] Notably, high regioselectivity in favor of 2,5-disubstituted tetrazoles was also observed. When AcOLeDMAP (*S*,*S*)–**1a** was employed as a catalyst instead of the chiral DMAP (*S*)–**2**, the hemiaminal ester of 5-phenyl tetrazole was formed with poor enantioselectivity (57:43 er). Initial attempts to increase the enantioselectivity of the AcOLeDMAP-catalyzed DKR by optimizing the reaction conditions resulted only in a slight improvement of enantiocontrol (68:32 er). This was achieved by 5-fold dilution of the reaction mixture (from [0.4M] to [0.08M] in tetrazole). It had also become apparent that further increase of the enantiocontrol in the DKR of azole-derived hemiaminals would require optimization of the chiral subunit of the catalyst (*S*,*S*)–**1a**.

Results and Discussion

The chiral subunit of the catalyst (*S*,*S*)–**1a** comprises a 1,2-amino alcohol core, flanked by a *t*-Bu group and a DMAP moiety (Figure 1). The bulky *t*-Bu group helps to stabilize the well-defined catalyst geometry with an *anti*-relationship between the DMAP and *t*-Bu moieties and OAc and NHBz substituents in the *gauche* conformation.[19] Hence, modifications of the chiral subunit in (*S*,*S*)–**1a** were focused on functionalization of the amine and the alcohol moieties.[32] We envisioned that 1,2-aminoalcohol (*S*,*S*)–**8** could serve as a versatile building block for the synthesis of AcOLeDMAP analogues. The building block (*S*,*S*)–**8** was synthesized by addition of 3-Li-DMAP (from 3-Br-DMAP[33]) to azido aldehyde (*S*)–**6**, followed by $LiAlH_4$ reduction of the azide moiety (36% yield in two steps). Diastereoselectivity of the addition was moderate (3:1 dr, *S*,*S* diastereomer major), however the diastereomeric azides (*S*,*S*)–**7** and (*R*,*S*)–**7** could be easily separated by column chromatography. The (*S*,*S*)-configuration of the major diastereomer was confirmed by its conversion to the known AcOLeDMAP (*S*,*S*)–**1**.[19] The azidoaldehyde (*S*)–**6** was synthesized from commercially available (*S*)-*tert*-leucinol using the diazotransfer reagent **4**,[34] followed by oxidation of the azido alcohol (*S*)–**5** with Dess-Martin periodinane. With the pure nonracemic 1,2-aminoalcohol (*S*,*S*)–**8** in hand, a series of AcOLeDMAP analogues (*S*,*S*)–**1a-c** and (*S*,*S*)–**1f-s** were prepared by initial amide bond formation, followed by *O*-acylation (Figure 2). *O*-Me substituted chiral DMAP (*S*,*S*)–**1d** was synthesized from azide (*S*,*S*)–**7** in a three step sequence involving *O*-methylation, reduction with $LiAlH_4$ and *N*-benzoylation (27% yield over three steps; Figure 2).

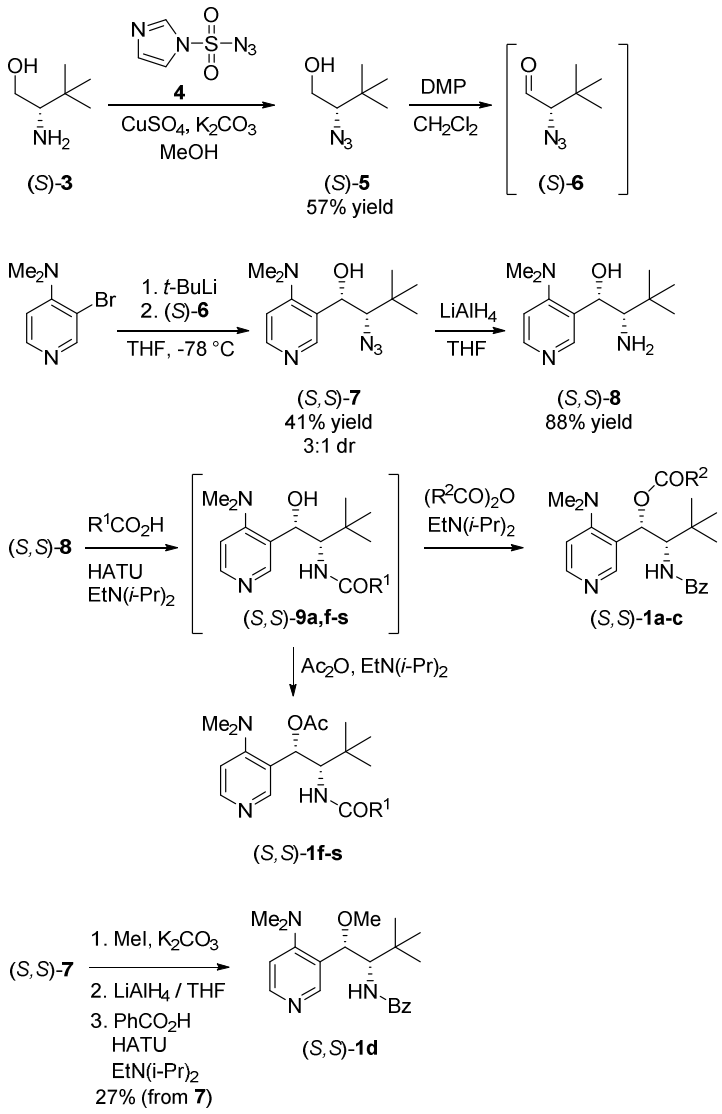


Figure 2. Synthesis of chiral DMAP catalysts (*S*,*S*)–**1a-s**.

All synthesized chiral DMAP derivatives (*S*,*S*)–**1a-w** were tested as catalysts in the reaction of 5-phenyltetrazole (**10a**) with acetaldehyde and isobutyric anhydride under the published DKR conditions[31] (Figure 3). First, influence of the catalyst *O*-substituent on enantioselectivity in the DKR was examined. The *O*-acetyl moiety ((*S*,*S*)–**1a**) proved to be superior in terms of enantiocontrol in the DKR compared to other substituents, such as the sterically more demanding *O*-isobutyryl group ((*S*,*S*)–**1b**) and the less hindered *O*-formyl moiety ((*S*,*S*)–**1c**). Poor enantioselectivity of the DKR reaction, catalyzed by the *O*-Me substituted DMAP derivative (*S*,*S*)–**1d** suggests that the presence of an acyl group in the catalyst is important to achieve good enantiocontrol (Figure 3). Next, the optimization of the *N*-acyl substituent was performed. Replacement of the *N*-Bz group in (*S*,*S*)–**1a** by

the sterically hindered *N*-pivaloyl ((*S*,*S*)–**1e**) and *N*-diphenylacetyl ((*S*,*S*)–**1f**) moieties resulted in decreased enantioselectivities (Figure 3). Importantly, 1-naphthoyl substituted DMAP ((*S*,*S*)–**1g**) afforded poor enantiocontrol (55:45 er), whereas attachment of a 2-naphthoyl group to the nitrogen atom of the chiral subunit ((*S*,*S*)–**1h**) resulted in improved enantioselectivity of the DKR as compared to the AcOLeDMAP (75:25 er for (*S*,*S*)–**1h** vs. 68:32 er for (*S*,*S*)–**1a**, Figure 3). The latter result pointed out that a *meta*- and/or *para*-substitution pattern of the *N*-aroyl moiety is beneficial for good enantiocontrol as opposed to *ortho*-substitution. To choose between *meta*- and *para*- substitution, the corresponding *N*-biphenyl-4-carbonyl and *N*-biphenyl-3-carbonyl moieties were introduced in the chiral subunit of the DMAP (catalysts (*S*,*S*)–**1i** and (*S*,*S*)–**1j**, respectively). Superior enantiocontrol in the DKR using chiral DMAP (*S*,*S*)–**1j** (*meta*-substitution, 68:32 er) as compared to (*S*,*S*)–**1i** (*para*-substitution, 55:45 er; see Figure 2) prompted us to rely on the *meta*-substitution pattern in all the subsequent catalyst optimization studies. Indeed, replacement of the *meta*-Ph substituent on the *N*-benzoyl moiety ((*S*,*S*)–**1j**) with a *meta*-CF_3 group ((*S*,*S*)–**1k**) resulted in a significant increase of enantioselectivity (77:23 er, Figure 3). The most selective chiral DMAP catalyst in the series was prepared by attachment of two CF_3 groups in the *meta*-positions of the *N*-benzoyl moiety (catalyst (*S*,*S*)–**1m**, 84:16 er, Figure 3). Surprisingly, the corresponding 3,5-diphenyl substituted benzamide (*S*,*S*)–**1l** was less selective (67:33 er). Likewise, 3,5-di-(*t*-Bu)phenyl-containing catalyst (*S*,*S*)–**1n** was also inferior to (*S*,*S*)–**1m** suggesting that a steric effect likely is not responsible for the high enantioselectivity of DKR using the DMAP derivative (*S*,*S*)–**1m**. We also hypothesized that the increased acidity of the amide N-H bond in (*S*,*S*)–**1m** (pK_a(DMSO)=20.4)[35] due to the presence of the two electron-withdrawing CF_3 groups as compared to the AcOLeDMAP (*S*,*S*)–**1a** (pK_a(DMSO)=23.3)[36] could be responsible for improved enantioselectivity of the DKR. To verify this hypothesis, a series of more N-H acidic chiral DMAP catalysts, such as thiocarboxamide (*S*,*S*)–**1t**[37] (pK_a(DMSO)=16.9)[36] and 3,5-di-(NO_2)-substituted catalyst (*S*,*S*)–**1o** were tested (Figure 3). Disappointingly, both DMAP derivatives (*S*,*S*)–**1t** and (*S*,*S*)–**1o** afforded inferior enantioselectivities in the DKR as compared to (*S*,*S*)–**1m**. Likewise, benzene sulfonamide (*S*,*S*)–**1u** (pK_a(DMSO)=16.1)[35] and the corresponding 3,5-di-(CF_3)-substituted analogue (*S*,*S*)–**1v**[38] were non-selective (52:48 er and 50:50 er, respectively). Possibly, the N-H acidity of chiral DMAP derivative (*S*,*S*)–**1m**

(pK_a(DMSO)=20.4) is optimal for the high enantiocontrol in the DKR and deviations from the optimal pK_a value result in drop of enantioselectivity. Consequently, we looked for other *N*-benzoyl substituents with N-H pK_a values similar to those of the amide (*S*,*S*)–**1m**. A literature survey of experimentally determined acidity values in DMSO helped to estimate that equilibrium acidity of 3,5-dihalobenzoic acid amides should differ by only ca. 1 pK_a(DMSO) unit from that of 3,5-di-(CF_3)-benzoic acid amides.[39] Hence a series of 3,5-dihalobenzoyl substituted DMAP derivatives (*S*,*S*)–**1p-s** was synthesized and tested in the DKR reaction (Figure 3). Gratifyingly, 3,5-dibromo-benzoyl DMAP derivative (*S*,*S*)–**1p** turned out to be the second most selective catalyst (80:20 er) among all tested chiral DMAP derivatives. Inferior enantiocontrol was observed using 3,5-dichloro- and 3,5-diiodo-substituted catalysts ((*S*,*S*)–**1r** and (*S*,*S*)–**1s**, respectively), and 3,5-difluorobenzoyl-DMAP (*S*,*S*)–**1q** was the least selective catalyst in the series (59:41 er). Evidently, the observed enantioselectivity trends in the DKR cannot be explained only by the N-H acidity values.[40,41] Finally, thiourea (*S*,*S*)–**1w**,[42] possessing two relatively acidic N-H bonds, was also found to be less selective (66:34 er) than the best DMAP derivative (*S*,*S*)–**1m**.

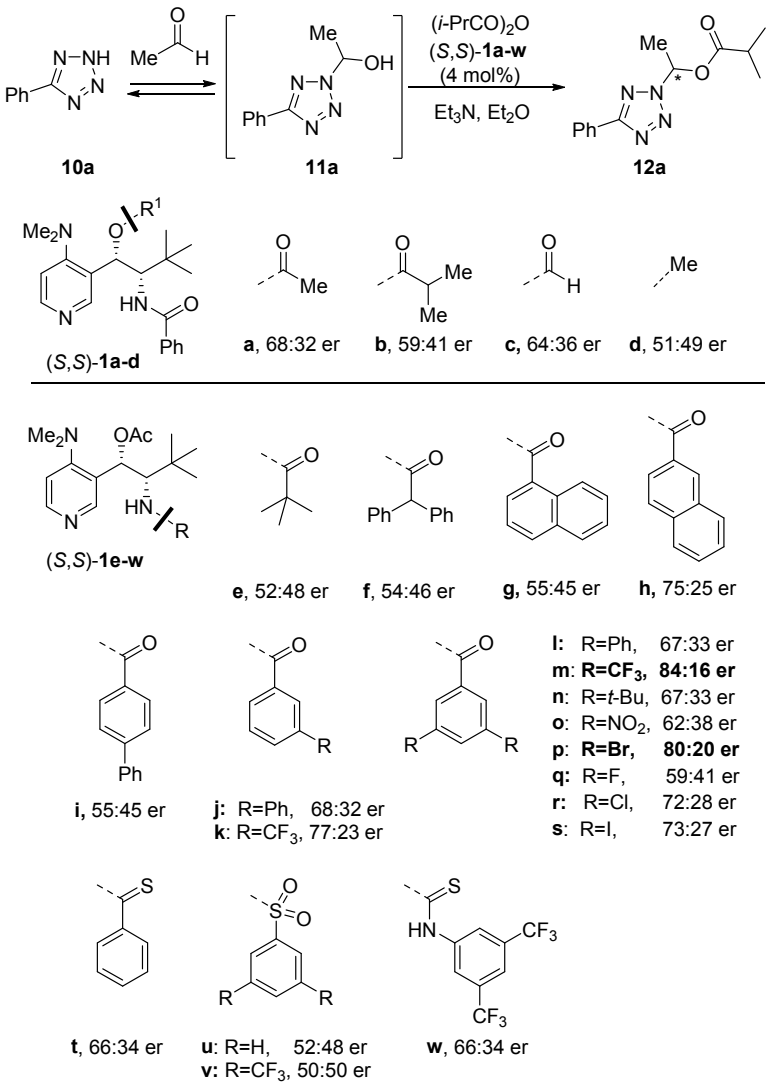
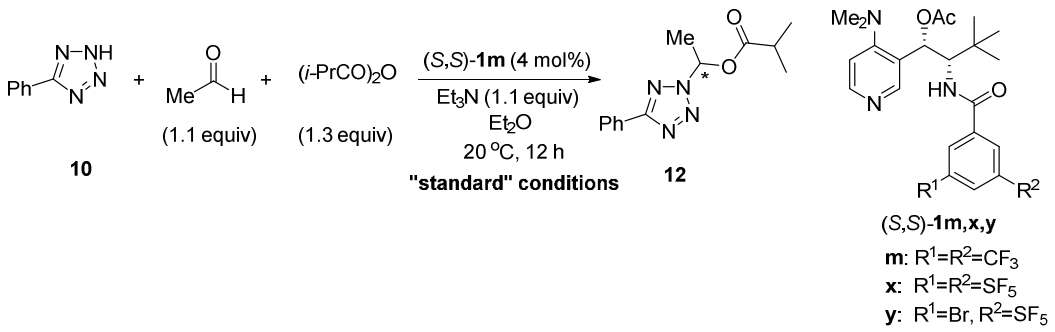


Figure 3. Chiral DMAP catalysts (*S*,*S*)-**1a-w**.

With the chiral DMAP derivative (*S*,*S*)–**1m** as the most selective catalyst in hand, optimization of the DKR conditions was addressed (Table 1). Incomplete conversion of the starting tetrazole **10** was observed in relatively polar solvents such as THF, EtOAc, CH_2Cl_2 and MeCN. Furthermore, enantioselectivity of the DKR in these solvents was lower than that in Et_2O (entries 2-5 vs. 1, Table 1). In contrast, enantioselectivity of the DKR in non-polar toluene was equal to that in Et_2O (entry 6 vs. 1), and in MeO*t*Bu the enantiocontrol of DKR was even higher (entry 7). Importantly, the DKR in MeO*t*Bu does not require addition of an external base such as NEt_3 (entry 8).[43a] Apparently, the stoichiometric base in the DKR reaction is an isobutyrate counter anion of the *N*-acylpyridinium ion pair that is generated in the reaction of isobutyric anhydride with the chiral DMAP catalyst (*S*,*S*)–**1m**.[43b] In fact, tetrazole (pK_a(DMSO)=8.2)[36] is more acidic than the isobutyric acid (pK_a(DMSO)=12.6 for acetic acid),[44] so tetrazole deprotonation by the isobutyrate counter anion should be thermodynamically favored. Furthermore, isobutyric acid is less acidic (pK_a(MeCN)=23.5) than the conjugated acid of the DMAP (pK_a(MeCN)=18.0).[45] This also implies that isobutyrate counter anion is the strongest base in the DKR and that most of the chiral DMAP catalyst (*S*,*S*)–**1m** apparently is not protonated under the DKR conditions. Indeed, addition of AcOH (1.1 equiv) to the reaction mixture neither influenced the rate nor the enantioselectivity of the DKR (entry 9). Finally, changing the solvent to a 1:1 mixture of MeO*t*Bu and cyclohexane and performing the DKR at 0 ^{o}C allowed for an increase of enantioselectivity up to 97:3 er (entry 10).

At this point, a brief optimization of the best chiral DMAP catalyst (*S*,*S*)–**1m** structure was attempted. Accordingly, the CF_3 groups in the 3,3'-positions of the *N*-benzoyl moiety were replaced by the sterically more demanding and more electron withdrawing pentafluorothio groups.[46] The pentafluorothio substituent has recently been successfully employed as an alternative to the CF_3 group in the design of chiral Brønsted acids.[47,48] The 3,5-bis(pentafluorothio)phenyl substituted chiral DMAP derivative (*S*,*S*)–**1x** turned out to be equally selective as the catalyst (*S*,*S*)–**1m** (entry 11), whereas the corresponding mono-SF_5 analogue (*S*,*S*)–**1y** afforded inferior enantioselectivity in the DKR (entry 12). Hence, chiral DMAP derivative (*S*,*S*)–**1m** and the reaction conditions from entry 10 (Table 1) were employed to examine the scope of the DKR.

Table 1. Optimization of the DKR conditions.



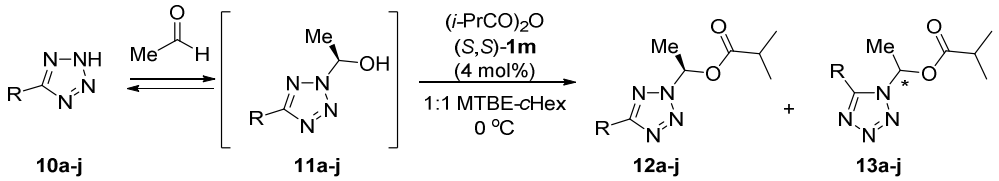
entry	variation from the "standard" conditions	conv. (%)[a]	er
1	None	>99%	84:16
2	THF instead of Et_2O	86%	63:37
3	EtOAc instead of Et_2O	58%	66:34
4	CH_2Cl_2 instead of Et_2O	64%	68:32
5	MeCN instead of Et_2O	62%	55:45
6	Toluene instead of Et_2O	>99%	83:17
7	MeO*t*Bu instead of Et_2O	>99%	90:10
8	without Et_3N, MeO*t*Bu instead of Et_2O	>99%	94:6
9	AcOH instead of Et_3N; MeO*t*Bu instead of Et_2O	>99%	94:6
10	without Et_3N, 1:1 MeO*t*Bu:cyclohexane instead of Et_2O, 0 °C	>99%	97:3
11	catalyst (*S*,*S*)-**1x**, conditions from entry 10	>99%	97:3
12	catalyst (*S*,*S*)-**1y**, conditions from entry 10	>99%	88:12

[a] Conversion determined by ^{1}H-NMR spectroscopy.

The three-component reaction between acetaldehyde, isobutyric anhydride and 5-phenyltetrazole (**10a**) as well as 5-aryltetrazoles possessing a *para*-substituted phenyl moiety (**10b-d**) afforded *O*-acyl hemiaminals as the sole 2,5-regioisomers (entries 1-4, Table 2). Importantly, there was no evidence of formation of any regioisomeric 1,5-adducts for these substrates. In contrast, the presence of *ortho*-substituents on the phenyl moiety of the 5-aryltetrazoles (**10f,g**) resulted in the formation of 1,5-adducts as minor products along with the major 2,5-regioisomers (entries 6,7). Likewise, traces of the 1,5-adduct were observed for 2-pyridyl substituted tetrazole **10e** (entry 5). Possibly, greater steric demand of the *ortho*-substitutent twists the aryl moiety out of conjugation with the tetrazole ring making its 1-position more accessible. Indeed, increased amounts of the 1,5-adducts were formed using less sterically demanding 5-*i*Pr and 5-Me substituted tetrazoles **10h,i** (entries 8,9). Furthermore, the 1,5-hemiaminal **13j** was the major product in the DKR of 5-unsubstituted tetrazole **10j** (entry 10). These results support the influence of steric effects on the ratio of 2,5- vs. 1,5-regioisomers. Steric effects can also be invoked to explain the completely regioselective formation of

hemiaminal esters of 2-phenyl- and 4-phenyl imidazoles **10k**,**l**, 3-phenyl pyrazole **10m**, 3-phenyl 1,2,4-triazole **10n** and theophylline **10q** (Figure 4). As anticipated, a mixture of 2,4- and 1,4-adducts (9:1 ratio, respectively) was observed for the less sterically biased 4-phenyl-2*H*-1,2,3-triazole (**10o**) (Figure 4). It should be noted that the 1,5- and 2,5-substituted azole *O*-acyl hemiaminals could be easily separated by flash chromatography on silica gel to afford the individual regioisomers.

Table 2. Scope of tetrazoles in the DKR.



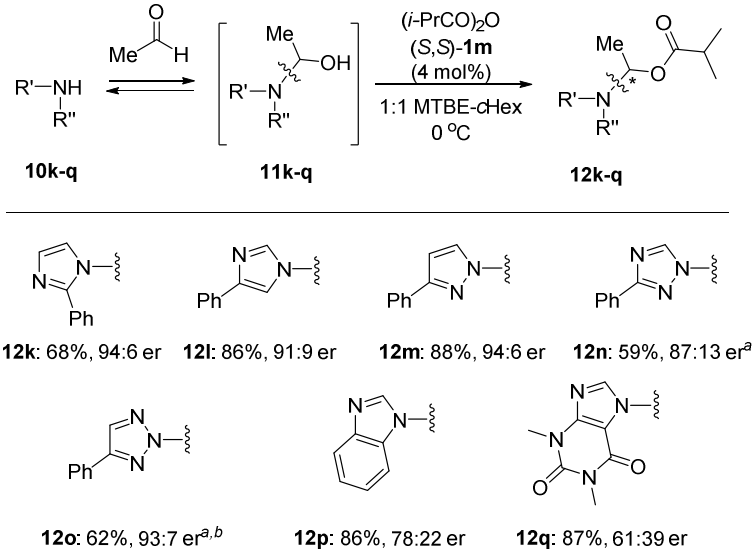
entry	R	**12**:**13**[a]	for **12**	for **13**
1	**a**	100:0	88%, 97:3 er	-
2	**b**	100:0	47%, 95:5 er[b]	-
3	**c**	100:0	72%, 92:8 er	-
4	**d**	100:0	85%, 96:4 er[b]	-
5	**e**	98:2	92%, 97:3 er	nd
6	**f**	97:3	97%, 96:4 er	nd
7	**g**	88:12	84%, 96:4 er	8%, 85:15 er
8	*i*Pr, **h**	89:11	77%, 96:4 er	6%, 87:13 er
9	Me, **i**	73:27	65%, 97:3 er	25%, 85:15 er
10	H, **j**	41:59	39%, 91:9 er	57%, 58:42 er

[a] Ratio determined by ^{1}H-NMR for crude reaction mixture. [b] in MTBE at rt

Importantly, the 2,5-regioisomers of the tetrazole *O*-acyl hemiaminals **12a-j** were formed with high enantioselectivities (Table 2). In contrast, formation of the regioisomeric 1,5-adducts **13g-j** proceeded with inferior enantiocontrol (entries 7-10, Table 2). A variety of azole-derived hemiaminals **11k-o** also underwent highly enantioselective DKR to afford the corresponding hemiaminal esters **12k-o** with high enantiomeric purity (Figure 4). However, a decrease of enantioselectivity was observed in the DKR of benzimidazole **10p** and theophylline **10q** (Figure 4). The newly created stereogenic center in products **12a** and **12t** (see Table 3 below) was assigned an absolute

configuration of *R* based on the comparison of chiral stationary phase HPLC data with that of the enantiomeric (*S*)–**12a,t**, obtained using Connon's catalyst.[31] Furthermore, the *R* absolute configuration was also determined for the crystalline hemiaminal (*R*)–**12x** (see Table 4 below) by X-ray crystallographic analysis (see Supporting Information). Hence, the *R* absolute configuration was assigned for all hemiaminals **12a-j** by analogy with (*R*)–**12a,t** and (*R*)–**12x**.

Figure 4. Scope of azoles.

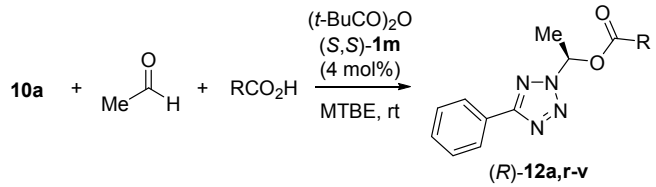


[a] in MTBE at rt. [b] Accompanied by the corresponding 1,4-disubstituted triazole **13o**, 8%, 4:1 er.

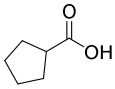
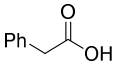
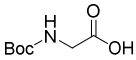
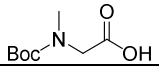
The acylation reagent in the DKR could be varied from isobutyric anhydride to other aliphatic carboxylic anhydrides such as propionic and phenyl acetic anhydrides. However, pivalic anhydride is poorly reactive as the acylating agent under standard DKR conditions (<5% yield after 4 h). This allowed for a mixed anhydride to be generated *in situ* from the corresponding carboxylic acid and Piv_2O (Table 3). The new conditions avoid preparation of the carboxylic anhydrides from the corresponding acids prior the DKR and, hence, improve the versatility of the modular three-component reaction between azole, aldehyde and carboxylic acid. Importantly, enantioselectivity of the DKR with pre-formed isobutyric anhydride and with the *in situ* generated mixed anhydride using pivalic acid was almost identical (entry 1, Table 2 and entry 1, Table 3). Propionic acid yielded hemiaminal ester (*R*)–**12r** with high enantioselectivity (entry 2, Table 3), however decreased levels of

enantiocontrol were observed using other carboxylic acids such as cyclopentane carboxylic acid (entry 3), phenyl acetic acid (entry 4), *N*-Boc glycine (entry 5) and *N*-Boc sarcosine (entry 6).

Table 3. DKR with the *in situ* generated mixed anhydrides.[a]



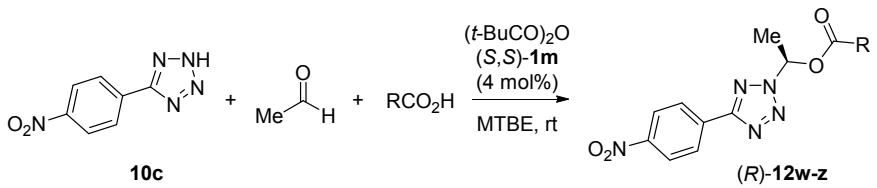
(*R*)-**12a,r-v**

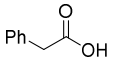
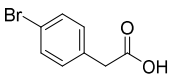
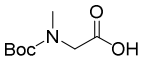
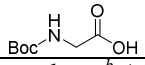
entry	RCO_2H	product	er	yield, %
1		(*R*)–**12a**	95:5	84
2		(*R*)–**12r**	95:5	87
3		(*R*)–**12s**	90:10	84
4		(*R*)–**12t**	83:17	95
5		(*R*)–**12u**	78:22	73
6		(*R*)–**12v**	85:15	79

[a] Reactions were conducted at 0.08 M tetrazole **10a** (1.0 equiv), acetaldehyde (1.1 equiv), carboxylic acid (1.3 equiv) and Piv_2O (1.3 equiv)

A purification method to access individual enantiomers was required and we envisioned that the enantiomeric purity of the enantioenriched hemiaminal esters could be increased by crystallization. The purification by crystallization turned out to be a challenging approach because of the poor crystallinity of the hemiaminals (*R*)–**12**. After much experimentation it was found that the crystalline products can be obtained using nitrophenyl tetrazole **10c** in the DKR (Table 4). Gratifyingly, a single recrystallization of the crude solid hemiaminal esters (*R*)–**12w-z** resulted in considerable improvement of the enantiomeric ratio (up to 99:1; see Table 4). Notably, the major enantiomers of hemiaminals (*R*)–**12x-z** turned out to be more soluble than the minor enantiomers (entries 2-4, Table 4). Hence, the recrystallization afforded almost racemic crystalline material, while enantiomerically pure products (*R*)–**12x-z** were recovered from the filtrate. In contrast, the major enantiomer of (*R*)–**12w** was obtained from a solid crop after the recrystallization (Table 4).

Table 4. Recrystallization of hemiaminal esters (*R*)–**12w-z**.



entry	RCO_2H	product	er[a]	er (cryst)[b]	yield, %[c]
1		**12w**	90:10	99:1[d]	77
2		**12x**	90:10	99:1[e]	40
3		**12y**	87:13	96:4[e]	61
4		**12z**	79:21	97:3[e]	53

[a] Crude product. [b] After single recrystallization. [c] Enantiomerically enriched product. [d] Solid crop after recrystallization. [e] Filtrate after recrystallization

Conclusions

Modular design of the established AcOLeDMAP catalyst (*S*,*S*)–**1a** is well-suited for the optimization of its structure for various stereoselective applications. In this work we have demonstrated that relatively simple modifications of the chiral subunit in the catalyst (*S*,*S*)–**1a** resulted in the development of a new chiral DMAP analogue (*S*,*S*)–**1m** capable of catalyzing the DKR of azole-derived hemiaminals with remarkably improved enantiocontrol as compared to the parent (*S*,*S*)–**1a** (97:3 er vs. 57:43 er, respectively, for hemiaminal **11a**). A wide range of azoles such as tetrazoles, 1,2,3- and 1,2,4-triazoles, imidazoles, pyrazoles, benzimidazole and even theophylline can be converted into chiral hemiaminal esters with good to excellent enantioselectivities, high regioselectivity and chemical yields. The chiral DMAP-catalyzed three component DKR reaction between azole, acetaldehyde and carboxylic acid anhydride does not require addition of external base. Furthermore, the carboxylic acid anhydride can be conveniently generated *in situ* from the carboxylic acid and pivalic anhydride. The latter finding allows for the carboxylic acid to be used directly in the DKR and, hence, improves versatility of the modular three-component DKR reaction.

With a one-step method for the preparation of enantiomerically pure hemiaminal esters from carboxylic acids in hand, synthetic applications of these chiral species was also briefly explored. We hypothesized that the stereogenic center in the hemiaminal moiety could provide diastereocontrol in reactions of the corresponding lithium enolates with a suitable electrophile. Indeed, deprotonation of

enantiopure (*R*)–**12w** with LiHMDS at -100 °C, followed by the addition of *N*-fluorobenzenesulfonimide (NFSI) and TMS-Cl afforded the α-fluorinated product (*R,S*)–**14** with excellent 94:6 diastereoselectivity (Figure 5). The relative stereochemistry of the newly created stereogenic center was assigned as *S* based on X-ray crystallographic analysis of (*R,S*)–**14** (see Supporting Information). Importantly, the hemiaminal moiety can be readily hydrolyzed to the carboxylic acid (*S*)–**14** under mild conditions (pH~10) or transformed into ethyl ester (*S*)–**15** (Figure 5). Notably, both transformations proceeded without racemization of the newly created stereogenic center. The relatively mild cleavage conditions of the hemiaminal-based chiral auxiliary is an important advantage compared to the widely used alternative auxiliaries such as Evans chiral oxazolidinones[49,50] or Myers pseudoephedrine.[51] Studies to explore the application of the hemiaminal ester chiral auxiliary in diastereoselective synthesis are currently ongoing in our laboratories.

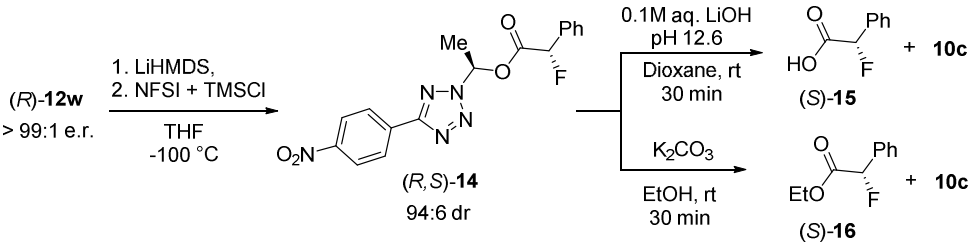


Figure 5. Application of hemiaminal ester as an easily removable chiral auxiliary for α-functionalization of carboxylic acids.

Experimental Section

General Information

Unless otherwise noted, all chemicals were used as obtained from commercial sources and all reactions were performed under argon atmosphere. Analytical thin-layer chromatography (TLC) was performed on precoated silica gel F-254 plates. Nuclear magnetic resonance spectra were recorded on NMR spectrometers at the following frequencies: ^{1}H, 400 or 300 MHz; ^{13}C{^{1}H}, 101 or 75 MHz. Chemical shifts are reported in parts per million (ppm) relative to TMS or with the residual solvent peak as an internal reference. Infrared (IR) spectra were recorded with KBr pellet, and wavenumbers were given in cm^{-1}. High resolution mass spectra (HRMS) were recorded on an TOF MS instrument using the ESI or the APCI techniques.

Synthesis of 1,2-aminoalcohol (*S*,*S*)–8

(*S*)-2-Azido-3,3-dimethylbutan-1-ol ((*S*)–**5**). K_2CO_3 (1.31 g, 9.50 mmol, 1.5 equiv) and anhydrous $CuSO_4$ (0.01 g, 0.000063 mmol, 0.01 equiv) were added to a solution of (*S*)-2-amino-3,3-dimethylbutan-1-ol ((*S*)-**3**) (0.74 g, 6.30 mmol, 1 equiv) in MeOH (15 mL). The reaction mixture was cooled to 0 °C (crushed ice) and solution of 1*H*-imidazole-1-sulfonyl azide (**4**)[52] (1.09 g, 6.30 mmol, 1 equiv) in EtOAc (6.30 mL) was added. The brown suspension was stirred for 60 h under argon atmosphere and reaction progress was monitored by ^{1}H-NMR analysis. Solids were filtered and filtrate was concentrated under reduced pressure. Brown oily residue was purified by column chromatography on silica gel (120 g silica gel) using gradient elution from 0% EtOAc in hexanes to 25% EtOAc in hexanes to afford (*S*)-**5** as a colorless oil (510 mg, 57% yield); analytical TLC on silica gel, 2:5 EtOAc/hexanes, R_f=0.45. IR (KBr, cm^{-1}) 3350 (OH), 2099 (N_3); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 3.85 (1H, dd, *J*=11.3, 2.7 Hz), 3.54 (1H, dd, *J*=11.3, 9.6 Hz), 3.24 (1H, dd, *J*=9.6, 2.7 Hz), 2.27-2.10 (1H, br s), 0.94 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 75.2, 62.7, 34.8, 26.8. GC–MS m/z (% relative intensity, ion): 143.0 (0.3, M^+), 70.1 (19.7, $C_2H_4N_3^+$), 57.1 (100.0, *t*-Bu^+). HRMS-APCI (m/z) calcd for $C_6H_{13}N_3O$ $[M–H]^-$ 143.1064, found 143.1063. Optical rotation $[\alpha]^{20}_D$ +5.8 (*c* 0.14, CH_2Cl_2).

(*S*)-2-Azido-3,3-dimethylbutanal ((*S*)–**6**).Dess-Martin periodinane (1.42 g, 3.352 mmol, 1.2 equiv) was added portion wise to a solution of (*S*)-2-azido-3,3-dimethylbutan-1-ol ((*S*)-**5**) (400 mg, 2.79 mmol, 1 equiv) in CH_2Cl_2 (10 mL) at 0 °C. After 10 min the suspension was warmed to room temperature and stirred for 2 h. The white suspension was diluted with Et_2O (80 mL) and poured into solution of $Na_2S_2O_3 \cdot 5H_2O$ (6.93 g, 27.9 mmol, 10 equiv) in saturated $NaHCO_3$ solution (80 mL). The resulting two-phase system was stirred vigorously until organic layer became clear. Layers were separated and the organic layer was washed with saturated $NaHCO_3$ solution (3x80 mL) and brine (80 mL). Organic extract was dried over Na_2SO_4, filtered and carefully concentrated (rotary evaporator, 400 mbar) keeping water bath temperature at 20 °C to avoid evaporation of product (*S*)-**6**. The crude residue (colorless oil) was used immediately in the next step without purification. ^{1}H NMR (400

MHz, $CDCl_3$, ppm) δ 9.69 (1H, d, *J*=2.0 Hz), 3.61 (1H, d, *J*=2.0 Hz), 1.07 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 198.6, 77.4, 36.0, 26.7. GC–MS m/z (% relative intensity, ion): 141.0 (0.02, M^+), 84.1 (11.7, M^+-*t*-Bu), 57.1 (100.0, *t*-Bu^+). Optical rotation $[\alpha]^{20}_D$ –12.5 (*c* 0.83, CH_2Cl_2).

(1*S*,2*S*)-2-Azido-1-(4-(dimethylamino)pyridin-3-yl)-3,3-dimethylbutan-1-ol ((*S*,*S*)–**7**). *t*-BuLi (1.79 M solution in pentane, 7.9 mL, 14.13 mmol, 2.1 equiv) was added to the anhydrous THF (10 mL) at –78 °C under argon atmosphere. A solution of 3-bromo-*N*,*N*-dimethylpyridin-4-amine (**17**)[33] (1.49 g, 7.40 mmol, 1.1 equiv) in anhydrous THF (10 mL) was added dropwise at a rate to keep temperature below -75 °C. After stirring for 30 minutes at –78 °C, a solution of crude (*S*)-2-azido-3,3-dimethylbutanal ((*S*)–**6**) from above (950 mg, 6.73 mmol, 1.0 equiv) in anhydrous THF (4 mL) was gradually added to the reaction mixture (light orange solution) keeping temperature below -75 °C. The light orange solution was stirred at -78 °C for 30 minutes whereupon it was quenched by water (5 mL) and warmed to room temperature. ^1H NMR of the aliquot from the reaction mixture showed formation of azidoalcohol **7** as a 3:1 mixture of diastereomers. Volatiles were removed under reduced pressure, light brown oil residue was dissolved in EtOAc (50 mL), washed with water (30 mL), brine (30 mL) and dried on Na_2SO_4. Column chromatography (30 g of RP-18 silica gel) using gradient elution from 0% MeCN in water containing 0.1% AcOH to 60% MeCN in water containing 0.1% AcOH afforded, major (*S*,*S*)-**7** isomer as a pale yellow amorphous solid (728 mg, 41% yield); analytical TLC on silica gel, 1:9 MeOH/$CHCl_3$, R_f=0.53. ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.58 (1H, s), 8.44 (1H, d, *J*=5.5 Hz), 6.89 (1H, d, *J*=5.5 Hz), 5.42-4.15 (1H, br s), 5.27 (1H, d, *J*=2.9 Hz), 3.35 (1H, d, *J*=2.9 Hz), 2.80 (6H, s, *J*=6.0 Hz), 1.04 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 159.0, 149.3, 148.7, 131.3, 114.5, 77.5, 68.9, 44.3, 36.7, 27.5. HRMS-ESI (m/z) calcd for $C_{13}H_{22}N_5O$ $[M+H]^+$ 264.1824, found 264.1828. Optical rotation $[\alpha]^{20}_D$ –48.1 (*c* 0.19, CH_2Cl_2).

(1*S*,2*S*)-2-Amino-1-(4-(dimethylamino)pyridin-3-yl)-3,3-dimethylbutan-1-ol ((*S*,*S*)–**8**). $LiAlH_4$ (1.0 M solution in THF, 0.23 mL, 0.23 mmol, 1.2 equiv) was added dropwise to a cooled solution (0 °C) of (1*S*,2*S*)-2-azido-1-(4-dimethylaminopyridin-3-yl)-3,3-dimethyl-butan-1-ol ((*S*,*S*)-**7**) (50 mg, 0.19 mmol, 1 equiv) in anhydrous THF (3 mL). After stirring for 30 min, the white suspension was

warmed to room temperature. After 1 h of stirring at room temperature UPLC-MS analysis of the reaction mixture showed full conversion. The reaction mixture was cooled to 0 °C and quenched by sequential (within intervals of 10 minutes) addition of water (10 μL), 4 M aqueous NaOH solution (20 μL) and more water (30 μL). Ten minutes after addition of final amount of water, the white suspension was filtered through a Celite pad. The filter cake was washed with EtOAc (30 mL). The filtrate was evaporated to dryness yielding 40 mg (88%) of aminoalcohol (*S*,*S*)–**8** as yellow oil, which was used in subsequent step without purification. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.55 (1H, s), 8.35 (1H, d, *J*=5.5 Hz), 6.88 (1H, d, *J*=5.5 Hz), 5.01 (1H, d, *J*=3.7 Hz), 2.80 (6H, s), 2.68 (1H, d, *J*=3.7 Hz), 0.92 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 158.7, 149.6, 149.3, 133.4, 113.8, 66.6, 64.1, 44.3, 34.5, 27.2. HRMS-ESI (m/z) calcd for $C_{13}H_{24}N_3O$ $[M+H]^+$ 238.1925, found 238.1919. Optical rotation $[\alpha]^{20}_D$ +64.9 (*c* 0.07, CH_2Cl_2).

General procedure A for synthesis of chiral DMAP catalysts (*S*,*S*)**-1a–c,f–s,x,y** (see Figure 2). An oven-dried flask was cooled under stream of argon and then charged with corresponding acid (1.1 equiv), 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium-3-oxide hexafluorophosphate (HATU) (1.2 equiv) and anhydrous CH_2Cl_2 (0.1 mmol of acid/1 mL of solvent). After stirring at room temperature for 15 minutes (1*S*,2*S*)-2-amino-1-(4-(dimethylamino)pyridin-3-yl)-3,3-dimethylbutan-1-ol ((*S*,*S*)–**8**) (0.1 M solution in anhydrous CH_2Cl_2; 1 equiv) was added and stirring was continued for another 15 minutes. Then the colorless reaction mixture was cooled to 0 °C and *N*,*N*-diisopropylethylamine (3 equiv) was added. The pale yellow solution was stirred at room temperature and reaction progress was monitored by UPLC-MS analysis. Acetic anhydride (2 equiv) was added upon complete conversion of (*S*,*S*)–**8** and stirring at room temperature was continued (UPLC-MS control of the reaction progress). All volatiles were removed under reduced pressure and pure catalyst was obtained by column chromatography (12 g of RP-18 silica gel) using 40% MeCN in water containing 0.1% AcOH as a mobile phase.

(1*S*,2*S*)-2-Benzamido-1-(4-(dimethylamino)pyridin-3-yl)-3,3-dimethylbutyl acetate ((*S*,*S*)–**1a**). The title compound was obtained as light yellow amorphous solid (14 mg, 82%) by following general procedure A from benzoic acid (6 mg, 0.049 mmol, 1.1 equiv), HATU (20.4 mg, 0.054 mmol, 1.2 equiv), 1,2-amino alcohol (*S*,*S*)–**8** (10.6 mg, 0.045 mmol, 1 equiv), *N*,*N*-diisopropylethylamine (22 µL, 0.134 mmol, 3 equiv) and acetic anhydride (8.5 µL, 0.09 mmol, 2 equiv). ^{1}H NMR spectra was identical to that from the literature.[19]

(1*S*,2*S*)-2-benzamido-1-(4-(dimethylamino)pyridin-3-yl)-3,3-dimethylbutyl isobutyrate ((*S*,*S*)–**1b**). The title compound was obtained as pale yellow amorphous solid (20 mg, 47%) by following general procedure A benzoic acid (14.2 mg, 0.127 mmol, 1.1 equiv), HATU (53 mg, 0.139 mmol, 1.2 equiv), 1,2-amino alcohol (*S*,*S*)–**8** (27.5 mg, 0.116 mmol,1 equiv), *N*,*N*-diisopropylethylamine (57 µL, 0.348 mmol, 3 equiv) and isobutyric anhydride (38 µL, 0.232 mmol, 2 equiv). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.14 (1H, s), 7.79 (1H, d, *J*=7.0 Hz), 7.60 (2H, dd, *J*=6.7, 1.5 Hz), 7.50-7.36 (3H, m), 6.85 (1H, d, *J*=7.0 Hz), 6.59 (1H, d, *J*=1.4 Hz), 6.41 (1H, d, *J*=10.5 Hz), 4.12 (1H, dd, *J*=10.5, 1.4 Hz), 3.33 (6H, s), 2.85 (1H, hept, *J*=7.0 Hz), 1.26 (3H, d, *J*=7.0 Hz), 1.22 (3H, d, *J*=7.0 Hz), 1.08 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 176.8, 168.3, 160, 139.5, 138.8, 133.3, 132.2, 129.2, 126.8, 124.1, 111.9, 77.2, 69.4, 57.8, 43.5, 35.7, 33.9, 27.6, 19, 18.9. HRMS-ESI (m/z) calcd for $C_{24}H_{34}N_3O_3$ $[M+H]^+$ 412.2600, found 412.2595. Optical rotation $[\alpha]^{20}_D$ –27.2 (*c* 0.18, CH_2Cl_2).

(1*S*,2*S*)-2-Benzamido-1-(4-(dimethylamino)pyridin-3-yl)-3,3-dimethylbutyl formate ((*S*,*S*)–**1c**). The title compound was obtained as yellow amorphous solid (17 mg, 39%) by following general procedure A from benzoic acid (14.2 mg, 0.127 mmol, 1.1 equiv), HATU (53 mg, 0.139 mmol, 1.2 equiv), 1,2-amino alcohol (*S*,*S*)–**8** (27.5 mg, 0.116 mmol,1 equiv) and *N*,*N*-diisopropylethylamine (57 µL, 0.348 mmol, 3 equiv). Formylation of intermediate alcohol was achieved with mixture of acetic anhydride (22 µL, 0.232 mmol, 2 equiv) and formic acid (9 µL, 0.232 mmol, 2 equiv) that was stirred at 60 °C for 1h before the use. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.22 (1H, s), 8.09 (1H, s), 7.69 (1H, d, *J*=7.1 Hz), 7.59 (2H, d, *J*=7.2 Hz), 7.49-7.32 (3H, m), 6.81 (1H, d, *J*=7.1 Hz), 6.66 (1H, s),

6.61 (1H, d, *J*=10.5 Hz), 4.09 (1H, d, *J*=10.5 Hz), 3.30 (6H, s), 1.08 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 168.5, 160.6, 159.9, 139.1, 138.4, 133.1, 132.2, 129.1, 126.9, 122.7, 111.6, 68.7, 57.8, 43.4, 35.8, 27.5. HRMS-ESI (m/z) calcd for $C_{21}H_{28}N_3O_3$ $[M+H]^+$ 370.2131, found 370.2122. Optical rotation $[\alpha]^{20}_D$ –21.6 (*c* 1.14, CH_2Cl_2).

(1*S*,2*S*)-1-(4-(dimethylamino)pyridin-3-yl)-2-(2,2-diphenylacetamido)-3,3-dimethylbutyl acetate ((*S*,*S*)–**1f**). The title compound was obtained as white amorphous solid (18 mg, 30%) by following general procedure A from 2,2-diphenylacetic acid (30 mg, 0.139 mmol, 1.1 equiv), HATU (59 mg, 0.152 mmol, 1.2 equiv), 1,2-amino alcohol (*S*,*S*)–**8** (30 mg, 0.127 mmol, 1 equiv), *N*,*N*-diisopropylethylamine (62 µL, 0.380 mmol, 3 equiv) and acetic anhydride (29 µL, 0.253 mmol, 2 equiv). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.39 (1H, d, *J*=5.6 Hz), 8.08 (1H, s), 7.42-7.33 (2H, m), 7.33-7.26 (3H, m), 7.25-7.20 (1H, m), 7.20-7.13 (4H, m), 6.92 (1H, d, *J*=5.6 Hz), 6.37 (1H, d, *J*=1.4 Hz), 5.92 (1H, d, *J*=10.6 Hz), 4.86 (1H, s), 4.12 (1H, dd, *J*=10.6, 1.4 Hz), 2.83 (6H, s), 1.95 (3H, s), 0.91 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 171.3, 169.5, 158.6, 151.1, 149.9, 147.0, 140.0, 139.5, 129.4, 129.2, 129.0, 128.8, 127.5, 127.2, 70.0, 58.4, 43.8, 35.3, 27.2, 21.0. HRMS-ESI (m/z) calcd for $C_{29}H_{36}N_3O_3$ $[M+H]^+$ 474.2757, found 474.2763. Optical rotation $[\alpha]^{20}_D$ –19.3 (*c* 0.90, CH_2Cl_2).

(1*S*,2*S*)-2-(1-Naphthamido)-1-(4-(dimethylamino)pyridin-3-yl)-3,3-dimethylbutyl acetate ((*S*,*S*)–**1g**). The title compound was obtained as pale yellow amorphous solid (6 mg, 9%) by following general procedure A from 1-naphthoic acid (29 mg, 0.169 mmol, 1.1 equiv), HATU (72 mg, 0.185 mmol, 1.2 equiv), 1,2-amino alohol (*S*,*S*)–**8** (36 mg, 0.154 mmol, 1 equiv), *N*,*N*-diisopropylethylamine (75 µL, 0.461 mmol, 3 equiv) and acetic anhydride (29 µL, 0.308 mmol, 2 equiv). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.43 (1H, d, *J*=5.4 Hz), 8.33 (1H, s), 7.89 (1H, dd, *J*=7.1, 2.4 Hz), 7.87-7.78 (2H, m), 7.56-7.43 (4H, m), 7.00 (1H, d, *J*=5.4 Hz), 6.62 (1H, d, *J*=1.4 Hz), 6.26 (1H, d, *J*=10.8 Hz), 4.55 (1H, dd, *J*=10.8, 1.4 Hz), 2.94 (6H, s), 2.16 (3H, s), 1.14 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 169.8, 169.3, 157.7, 135.0, 133.7, 130.5, 130.1, 128.2, 127.2, 126.6,

125.6, 125.0, 124.4, 114.7, 70.6, 58.1, 43.9, 35.4, 27.5, 21.4. HRMS-ESI (m/z) calcd for $C_{26}H_{32}N_3O_3$ $[M+H]^+$ 434.2444, found 434.2433. Optical rotation $[\alpha]^{20}_D$ –30.5 (*c* 0.18, CH_2Cl_2).

(1*S*,2*S*)-2-(2-Naphthamido)-1-(4-(dimethylamino)pyridin-3-yl)-3,3-dimethylbutyl acetate ((*S*,*S*)–**1h**). The title compound was obtained as light yellow amorphous solid (17 mg, 28%) by following general procedure A from 2-naphthoic acid (29 mg, 0.169 mmol, 1.1 equiv), HATU (72 mg, 0.185 mmol, 1.2 equiv), 1,2-amino alcohol (*S*,*S*)–**8** (36 mg, 0.154 mmol, 1 equiv), *N*,*N*-diisopropylethylamine (75 µL, 0.461 mmol, 3 equiv) and acetic anhydride (29 µL, 0.308 mmol, 2 equiv). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.32 (1H, d, *J*=5.5 Hz), 8.28 (1H, s), 8.13 (1H, s), 7.97-7.82 (3H, m), 7.65 (1H, dd, *J*=8.5, 1.8 Hz), 7.60-7.49 (2H, m), 6.94 (1H, d, *J*=5.5 Hz), 6.60 (1H, d, *J*=1.7 Hz), 6.49 (1H, d, *J*=10.7 Hz), 4.40 (1H, dd, *J*=10.7, 1.7 Hz), 2.90 (6H, s), 2.21 (3H, s), 1.10 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 169.9, 167.6, 158.5, 150.3, 147.4, 134.8, 132.8, 129.0, 128.8, 128.6, 127.9, 127.7, 127.2, 126.9, 123.5, 114.6, 70.4, 58.8, 44.0, 35.4, 27.4, 21.4. HRMS-ESI (m/z) calcd for $C_{26}H_{32}N_3O_3$ $[M+H]^+$ 434.2444, found 434.2438. Optical rotation $[\alpha]^{20}_D$ +58.0 (*c* 1.12, CH_2Cl_2).

(1*S*,2*S*)-2-([1,1'-Biphenyl]-4-carboxamido)-1-(4-(dimethylamino)pyridin-3-yl)-3,3-dimethylbutyl acetate ((*S*,*S*)–**1i**). The title compound was obtained as white amorphous solid (24 mg, 39%) by following general procedure A from [1,1'-biphenyl]-4-carboxylic acid (29 mg, 0.147 mmol, 1.1 equiv), HATU (62 mg, 0.161 mmol, 1.2 equiv), 1,2-amino alcohol (*S*,*S*)–**8** (32 mg, 0.134 mmol, 1 equiv), *N*,*N*-diisopropylethylamine (65 µL, 0.402 mmol, 3 equiv) and acetic anhydride (26 µL, 0.268 mmol, 2 equiv). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.21 (1H, s), 7.74-7.66 (2H, m), 7.67-7.58 (3H, m), 7.57-7.48 (2H, m), 7.45-7.36 (2H, m), 7.38-7.29 (1H, m), 6.63 (1H, d, *J*=7.2 Hz), 6.58 (1H, d, *J*=1.7 Hz), 6.51 (1H, d, *J*=10.5 Hz), 4.13 (1H, dd, *J*=10.5, 1.7 Hz), 3.25 (6H, s), 2.27 (3H, s), 1.07 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 170.5, 167.7, 159.6, 144.5, 139.8, 139.4, 138.2, 131.7, 128.9, 127.9, 127.5, 127.2, 123.2, 111.1, 69.2, 57.3, 43.2, 35.5, 27.4. HRMS-ESI (m/z) calcd for $C_{28}H_{34}N_3O_3$ $[M+H]^+$ 460.2600, found 460.2594. Optical rotation $[\alpha]^{20}_D$ +20.5 (*c* 1.95, CH_2Cl_2).

(1*S*,2*S*)-2-([1,1'-Biphenyl]-3-carboxamido)-1-(4-(dimethylamino)pyridin-3-yl)-3,3-dimethylbutyl acetate ((*S*,*S*)–**1j**). The title compound was obtained as pale yellow oil (15 mg, 24%) by following general procedure A from [1,1'-biphenyl]-3-carboxylic acid (30 mg, 0.150 mmol, 1.1 equiv), HATU (63 mg, 0.163 mmol, 1.2 equiv), 1,2-amino alcohol (*S*,*S*)–**8** (32 mg, 0.136 mmol, 1 equiv), *N*,*N*-diisopropylethylamine (66 µL, 0.408 mmol, 3 equiv) and acetic anhydride (26 µL, 0.272 mmol, 2 equiv). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.26 (1H, s), 7.84-7.76 (2H, m), 7.67 (1H, ddd, *J*=7.6, 1.5, 1.5 Hz), 7.64-7.55 (3H, m), 7.53 (1H, d, *J*=7.6 Hz), 7.50-7.40 (2H, m), 7.40-7.32 (1H, m), 6.80 (1H, d, *J*=7.1 Hz), 6.62 (1H, d, *J*=1.6 Hz), 6.48 (1H, d, *J*=10.5 Hz), 4.18 (1H, dd, *J*=10.5, 1.6 Hz), 3.33 (6H, s), 2.30 (3H, s), 1.11 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 170.6, 168.1, 160.0, 142.0, 140.2, 140.1, 138.8, 133.9, 130.9, 129.8, 129.1, 127.9, 127.4, 125.3, 123.9, 111.6, 69.4, 57.5, 43.5, 35.7, 27.6, 21.0. HRMS-ESI (m/z) calcd for $C_{28}H_{34}N_3O_3$ $[M+H]^+$ 460.2600, found 460.2591. Optical rotation $[\alpha]^{20}_D$ –5.9 (*c* 1.12, CH_2Cl_2).

(1*S*,2*S*)-1-(4-(Dimethylamino)pyridin-3-yl)-3,3-dimethyl-2-(3-(trifluoromethyl)benzamido) butyl acetate ((*S*,*S*)–**1k**). The title compound was obtained as light yellow amorphous solid (10 mg, 38%) by following general procedure A from 3-(trifluoromethyl)benzoic acid (12 mg, 0.066 mmol, 1.1 equiv), HATU (28 mg, 0.072 mmol, 1.2 equiv), 1,2-amino alcohol (*S*,*S*)–**8** (14 mg, 0.06 mmol, 1 equiv), *N*,*N*-diisopropylethylamine (39 µL, 0.24 mmol, 3 equiv) and acetic anhydride (17 µL, 0.18 mmol, 2 equiv). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.31 (1H, s), 7.90-7.78 (3H, m), 7.74-7.65 (1H, m), 7.63-7.53 (1H, m), 6.86 (1H, d, *J*=6.9 Hz), 6.61 (1H, d, *J*=1.7 Hz), 6.50 (1H, d, *J*=10.5 Hz), 4.18 (1H, dd, *J*=10.5, 1.7 Hz), 3.32 (6H, s), 2.29 (3H, s), 1.09 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 170.5, 166.7, 159.8, 141.3, 140.2, 134.1, 131.3 (q, *J* = 32.9 Hz), 130.1, 129.6, 128.6, 124.6, 123.8 (q, *J* = 271.6 Hz), 111.9 , 69.5, 57.7, 43.6, 35.6, 27.6, 21.0. ^{19}F NMR (376.5 MHz, $CDCl_3$, ppm) δ -62.9. HRMS-ESI (m/z) calcd for $C_{23}H_{29}N_3O_3F_3$ $[M+H]^+$ 452.2161, found 452.216. Optical rotation $[\alpha]^{20}_D$ –13.9 (*c* 0.43, CH_2Cl_2).

(1*S*,2*S*)-2-([1,1':3',1''-Terphenyl]-5'-carboxamido)-1-(4-(dimethylamino)pyridin-3-yl)-3,3-dimethylbutyl acetate ((*S*,*S*)–**1l**). The title compound was obtained as colorless oil (9 mg, 25%) by

following general procedure A from [1,1':3',1"-terphenyl]-5'-carboxylic acid (15 mg, 0.074 mmol, 1.1 equiv), HATU (31 mg, 0.081 mmol, 1.2 equiv), 1,2-amino alcohol (*S*,*S*)–**8** (16 mg, 0.067 mmol, 1 equiv), *N*,*N*-diisopropylethylamine (33 µL, 0.202 mmol, 3 equiv) and acetic anhydride (13 µL, 0.134 mmol, 2 equiv). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.28 (1H, s), 7.94 (1H, d, *J*=6.6 Hz), 7.89 (1H, dd, *J*=1.6, 1.6 Hz), 7.73 (2H, d, *J*=1.6 Hz), 7.69-7.61 (4H, m), 7.52-7.43 (4H, m), 7.43-7.32 (2H, m), 6.82 (1H, d, *J*=6.6 Hz), 6.60 (1H, d, *J*=1.7 Hz), 6.49 (1H, d, *J*=10.5 Hz), 4.23 (1H, dd, *J*=10.5, 1.7 Hz), 3.17 (6H, s), 2.23 (3H, s), 1.09 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 170.0, 167.6, 158.8, 149.3, 142.5, 140.5, 136.1, 129.3, 129.1, 128.0, 127.5, 124.5, 70.3, 58.7, 43.9, 35.4, 27.5, 21.4. HRMS-ESI (m/z) calcd for $C_{34}H_{38}N_3O_3$ $[M+H]^+$ 536.2913, found 536.2914. Optical rotation $[\alpha]^{20}_D$ +6.8 (*c* 0.360, CH_2Cl_2).

(1*S*,2*S*)-2-(3,5-Di-*tert*-butylbenzamido)-1-(4-(dimethylamino)pyridin-3-yl)-3,3-dimethylbutyl acetate ((*S*,*S*)–**1n**). The title compound was obtained as pale yellow oil (11 mg, 16%) by following general procedure A from 3,5-di-*tert*-butylbenzoic acid (36 mg, 0.153 mmol, 1.1 equiv), HATU (65 mg, 0.139 mmol, 1.2 equiv), 1,2-amino alcohol (*S*,*S*)-**8** (33 mg, 0.139 mmol, 1 equiv), *N*,*N*-diisopropylethylamine (68 µL, 0.416 mmol, 3 equiv) and acetic anhydride (26 µL, 0.277 mmol, 2 equiv). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.18 (1H, s), 7.95 (1H, d, *J*=6.8 Hz), 7.60 (1H, dd, *J*=1.8, 1.8 Hz), 7.37 (2H, d, *J*=1.8 Hz), 6.92 (1H, d, *J*=6.8 Hz), 6.59 (1H, d, *J*=1.8 Hz), 6.30 (1H, d, *J*=10.5 Hz), 4.16 (1H, dd, *J*=10.5, 1.8 Hz), 3.28 (6H, s), 2.25 (3H, s), 1.34 (18H, s), 1.09 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 170.3, 169.0, 160.2, 151.9, 133.3, 126.8, 120.7, 112.2, 99.2, 69.4, 57.8, 56.0, 43.6, 35.6, 35.1, 31.5, 31.3, 27.6, 27.5. HRMS-ESI (m/z) calcd for $C_{30}H_{46}N_3O_3$ $[M+H]^+$ 496.3539, found 496.3533. Optical rotation $[\alpha]^{20}_D$ –16.5 (*c* 0.17, CH_2Cl_2).

(1*S*,2*S*)-1-(4-(Dimethylamino)pyridin-3-yl)-2-(3,5-dinitrobenzamido)-3,3-dimethylbutyl acetate ((*S*,*S*)–**1o**). The title compound was obtained as light yellow amorphous solid (17 mg, 43%) by following general procedure A from 3,5-dinitrobenzoic acid (20 mg, 0.092 mmol, 1.1 equiv), HATU (38 mg, 0.101 mmol, 1.2 equiv), 1,2-amino alcohol (*S*,*S*)-**8** (20 mg, 0.084 mmol, 1 equiv), *N*,*N*-diisopropylethylamine (42 µL, 0.252 mmol, 3 equiv) and acetic anhydride (20 µL, 0.168 mmol, 2

equiv). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.94 (1H, dd, *J*=2.0, 2.0 Hz), 8.59 (2H, d, *J*=2.0 Hz), 8.15 (1H, s), 7.99 (1H, d, *J*=7.1 Hz), 6.98 (1H, d, *J*=7.1 Hz), 6.94 (1H, d, *J*=10.5 Hz), 6.64 (1H, d, *J*=1.7 Hz), 4.15 (1H, dd, *J*=10.5, 1.7 Hz), 3.40 (6H, s), 2.25 (3H, s), 1.14 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 170.7, 164.6, 160.0, 148.7, 139.7, 138.6, 136.7, 127.5, 123.2, 121.2, 111.6, 69.0, 58.3, 43.6, 35.8, 27.7, 20.8. HRMS-ESI (m/z) calcd for $C_{22}H_{27}N_5O_7$ $[M+H]^+$ 474.1989, found 474.1999. Optical rotation $[\alpha]^{20}_D$ –20.0 (*c* 0.13, CH_2Cl_2).

(1*S*,2*S*)-2-(3,5-Dibromobenzamido)-1-(4-(dimethylamino)pyridin-3-yl)-3,3-dimethylbutyl acetate ((*S*,*S*)–**1p**). The title compound was obtained as light yellow oil (15 mg, 24%) by following general procedure A from 3,5-dibromo-benzoic acid (35.5 mg, 0.127 mmol, 1.1 equiv), HATU (53 mg, 0.116 mmol, 1.2 equiv), 1,2-amino alcohol (*S*,*S*)-**8** (25 mg, 0.096 mmol, 1 equiv), *N*,*N*-diisopropylethylamine (57 µL, 0.35 mmol, 3 equiv) and acetic anhydride (24 µL, 0.23 mmol, 2 equiv). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.28 (1H, s), 7.95 (1H, d, *J*=7.0 Hz), 7.72 (1H, dd, *J*=1.4, 1.4 Hz), 7.61 (2H, d, *J*=1.4 Hz), 6.91 (1H, d, *J*=7.0 Hz), 6.59 (1H, s), 6.53 (1H, d, *J*=10.4 Hz), 4.11 (1H, d, *J*=10.4 Hz), 3.34 (6H, s), 2.27 (3H, s), 1.09 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 170.6, 165.7, 160.0, 140.1, 138.8, 137.5, 136.7, 128.9, 123.6, 123.5, 111.6, 69.2, 57.9, 43.5, 35.7, 27.6, 21.0. HRMS-ESI (m/z) calcd for $C_{22}H_{28}N_3O_3Br_2$ $[M+H]^+$ 540.0497, found 540.049. Optical rotation $[\alpha]^{20}_D$ –19.9 (*c* 0.29, CH_2Cl_2).

(1*S*,2*S*)-2-(3,5-Difluorobenzamido)-1-(4-(dimethylamino)pyridin-3-yl)-3,3-dimethylbutyl acetate ((*S*,*S*)–**1q**). The title compound was obtained as white amorphous solid (45 mg, 47%) by following general procedure A from 3,5-difluoro-benzoic acid (20 mg, 0.127 mmol, 1.1 equiv), HATU (96 mg, 0.25 mmol, 1.2 equiv), 1,2-amino alcohol (*S*,*S*)–**8** (27.5 mg, 0.116 mmol, 1 equiv), *N*,*N*-diisopropylethylamine (104 µL, 0.63 mmol, 3 equiv) and acetic anhydride (40 µL, 0.42 mmol, 2 equiv). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.83 (1H, dddd, *J*=8.6, 8.6, 1.9, 1.9 Hz), 8.23 (1H, s), 7.92 (1H, d, *J*=7.0 Hz), 7.11 (2H, dd, *J*=7.1, 1.9 Hz), 6.90 (1H, d, *J*=7.0 Hz), 6.59 (1H, d, *J*=1.2 Hz), 6.58 (1H, d, *J*=10.5 Hz), 4.11 (1H, dd, *J*=10.5, 1.2 Hz), 3.33 (6H, s), 2.26 (3H, s), 1.08 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 170.8, 166.1, 164.3 (d, *J* = 12.2 Hz), 161.8 (d, *J* = 12.2 Hz), 160.0,

139.7, 138.7, 136.6 , 123.4, 111.6, 110.3 (d, J = 26.0 Hz), 107.3 (dd, J = 26.0, 26.0 Hz), 69.2, 57.8, 43.4, 35.7, 27.6, 20.8. ^{19}F NMR (376.5 MHz, $CDCl_3$, ppm) δ -107.8 (dd, J = 7.0, 7.0 Hz). HRMS-ESI (m/z) calcd for $C_{22}H_{28}N_3O_3F_2$ $[M+H]^+$ 420.2099, found 420.2114. Optical rotation $[\alpha]^{20}_D$ –35.5 (*c* 1.52, CH_2Cl_2).

(1*S*,2*S*)-2-(3,5-Dichlorobenzamido)-1-(4-(dimethylamino)pyridin-3-yl)-3,3-dimethylbutyl acetate ((*S*,*S*)–**1r**). The title compound was obtained as pale yellow amorphous solid (23 mg, 47%) by following general procedure A from 3,5-dichloro-benzoic acid (44 mg, 0.23 mmol, 1.1 equiv), HATU (53 mg, 0.116 mmol, 1.2 equiv), 1,2-amino alcohol (*S*,*S*)–**8** (25 mg, 0.096 mmol, 1 equiv), *N*,*N*-diisopropylethylamine (57 µL, 0.35 mmol, 3 equiv) and acetic anhydride (24 µL, 0.23 mmol, 2 equiv). ^{1}H NMR (400 MHz, MeOH-d_3, ppm) δ 8.30-8.04 (2H, m), 7.62 (1H, dd, J=1.9, 1.9 Hz), 7.55 (2H, d, J=1.9 Hz), 7.12 (1H, s), 6.60 (1H, d, J=1.5 Hz), 4.24 (1H, d, J=1.5 Hz), 3.05 (6H, s), 2.23 (3H, s), 1.10 (9H, s). ^{13}C NMR (100.6 MHz, MeOH-d_3, ppm) δ 171.7, 168.2, 160.2, 138.9, 136.3, 132.1, 127.1, 111.4, 70.9, 60.2, 54.8, 49.9, 43.8, 36.1, 27.9, 21.0. HRMS-ESI (m/z) calcd for $C_{22}H_{28}N_3O_3Cl_2$ $[M+H]^+$ 452.1508, found 452.1511. Optical rotation $[\alpha]^{20}_D$ +19.8 (*c* 0.06, CH_2Cl_2).

(1*S*,2*S*)-2-(3,5-Diiodobenzamido)-1-(4-(dimethylamino)pyridin-3-yl)-3,3-dimethylbutyl acetate ((*S*,*S*)–**1s**). The title compound was obtained as light yellow oil (10 mg, 7%) by following general procedure A from 3,5-diiodo-benzoic acid (87 mg, 0.23 mmol, 1.1 equiv), HATU (96 mg, 0.25 mmol, 1.2 equiv), 1,2-amino alcohol (*S*,*S*)-**8** (50 mg, 0.21 mmol, 1 equiv), *N*,*N*-diisopropylethylamine (104 µL, 0.63 mmol, 3 equiv) and acetic anhydride (40 µL, 0.42 mmol, 2 equiv). ^{1}H NMR (400 MHz, MeOH-d_3, ppm) δ 8.29-8.19 (1H, m), 8.24 (1H, dd, J=1.5, 1.5 Hz), 8.14-8.05 (1H, m), 7.90 (2H, d, J=1.5 Hz), 7.24-7.02 (1H, m), 6.59 (1H, d, J=1.5 Hz), 4.25 (1H, d, J=1.5 Hz), 3.01 (6H, s), 2.23 (3H, s), 1.09 (9H, s). ^{13}C NMR (100.6 MHz, MeOH-d_3, ppm) δ 171.7, 167.8, 160.7, 149.0, 148.0, 146.0, 139.2, 136.7, 95.3, 71.0, 60.2, 49.9, 43.8, 36.1, 27.9, 21.0. HRMS-ESI (m/z) calcd for $C_{22}H_{28}N_3O_3I_2$ $[M+H]^+$ 636.022, found 636.0223. Optical rotation $[\alpha]^{20}_D$ +25.6 (*c* 0.06, CH_2Cl_2).

2-(3,5-Bis(pentafluoro-λ^6-sulfanyl)benzamido)-1-(4-(dimethylamino)pyridin-3-yl)-3,3-dimethylbutyl acetate ((*S*,*S*)–**1x**). The title compound was obtained as white amorphous solid (300 mg, 66%) by following general procedure A from 3,5-bis(pentafluoro-λ^6-sulfanyl)benzoic acid (295 mg, 0.788 mmol, 1.1 equiv), HATU (327 mg, 0.860 mmol, 1.2 equiv), 1,2-amino alcohol (*S*,*S*)-**8** (170 mg, 0.716 mmol, 1 equiv), *N*,*N*-diisopropylethylamine (371 µL, 2.149 mmol, 3 equiv) and acetic anhydride (203 µL, 2.149 mmol, 3 equiv). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.35 (1H, d, *J*=5.5 Hz), 8.24 (1H, dd, *J*=1.9, 1.9 Hz), 8.17 (1H, s), 8.08 (2H, d, *J*=1.9 Hz), 6.94 (1H, d, *J*=5.5 Hz), 6.58 (1H, d, *J*=1.7 Hz), 6.32 (1H, d, *J*=10.6 Hz), 4.34 (1H, dd, *J*=10.6, 1.7 Hz), 2.88 (6H, s), 2.22 (3H, s), 1.08 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 169.7, 163.8, 158.5, 154.1, 150.7, 147, 136.9, 128.1, 127.4, 126.7, 114.7, 70.2, 59.6, 43.3, 27.3, 21.3. ^{19}F NMR (376.5 MHz, $CDCl_3$, ppm) δ 80.7 (p, *J* = 151.0 Hz), 63.0 (d, *J* = 151.0 Hz). HRMS-ESI (m/z) calcd for $C_{22}H_{28}N_3O_3S_2F_{10}$ $[M+H]^+$ 636.1412, found 636.1414. Optical rotation $[\alpha]^{20}_D$ +1.2 (*c* 0.85, CH_2Cl_2).

2-(3-Bromo-5-(pentafluoro-λ^6-sulfanyl)benzamido)-1-(4-(dimethylamino)pyridin-3-yl)-3,3-dimethylbutyl acetate ((*S*,*S*)–**1y**). The title compound was obtained as white amorphous solid (51 mg, 31%) by following general procedure A from 3-bromo-5-(pentafluoro- λ^6-sulfanyl)benzoic acid (100 mg, 0.307 mmol, 1.1 equiv), HATU (127 mg, 0.335 mmol, 1.2 equiv), 1,2-amino alcohol (*S*,*S*)–**8** (66 mg, 0.279 mmol, 1 equiv), *N*,*N*-diisopropylethylamine (135 µL, 0.837 mmol, 3 equiv) and acetic anhydride (52 µL, 0.558 mmol, 2 equiv). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.33 (1H, d, *J*=5.4 Hz), 8.21 (1H, s), 7.99 (1H, dd, *J*=1.8, 1.8 Hz), 7.89 (1H, dd, *J*=1.8, 1.8 Hz), 7.81 (1H, dd, *J*=1.8, 1.8 Hz), 6.93 (1H, d, *J*=5.4 Hz), 6.57 (1H, d, *J*=1.6 Hz), 6.32 (1H, d, *J*=10.7 Hz), 4.31 (1H, dd, *J*=10.7, 1.6 Hz), 2.89 (6H, s), 2.21 (3H, s), 1.07 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 169.7, 164.3, 158.5, 150.2, 146.9, 137.3, 132.5, 131.8, 128.1, 123.7, 122.7, 114.6, 70.2, 59.2, 43.9, 35.3, 27.4, 21.4. ^{19}F NMR (376.5 MHz, $CDCl_3$, ppm) δ 81.7 (p, *J* = 150.8 Hz), 62.9 (d, *J* = 150.8 Hz). HRMS-ESI (m/z) calcd for $C_{22}H_{28}N_3O_3SBrF_5$ $[M+H]^+$ 588.0955, found 588.0952. Optical rotation $[\alpha]^{20}_D$ +64.6 (*c* 0.40, CH_2Cl_2).

General procedure B for multi-step synthesis of chiral DMAP catalysts (*S*,*S*)–**1e**,**m**,**u**,**v** (see Figure 6).

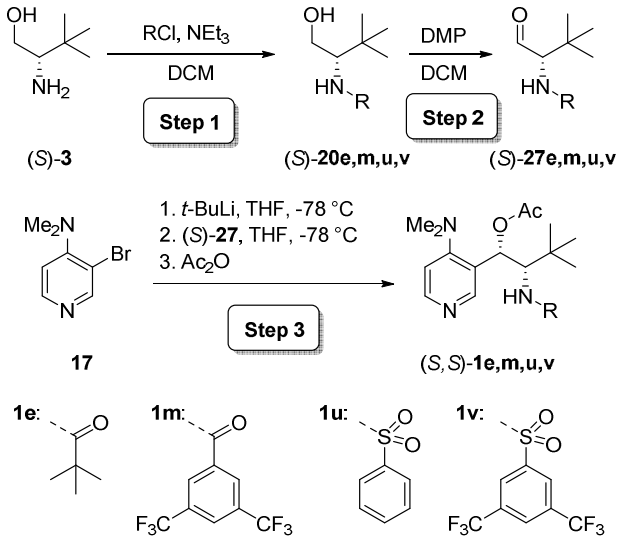


Figure 6. Multistep synthesis of chiral DMAP catalysts (*S*,*S*)–**1e**,**m**,**u**,**v**

Step 1. Acid chloride (1 equiv) was added dropwise to a colorless solution of triethylamine (2.2 equiv) and (*S*)-2-amino-3,3-dimethylbutan-1-ol ((*S*)–**3**) (1 equiv) in CH_2Cl_2 (1 mL of CH_2Cl_2 / 0.5 mmol aminoalcohol (*S*)-**3**) at 0 °C (crushed ice). The reaction progress was monitored by UPLC-MS analysis. Upon complete conversion of the starting (*S*)–**3** precipitates were filtered and filter cake was washed with CH_2Cl_2 (2 x 10 mL). Filtrate was concentrated and the colorless oily residue was purified by column chromatography (120 g silica gel) using gradient elution from 0% EtOAc in hexanes to 100% EtOAc.

Step 2. Dess-Martin periodinane (1.2 equiv) was added portion wise to a solution of amidoalcohol (*S*)-**20** (1 equiv) in CH_2Cl_2 (1 mL CH_2Cl_2 / 0.3 mmol amidoalcohol (*S*)-**20**) at 0 °C. After 10 min the suspension was warmed to room temperature. The reaction progress was monitored by UPLC-MS analysis. Upon complete conversion of the starting (*S*)–**20** the white suspension was diluted with Et_2O and poured into $Na_2S_2O_3 \cdot 5H_2O$ (0.3 M solution in saturated $NaHCO_3$ solution, 10 equiv). The resulting two-phase system was stirred vigorously until organic layer became clear. Layers were separated and the organic layer was washed with saturated $NaHCO_3$ solution and brine. Organic extract was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was used immediately in the next step without purification.

Step 3. The title compound was prepared using modified literature procedure.[19] Thus, an oven-dried flask was charged with *t*-BuLi (1.6 M solution in pentane, 4.6 equiv) and cooled to –100 °C (liquid nitrogen/Et_2O) then anhydrous THF was added to obtain 0.6 M *t*-BuLi solution. Then, a solution of 3-bromo-*N*,*N*-dimethylpyridin-4-amine (**17**) (0.1 M solution in anhydrous THF, 2.3 equiv) was added by syringe pump to the *t*-BuLi solution maintaining reaction temperature below -95 °C (addition rate 1.5 mL/min). The light orange solution was stirred at –100 °C for 1 h whereupon (*S*)-*N*-(3,3-dimethyl-1-oxobutan-2-yl)-3,5-bis(trifluoromethyl)benzamide ((*S*)-**27m**) (0.1 M solution in anhydrous THF, 1 equiv) was added by syringe pump to the reaction mixture maintaining reaction temperature below –95 °C (addition rate 1.5 mL/min). The orange solution was stirred at –100 °C for 2 h, quenched with neat Ac_2O (8 equiv) and warmed to room temperature. Volatiles were removed under reduced pressure, the light brown oil was dissolved in CH_2Cl_2 (30 mL) and washed with aqueous 1M NaOH solution (40 mL). Aqueous layer was washed with CH_2Cl_2 (2 x 30 mL), combined organic layers were dried over Na_2SO_4, filtered and concentrated. Purification of the crude product by column chromatography (120 g of RP-18 silica gel) using isocratic elution with 25% MeCN in water containing 0.1% AcOH afforded product as a light yellow amorphous solid.

(*S*)-*N*-(1-Hydroxy-3,3-dimethylbutan-2-yl)pivalamide ((*S*)–**20e**). The title compound was obtained as white amorphous solid (755 mg, 95%) by following general procedure B, step 1 from (*S*)-2-amino-3,3-dimethylbutan-1-ol ((*S*)–**3**) (463 mg, 3.95 mmol, 1 equiv), pivaloyl chloride (0.53 mL, 4.3 mmol, 1.1 equiv) and triethylamine (1.2 mL, 8.7 mmol, 2.2 equiv). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 5.84 (s, 1H), 3.77-3.92 (m, 2H), 3.57 (dd, J=10.7, 7.7 Hz, 1H), 1.26 (s, 9H), 0.98 (s, 9H). The ^{1}H NMR spectra is in full agreement with that reported in the literature.[53]

(*S*)-*N*-(1-Hydroxy-3,3-dimethylbutan-2-yl)-3,5-bis(trifluoromethyl)benzamide ((*S*)–**20m**). The title compound was obtained as white amorphous solid (4.54 g, 74%) by following general procedure B, step 1 from triethylamine (5.22 mL, 37.546 mmol, 2.2 equiv), (*S*)-2-amino-3,3-dimethylbutan-1-ol ((*S*)–**3**) (2.0 g, 17.1 mmol, 1 equiv) and 3,5-bis(trifluoromethyl)benzoyl chloride (3.1 mL, 17.1 mmol, 1 equiv). Analytical TLC on silica gel, 2:5 EtOAc/Hexanes, R_f=0.35. ^{1}H NMR (400 MHz, $CDCl_3$,

ppm) δ 8.18 (2H, s), 7.97 (1H, s), 6.52 (1H, d, *J*=9.5 Hz), 4.10 (1H, ddd, *J*=9.5, 7.2, 3.8 Hz), 3.99-3.90 (1H, m), 3.80-3.68 (1H, m), 2.44 (1H, s), 1.04 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 165.8, 137.0, 132.3 (q, *J* = 34.0 Hz), 127.4, 125.2, 123.0 (q, *J* = 272.8 Hz), 62.5, 60.0, 34.3, 27.2. ^{19}F NMR (376.5 MHz, $CDCl_3$) δ -63.0. HRMS-ESI (m/z) calcd for $C_{15}H_{18}NO_2F_6$ $[M+H]^+$ 358.1242, found 358.1238. Optical rotation $[\alpha]^{20}_D$ –6.5 (*c* 0.73, CH_2Cl_2).

(*S*)-*N*-(1-Hydroxy-3,3-dimethylbutan-2-yl)benzenesulfonamide ((*S*)–**20u**). The title compound was obtained as white amorphous solid (200 mg, 91%) by following general procedure B, step 1 from triethylamine (0.26 mL, 1.9 mmol, 2.2 equiv), (*S*)-2-amino-3,3-dimethylbutan-1-ol ((*S*)–**3**) (100 mg, 0.85 mmol, 1 equiv) and benzenesulfonyl chloride (166 mg, 0.94 mmol, 1.1 equiv). Analytical TLC on silica gel, 2:5 EtOAc/Hexanes, R_f=0.36. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.96-7.86 (2H, m), 7.63-7.45 (3H, m), 4.88-4.69 (1H, m), 3.71-3.53 (2H, m), 3.03 (1H, ddd, *J*=9.6, 6.0, 4.2 Hz), 2.07-1.95 (1H, m), 0.81 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 140.7, 132.9, 129.2, 127.4, 64.2, 62.4, 34.2, 27.1. HRMS-ESI (m/z) calcd for $C_{12}H_{18}NO_3S$ $[M-H]^+$ 256.1007, found 256.1018. Optical rotation $[\alpha]^{20}_D$ –17.6 (*c* 0.62, CH_2Cl_2).

(*S*)-*N*-(1-Hydroxy-3,3-dimethylbutan-2-yl)-3,5-bis(trifluoromethyl)benzenesulfonamide ((*S*)–**20v**). The title compound was obtained as white amorphous solid (285 mg, 85%) by following general procedure B, step 1 from triethylamine (0.26 mL, 1.9 mmol, 2.2 equiv), (*S*)-2-amino-3,3-dimethylbutan-1-ol ((*S*)–**3**) (100 mg, 0.85 mmol, 1 equiv) and 3,5-bis(trifluoromethyl)benzenesulfonyl chloride (293 mg, 0.94 mmol, 1.1 equiv). Analytical TLC on silica gel, 2:5 EtOAc/Hexanes, R_f=0.71. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.36 (2H, s), 8.04 (1H, s), 5.12 (1H, d, *J*=9.8 Hz), 3.72 (1H, dd, *J*=11.3, 3.8 Hz), 3.60 (1H, dd, *J*=11.3, 6.8 Hz), 3.19 (1H, ddd, *J*=9.8, 6.8, 3.8 Hz), 1.86-1.68 (1H, br s), 0.87 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 144.2, 132.8 (q, *J* = 34.5 Hz), 127.7, 126.0, 122.7 (q, *J* = 273.3 Hz), 64.8, 62.0, 34.3, 27.1. ^{19}F NMR (376.5 MHz, $CDCl_3$, ppm) δ -63.0. HRMS-ESI (m/z) calcd for $C_{14}H_{16}NO_3F_6S$ $[M-H]^+$ 392.0755, found 392.0771. Optical rotation $[\alpha]^{20}_D$ +2.2 (*c* 0.68, CH_2Cl_2).

(*S*)-*N*-(3,3-Dimethyl-1-oxobutan-2-yl)pivalamide ((*S*)–**27e**). The title compound was obtained as white amorphous solid (253 mg, 81%) by following general procedure B, step 2 from (*S*)-*N*-(1-hydroxy-3,3-dimethylbutan-2-yl)pivalamide ((*S*)–**20e**) (313 mg, 1.51 mmol, 1 equiv) and Dess Martin periodinane (1.318 g, 3.11 mmol, 2 equiv). IR (KBr, cm^{-1}) 3371 (NH), 2728 (C=O), 1734 (C=O), 1657 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.83 (1H, s), 6.31-6.16 (1H, br s), 4.55 (1H, d, *J*=8.2 Hz), 1.23 (9H, s), 1.03 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 201.2, 178.8, 65.5, 39.2, 36.1, 27.7, 27.0. HRMS-ESI (m/z) calcd for $C_{11}H_{22}NO_2$ $[M+H]^+$ 200.1651, found 200.1640. Optical rotation $[\alpha]^{20}_D$ +70.3 (*c* 2.00, CH_2Cl_2).

(*S*)-*N*-(3,3-Dimethyl-1-oxobutan-2-yl)-3,5-bis(trifluoromethyl)benzamide ((*S*)–**27m**). The title compound was obtained as a white amorphous solid (900 mg, 91%) by following general procedure B step 2 from (*S*)–**20m** (1.0 g, 2.8 mmol, 1 equiv) and Dess Martin periodinane (3.56 g, 8.4 mmol, 3 equiv) following oxidation procedure described in synthesis of (*S*)-2-azido-3,3-dimethylbutanal ((*S*)-6). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 9.95 (1H, s), 8.24 (2H, s), 8.04 (1H, s), 6.84 (1H, d, *J*=8.5 Hz), 4.86 (1H, d, *J*=8.5 Hz), 1.16 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 200.3, 165.1, 136.3, 132.5 (q, *J* = 34.1 Hz), 127.5, 125.5, 123.0 (q, *J* = 273.1 Hz), 66.7, 36.6, 27.2. ^{19}F NMR (376.5 MHz, $CDCl_3$, ppm) δ -62.9. HRMS-ESI (m/z) calcd for $C_{15}H_{16}NO_2F_6$ $[M+H]^+$ 356.1085, found 356.1084. Optical rotation $[\alpha]^{20}_D$ +104.9 (*c* 0.64, CH_2Cl_2).

(*S*)-*N*-(3,3-Dimethyl-1-oxobutan-2-yl)benzenesulfonamide ((*S*)–**27u**). Title compound was obtained as white amorphous solid (73 mg, 73%) by following general procedure B, step 2 from (*S*)-*N*-(1-hydroxy-3,3-dimethylbutan-2-yl)benzenesulfonamide ((*S*)–**20e**) (100 mg, 0.389 mmol, 1 equiv) and Dess Martin periodinane (329 mg, 0.777 mmol, 2 equiv). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.57 (1H, d, *J*=0.7 Hz), 7.88-7.76 (2H, m), 7.59-7.45 (3H, m), 5.41 (1H, d, *J*=8.7 Hz), 3.69 (1H, dd, *J*=8.7, 0.7 Hz), 1.02 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 199.5, 139.7, 133.1, 129.2, 127.3, 69.8, 36.0, 26.9. HRMS-ESI (m/z) calcd for $C_{12}H_{16}NO_3S$ $[M-H]^+$ 254.0851, found 254.0862. Optical rotation $[\alpha]^{20}_D$ +168.0 (*c* 0.66, CH_2Cl_2).

(*S*)-*N*-(3,3-Dimethyl-1-oxobutan-2-yl)-3,5-bis(trifluoromethyl)benzenesulfonamide ((*S*)–**27v**). Title compound (*S*)-27v was obtained as white amorphous solid (88 mg, 88%) by following general procedure B, step 2 from (*S*)-*N*-(1-hydroxy-3,3-dimethylbutan-2-yl)-3,5-bis(trifluoromethyl)benzenesulfonamide ((*S*)–**20v**) (100 mg, 0.254 mmol, 1 equiv) and Dess Martin periodinane (324 mg, 0.763 mmol, 3 equiv). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.64 (1H, s), 8.28 (2H, s), 8.05 (1H, s), 5.54 (1H, d, *J*=9.3 Hz), 3.82 (1H, d, *J*=9.3 Hz), 1.07 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 198.8, 142.9, 133.1 (q, *J* = 34.6 Hz), 127.7 (q, *J* = 3.7 Hz), 126.6 – 126.4 (m), 122.5 (q, *J* = 273.4 Hz), 70.4 , 36.1 , 26.9. ^{19}F NMR (376.5 MHz, $CDCl_3$, ppm) δ -63.1. HRMS-ESI (m/z) calcd for $C_{14}H_{14}NO_3F_6S$ $[M-H]^+$ 390.0599, found 390.0611. Optical rotation $[\alpha]^{20}_D$ +120.6 (*c* 0.69, CH_2Cl_2).

(1*S*,2*S*)-1-(4-(Dimethylamino)pyridin-3-yl)-3,3-dimethyl-2-pivalamidobutyl acetate ((*S*,*S*)–**1e**). The title compound (*S*,*S*)–**1e** was obtained as light yellow amorphous solid (76 mg, 28%) by following general procedure B, step 3 from *t*-BuLi (1.6 M solution in pentane, 1.4 mL, 3.3 mmol, 4.2 equiv), 3-bromo-*N*,*N*-dimethylpyridin-4-amine (**17**) (333 mg, 1.66 mmol, 2 equiv), (*S*)-*N*-(3,3-Dimethyl-1-oxobutan-2-yl)pivalamide ((*S*)–**27e**) (150 mg, 0.753 mmol, 1 equiv) and Ac_2O (0.355 mL, 3.77 mmol, 5 equiv). IR (KBr, cm^{-1}) 1743 (C=O), 1669 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.33 (1H, s), 8.22 (1H, d, *J*=6.2 Hz), 6.89 (1H, d, *J*=6.2 Hz), 6.49 (1H, d, *J*=1.5 Hz), 598 (1H, d, *J*=10.5 Hz), 4.02 (1H, dd, *J*=10.5, 1.5 Hz), 3.05 (6H, s), 2.23 (3H, s), 1.07 (9H, s), 0.99 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 178.1, 170.0, 160.0, 144.0, 143.0, 126.7, 113.3, 70.0, 56.6, 43.5, 39.0, 35.3, 27.6, 27.4, 21.3. HRMS-ESI (m/z) calcd for $C_{20}H_{34}N_3O_3$ $[M+H]^+$ 364.2600, found 364.2596. Optical rotation $[\alpha]^{20}_D$ –117 (*c* 1.18, CH_2Cl_2).

(1*S*,2*S*)-2-(3,5-Bis(trifluoromethyl)benzamido)-1-(4-(dimethylamino)pyridin-3-yl)-3,3-dimethylbutyl acetate ((*S*,*S*)–**1m**). The title compound (*S*,*S*)–**1m** was obtained by following general procedure B, step 3 from *t*-BuLi (1.6 M solution in pentane, 5.26 mL, 8.42 mmol, 4.6 equiv), 3-bromo-*N*,*N*-dimethylpyridin-4-amine (**17**) (846 mg, 4.21 mmol, 2.3 equiv), (*S*)-*N*-(3,3-dimethyl-1-oxobutan-2-yl)-3,5-bis(trifluoromethyl)benzamide ((*S*)–**27m**) (650 mg, 1.83 mmol, 1 equiv) and Ac_2O

(1.38 mL, 14.64 mmol, 8 equiv). Purification of the crude product by column chromatography (120 g of RP-18 silica gel) using isocratic elution with 25% MeCN in water containing 0.1% AcOH afforded product as a light yellow amorphous solid (741 mg, 78% yield). Pure material was obtained by crystallization of hydrochloric acid salt of (*S*,*S*)-1m (710 mg) from MeCN (4.4 mL) and Et_2O (33 mL), followed with conversion of the salt back to free base (*S*,*S*)-1m by washing the suspension of (*S*,*S*)–**1m** HCl salt in EtOAc (30 mL) with aqueous saturated $NaHCO_3$ solution (2x40 mL). Yield: 613 mg (65% yield) of (*S*,*S*)–**1m** as a white foam. Analytical TLC on silica gel, 95:5 MeOH/$CHCl_3$, R_f=0.32. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.34 (1H, d, *J*=5.4 Hz), 8.19-8.16 (1H, m), 8.03-7.96 (3H, m), 6.94 (1H, d, *J*=5.4 Hz), 6.59 (1H, d, *J*=1.6 Hz), 6.35 (1H, d, *J*=10.6 Hz), 4.36 (1H, dd, *J*=10.6, 1.6 Hz), 2.89 (6H, s), 2.22 (3H, s), 1.09 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 169.7, 164.5, 158.5, 150.6, 147.0, 136.8, 132.5 (q, *J* = 33.9 Hz), 128.2, 127.0, 125.3, 123.0 (q, *J* = 273.0 Hz), 114.7, 70.2, 59.3, 43.9, 35.3, 27.4, 21.4. ^{19}F NMR (376.5 MHz, $CDCl_3$, ppm) δ -62.9. HRMS-ESI (m/z) calcd for $C_{24}H_{28}N_3O_3F_6$ $[M+H]^+$ 520.2035, found 520.2032. Optical rotation (99% ee, HPLC/csp) $[\alpha]^{20}_D$ –5.0 (*c* 0.28, CH_2Cl_2). HPLC/csp assay: Daicel CHIRALPAK IC, 25 cm × 4.6 mm i.d., mobile phase 10% IPA/90% Hexanes, flow rate 1 mL/min, detector UV 254 nm, retention time 9.8 min, major and 7.6 min, minor.

(1*S*,2*S*)-1-(4-(Dimethylamino)pyridin-3-yl)-3,3-dimethyl-2-(phenylsulfonamido)butyl acetate ((*S*,*S*)–1u). The title compound was obtained as light yellow oil (5 mg, 7%) by following general procedure B, step 3 from *t*-BuLi (1.6 M solution in pentane, 0.22 mL, 0.42 mmol, 4.2 equiv), 3-bromo-*N*,*N*-dimethylpyridin-4-amine (**17**) (40 mg, 0.2 mmol, 2 equiv), (*S*)-*N*-(3,3-dimethyl-1-oxobutan-2-yl)-3,5-bis(trifluoromethyl)benzenesulfonamide ((*S*)–**27u**) (43 mg, 0.1 mmol, 1 equiv) and Ac_2O (0.047 mL, 0.5 mmol, 5 equiv). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.31 (1H, d, *J*=5.3 Hz), 8.20 (1H, s), 7.57-7.49 (2H, m), 7.49-7.43 (1H, m), 7.40-7.32 (2H, m), 6.93 (1H, d, *J*=5.3 Hz), 6.4 (1H, s), 4.97 (1H, d, *J*=10.5 Hz), 3.70 (1H, d, *J*=10.5 Hz), 2.81 (6H, s), 2.16 (3H, s), 0.92 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 170.0, 158.8, 149.9, 147.9, 142.1, 132.2, 129.0, 126.4, 114.5, 70.1, 65.1, 44.0, 35.8, 27.6, 21.3. HRMS-ESI (m/z) calcd for $C_{21}H_{30}N_3O_4S$ $[M+H]^+$ 420.1957, found 420.1959. Optical rotation $[\alpha]^{20}_D$ +5 (*c* 0.09, CH_2Cl_2).

(1*S*,2*S*)-2-((3,5-Bis(trifluoromethyl)phenyl)sulfonamido)-1-(4-(dimethylamino)pyridin-3-yl)-3,3-dimethylbutyl acetate ((*S*,*S*)–**1v**). The title compound was obtained as light yellow oil (11 mg, 12%) by following general procedure B, step 3 from *t*-BuLi (1.6 M solution in pentane, 0.22 mL, 0.42 mmol, 4.2 equiv), 3-bromo-*N*,*N*-dimethylpyridin-4-amine (**17**) (40 mg, 0.2 mmol, 2 equiv), (*S*)-*N*-(3,3-dimethyl-1-oxobutan-2-yl)-3,5-bis(trifluoromethyl)benzamide ((*S*)–**27v**) (55 mg, 0.1 mmol, 1 equiv) and Ac_2O (0.047 mL, 0.5 mmol, 5 equiv). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.24 (1H, s), 8.19 (1H, d, *J*=5.6 Hz), 8.04 (2H, s), 7.95 (1H, s), 6.92 (1H, d, *J*=5.6 Hz), 6.44 (1H, s), 6.30-6.13 (1H, br s), 3.62 (1H, s), 2.88 (6H, s), 2.17 (3H, s), 0.95 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 169.9, 159.0, 148.5, 146.9, 144.9, 132.6 (q, *J* = 34.4 Hz), 126.7, 125.8, 122.6 (d, *J* = 273.3 Hz), 114.2, 69.8, 65.7, 43.9, 36.0, 27.7, 21.2. ^{19}F NMR (376.5 MHz, $CDCl_3$) δ -62.9. HRMS-ESI (m/z) calcd for $C_{23}H_{27}F_6N_3O_4S$ $[M+H]^+$ 556.1705, found 556.1707. Optical rotation $[\alpha]^{20}_D$ –58.3 (*c* 0.48, CH_2Cl_2).

Synthesis and characterization of chiral DMAP catalyst (*S*,*S*)–1d (see Figure 7)

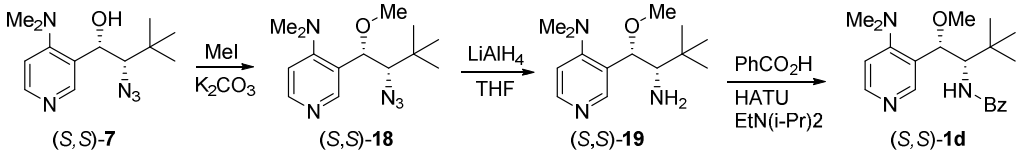


Figure 7. Synthesis of chiral DMAP catalyst (*S*,*S*)–**1d**

3-((1*S*,2*S*)-2-Azido-1-methoxy-3,3-dimethylbutyl)-*N*,*N*-dimethylpyridin-4-amine ((*S*,*S*)–**18**). A solution of azide (*S*,*S*)-**7** (50 mg, 0.19 mmol, 1 equiv) in anhydrous THF (4 mL) was cooled to –78 °C (anhydrous ice bath) and KHMDS (1.0 M solution in THF, 200 µL, 0.20 mmol, 1.05 equiv) was added dropwise under argon atmosphere. The resulting pale yellow solution was stirred at –78 °C for 15 min whereupon methyl iodide (13 µL, 0.20 mmol, 1.05 equiv) was added. After stirring at –78 °C for 15 min the pale yellow solution was quenched with aqueous saturated NH_4Cl solution (5 mL) and extracted with EtOAc (3 x 5 mL). Combined organic extracts were washed with brine (5 mL) and dried on Na_2SO_4. Column chromatography (6 g of silica gel) using gradient elution from 50% EtOAc in hexanes to 100% EtOAc afforded (*S*,*S*)–**18** as a colorless oil (52 mg, 98% yield); analytical TLC on

silica gel, 1:1 EtOAc/hexanes, R_f=0.2. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.92-8.61 (1H, m), 8.61-8.36 (1H, m), 6.95 (1H, d, *J*=5.3 Hz), 4.96 (1H, d, *J*=2.0 Hz), 3.35 (3H, s), 3.10 (1H, d, *J*=2.0 Hz), 2.78 (6H, s), 1.08 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 159.3, 150.4, 150.1, 117, 114.3, 77.7, 75.3, 57.1, 44.3, 36.7, 27.8. HRMS-ESI (m/z) calcd for $C_{14}H_{24}N_5O$ $[M+H]^+$ 278.1981, found 278.1987. Optical rotation $[\alpha]^{20}_D$ +15.1 (*c* 0.15, CH_2Cl_2).

3-((1*S*,2*S*)-2-Amino-1-methoxy-3,3-dimethylbutyl)-*N*,*N*-dimethylpyridin-4-amine ((*S*,*S*)–**19**). $LiAlH_4$ (1.0 M solution in THF, 0.22 mL, 1 M, 0.22 mmol, 1.2 equiv) was added dropwise to a cooled solution (0 °C) of 3-((1*S*,2*S*)-2-Azido-1-methoxy-3,3-dimethylbutyl)-*N*,*N*-dimethylpyridin-4-amine ((*S*,*S*)–**18**) (50 mg, 0.18 mmol, 1 equiv) in anhydrous THF (3 mL). After stirring for 30 min, the white suspension was warmed to room temperature. After 1 h of stirring at room temperature UPLC-MS analysis of the reaction mixture showed full conversion. The reaction mixture was cooled to 0 °C and quenched by sequential (within intervals of 10 minutes) addition of water (10 μL), 4 M aqueous NaOH solution (20 μL) and more water (30 μL). Ten minutes after addition of final amount of water, the white suspension was filtered through a Celite pad. The filter cake was washed with EtOAc (30 mL). The filtrate was evaporated to dryness yielding 42 mg (93%) of aminopyridine (*S*,*S*)–**19** as yellow oil, which was used in subsequent step without purification. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.56 (1H, s), 8.39 (1H, d, *J*=5.5 Hz), 6.93 (1H, d, *J*=5.5 Hz), 4.90 (1H, d, *J*=1.2 Hz), 3.29 (3H, s), 2.74 (6H, s), 2.30 (1H, d, *J*=1.2 Hz), 1.03 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 159.4, 149.7, 149.5, 130.1, 114.4, 77.3, 63.4, 56.5, 44.2, 35.1, 27.7. HRMS-ESI (m/z) calcd for $C_{14}H_{26}N_3O$ $[M+H]^+$ 252.2076, found 252.208. Optical rotation $[\alpha]^{20}_D$ –3.6 (*c* 0.12, CH_2Cl_2).

***N*-((1*S*,2*S*)-1-(4-(Dimethylamino)pyridin-3-yl)-1-methoxy-3,3-dimethylbutan-2-yl)benzamide** ((*S*,*S*)–**1d**). A solution of benzoic acid (24.2 mg, 0.198 mmol, 1.1 equiv) and HATU (83.3 mg, 0.216 mmol, 1.2 equiv) in anhydrous CH_2Cl_2 (2 mL) was stirred at room temperature for 15 minutes whereupon a solution of 3-((1*S*,2*S*)-2-amino-1-methoxy-3,3-dimethylbutyl)-*N*,*N*-dimethylpyridin-4-amine ((*S*,*S*)–**19**) (45 mg, 0.180 mmol, 1 equiv) in anhydrous CH_2Cl_2 (2 mL) was added. After stirring for 15 minutes at room temperature, the colorless solution was cooled to 0 °C (crushed ice) and *N*,*N*-

diisopropylethylamine (89 μL, 0.541 mmol, 3 equiv) was added. The pale yellow reaction mixture was stirred at room temperature and reaction progress was monitored by UPLC-MS analysis. Upon complete conversion volatiles were removed under reduced pressure. Column chromatography (12 g of RP-18 silica gel) using 20% MeCN in water containing 0.1% AcOH afforded (*S*,*S*)–**1d** as a pale yellow oil (19 mg, 30% yield); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.37 (1H, s), 8.32 (1H, d, *J*=5.4 Hz), 7.69-7.62 (2H, m), 7.48-7.36 (3H, m), 6.93 (1H, d, *J*=5.4 Hz), 6.62 (1H, d, *J*=10.4 Hz), 5.03 (1H, s), 4.07 (1H, d, *J*=10.4 Hz), 3.33 (3H, s), 2.78 (6H, s), 1.10 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 167.4, 159.7, 150.0, 148.5, 135.2, 131.2, 129.1, 128.7, 126.9, 114.8, 76.4, 60.1, 56.7, 44.4, 35.8, 27.6. HRMS-ESI (m/z) calcd for $C_{21}H_{29}N_3O_2$ $[M+H]^+$ 356.2338, found 356.2339. Optical rotation $[\alpha]^{20}_D$ +89.3 (*c* 0.97, CH_2Cl_2).

(1*S*,2*S*)-1-(4-(Dimethylamino)pyridin-3-yl)-3,3-dimethyl-2-phenylthioamidobutyl acetate ((*S*,*S*)–**1t**). A brown suspension of (1*S*,2*S*)-2-benzamido-1-(4-(dimethylamino)pyridin-3-yl)-3,3-dimethylbutyl acetate ((*S*,*S*)–**1a**) (7.4 mg, 0.019 mmol, 1 equiv) and Lawesson's reagent (7.8 mg, 0.019 mmol, 1 equiv) in anhydrous toluene (0.2 mL) in a sealed pressure vial (5 mL) was stirred at 120 °C (oil bath temperature) for 9 minutes, cooled to ambient temperature and solvent was removed under reduced pressure. Purification of the crude product by column chromatography (12 g of silica gel) using isocratic elution from 50% EtOAc in hexanes afforded (*S*,*S*)–**1t** as a colorless oil (4.9 mg, 29% yield); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.36 (1H, d, *J*=5.4 Hz), 8.15 (1H, s), 7.67 (1H, d, *J*=10.8 Hz), 7.58-7.49 (2H, m), 7.49-7.30 (3H, m), 6.90 (1H, d, *J*=5.4 Hz), 6.65 (1H, d, *J*=1.4 Hz), 5.26 (1H, dd, *J*=10.8, 1.4 Hz), 2.89 (6H, s), 2.19 (3H, s), 1.13 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 201.9, 169.7, 158.9, 150.4, 147.2, 143.2, 130.8, 128.8, 126.4, 114.7, 70.4, 63.4, 43.9, 36.2, 27.5, 21.4. HRMS-ESI (m/z) calcd for $C_{22}H_{30}N_3O_2S$ $[M+H]^+$ 400.2059, found 400.2059. Optical rotation $[\alpha]^{20}_D$ –59.9 (*c* 0.09, CH_2Cl_2).

(1*S*,2*S*)-2-(3-(3,5-Bis(trifluoromethyl)phenyl)thioureido)-1-(4-(dimethylamino)pyridin-3-yl)-3,3-dimethylbutyl acetate ((*S*,*S*)–**1w**). 1-Isothiocyanato-3,5-bis(trifluoromethyl)benzene (31 μL, 0.169 mmol, 1 equiv) was added to a solution of (1*S*,2*S*)-2-amino-1-(4-(dimethylamino)pyridin-3-yl)-3,3-

dimethylbutan-1-ol ((*S*,*S*)–**8**) (40 mg, 0.169 mmol, 1 equiv) in anhydrous THF (1.3 mL). The yellow solution was stirred at room temperature under argon atmosphere for 12 hours whereupon acetic anhydride (19 μL, 0.203 mmol, 1.2 equiv) and triethylamine (28 μL, 0.203, 1.2 equiv) were added. The brown solution was stirred for 3 h and then diluted with EtOAc (15 mL). Organic phase was washed with water (15 mL), brine (15 mL) and dried over Na_2SO_4. Solvent removal and purification by column chromatography (12 g of RP-18 silica gel) using gradient elution from 0% MeCN in water containing 0.1% AcOH to 100% MeCN afforded (*S*,*S*)–**1w** as a pale yellow oil (41 mg, 45% yield); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.99 (1H, s), 8.47 (1H, s), 8.10 (1H, d, *J*=6.2 Hz), 7.74 (2H, s), 7.53 (1H, s), 7.27 (1H, d, *J*=10.5 Hz), 6.88 (1H, d, *J*=6.2 Hz), 6.58 (1H, d, *J*=1.5 Hz), 4.89 (1H, dd, *J*=10.5, 1.5 Hz), 3.11 (6H, s), 1.89 (3H, s), 1.07 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ. ^{19}F NMR (376.5 MHz, $CDCl_3$) δ -63.02. HRMS-ESI (m/z) calcd for $C_{24}H_{29}N_4O_2F_6S$ $[M+H]^+$ 551.1915, found 551.193. Optical rotation $[\alpha]^{20}_D$ -28.1 (*c* 0.20, CH_2Cl_2).

General procedure C for DKR

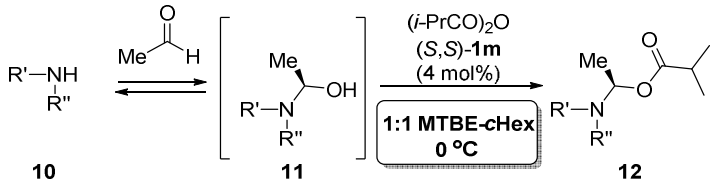


Figure 8. DKR of hemiaminals in 1:1 MTBE-*c*-Hex at 0 °C

A suspension of azole (1.0 equiv), catalyst (*S*,*S*)–**1m** (0.04 equiv) and isobutyric anhydride (1.3 equiv) in cyclohexane (1 mL cyclohexane / 0.16 mmol of azole) was cooled to 0 °C. Then a stock solution of acetaldehyde (1.1 equiv) in MTBE (equal volume to that of cyclohexane) was added (concentration of the reaction mixture must be 0.08 M relative to azole to achieve high enantioselectivity) and the suspension was stirred at 0 °C for 18 hours. Upon stirring the suspension gradually turned into clear solution which indicated that the DKR had reached completion. At that point the clear solution was diluted with EtOAc (10 mL), washed with aqueous saturated $NaHCO_3$ solution (2 x 10 mL), brine and dried over Na_2SO_4. Pure product was obtained by column chromatography (5 g of silica gel) using gradient elution from 0% EtOAc in hexane to 20% EtOAc in hexane.

General procedure D for DKR

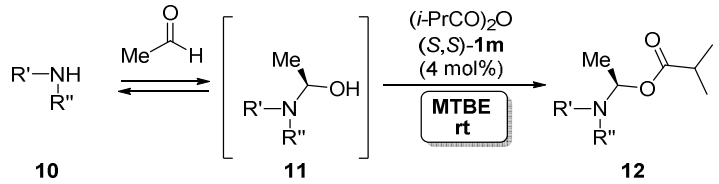


Figure 9. DKR of hemiaminals in MTBE at room temperature

A stock solution of acetaldehyde (1.1 equiv) in MTBE (1 mL MTBE / 0.16 mmol of azole) was added to a suspension of azole (1.0 equiv), catalyst (*S*,*S*)–**1m** (0.04 equiv) and isobutyric anhydride (1.3 equiv) in MTBE (equal volume to that of the stock solution) (concentration of the reaction mixture must be 0.08 M relative to azole to achieve high enantioselectivity) and the suspension was stirred at room temperature for 18 hours. Upon stirring the suspension gradually turned into clear solution which indicated that the DKR had reached completion. At that point the clear solution was diluted with EtOAc (10 mL), washed with aqueous saturated $NaHCO_3$ solution (2 x 10 mL), brine and dried over Na_2SO_4. Pure product was obtained by column chromatography (5 g of silica gel) using gradient elution from 0% EtOAc in hexane to 20% EtOAc in hexane.

General procedure E for DKR

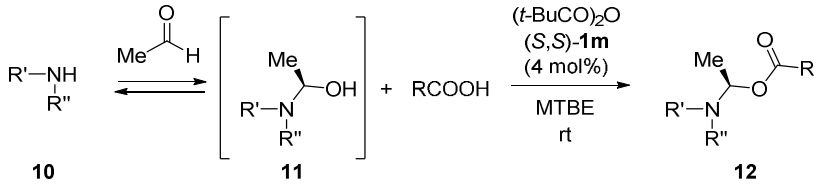


Figure 10. DKR of hemiaminals using *in situ* generated mixed anhydrides

A stock solution of acetaldehyde (1.1 equiv) in MTBE (1 mL MTBE / 0.16 mmol of azole) was added to a suspension of azole (1.0 equiv), catalyst (*S*,*S*)–**1m** (0.04 equiv), carboxylic acid (1.3) and pivalic anhydride (1.3 equiv)in MTBE (equal volume to that of the stock solution) (concentration of the reaction mixture must be 0.08 M relative to azole to achieve high enantioselectivity) and the suspension was stirred at room temperature for 18 hours. Upon stirring the suspension gradually turned into clear solution which indicated that the DKR had reached completion. At that point the

clear solution was diluted with EtOAc (10 mL), washed with aqueous saturated $NaHCO_3$ solution (2 x 10 mL), brine and dried over Na_2SO_4. Pure product was obtained by column chromatography (5 g of silica gel) using gradient elution from 0% EtOAc in hexane to 20% EtOAc in hexane.

DKR of azole hemiaminals 12a-z

(*R*)-1-(5-Phenyl-2*H*-tetrazol-2-yl)ethyl isobutyrate ((*R*)–**12a**). The title compound (*R*)–**12a** was obtained from 5-phenyl-1*H*-tetrazole (30 mg, 0.205 mmol, 1.0 equiv), (*S*,*S*)–**1m** (4.3 mg, 0.008 mmol, 0.04 equiv), isobutyric anhydride (44 μL, 0.267 mmol, 1.3 equiv) and acetaldehyde (12 μL, 0.225 mmol, 1.1 equiv) according to general procedures C and D.

Using General Procedure C: a colorless oil (47 mg, 88%, 93% ee);

Using General Procedure D: a colorless oil (49 mg, 92%, 90% ee).

Analytical TLC on silica gel, 1/10 EtOAc/Hexanes, R_f=0.32. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.21-8.14 (2H, m), 7.53-7.46 (3H, m), 7.36 (1H, q, *J*=6.2 Hz), 2.61 (1H, qq, *J*=7.0, 7.0 Hz), 2.02 (3H, d, *J*=6.2 Hz), 1.20 (3H, d, *J*=7.0 Hz), 1.16 (3H, d, *J*=7.0 Hz). ^{1}H NMR spectra is in agreement with that reported in the literature.[31] HPLC/csp assay (93% ee): Daicel CHIRALPAK IC, 25 cm × 4.6 mm i.d., mobile phase 10% IPA/90% Hexanes, flow rate 1 mL/min, detector UV 254 nm, retention time 8.3 min, major and 6.8 min, minor.

Methyl (*R*)-4-(2-(1-(isobutyryloxy)ethyl)-2*H*-tetrazol-5-yl)benzoate ((*R*)–**12b**). The title compound was obtained as a colorless oil (15 mg, 47%) from methyl 4-(1*H*-tetrazol-5-yl)benzoate (20 mg, 0.098 mmol, 1.0 equiv), catalyst (*S*,*S*)–**1m** (2.0 mg, 0.004 mmol, 0.04 equiv), isobutyric anhydride (21 μL, 0.127 mmol, 1.3 equiv) and acetaldehyde (6 μL, 0.109 mmol, 1.1 equiv) in accordance with general procedure D. Analytical TLC on silica gel, 1:10 EtOAc/Hexanes, R_f=0.35. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.28-8.23 (2H, m), 8.18-8.13 (2H, m), 7.37 (1H, q, *J*=6.2 Hz), 3.95 (3H, s), 2.61 (1H, qq, *J*=7.0, 7.0 Hz), 2.02 (3H, d, *J*=6.2 Hz), 1.20 (3H, d, *J*=7.0 Hz), 1.16 (3H, d, *J*=7.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 174.9, 166.6, 164.5, 132.0, 131.3, 130.3, 127.1, 80.2, 52.5, 33.9, 19.5, 18.7, 18.7. LC–MS m/z (% relative intensity, ion): 246.3 (37.9, $[C_{11}H_9N_4O_3+H]^+$), 205.3 (100.0,

$[C_9H_8N_4O_2+H]^+$). HRMS-ESI (m/z) calcd for $C_{15}H_{18}N_4O_4Na$ $[M+Na]^+$ 341.1226, found 341.1229. HPLC/csp assay (90% ee): Daicel CHIRALPAK IC, 25 cm×4.6 mm i.d., mobile phase 10% IPA/90% Hexanes, flow rate 1 mL/min, detector UV 254 nm, retention time 15.4 min, major and 12.9 min, minor.

(*R*)-1-(5-(4-Nitrophenyl)-2*H*-tetrazol-2-yl)ethyl isobutyrate ((*R*)–**12c**). The title compound was obtained as a colorless oil (45 mg, 72%) from 5-(4-nitrophenyl)-1*H*-tetrazole (39 mg, 0.204 mmol, 1.0 equiv), catalyst (*S*,*S*)–**1m** (4.2 mg, 0.008 mmol, 0.04 equiv), isobutyric anhydride (44 µL, 0.265 mmol, 1.3 equiv) and acetaldehyde (12 µL, 0.225 mmol, 1.1 equiv) in accordance with general procedure C. Analytical TLC on silica gel, 1:10 EtOAc/Hexanes, R_f=0.27. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.40-8.32 (4H, m), 7.38 (1H, q, *J*=6.3 Hz), 2.62 (1H, qq, *J*=7.0, 7.0 Hz), 2.03 (3H, d, *J*=6.3 Hz), 1.21 (3H, d, *J*=7.0 Hz), 1.17 (3H, d, *J*=7.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 174.9, 163.5, 149.2, 133.1, 128.0, 124.4, 80.4, 33.9, 19.6, 18.7, 18.7. LC–MS m/z (% relative intensity, ion): 306.4 (10.4, $[M+H]^+$), 233.3 (96.0, $[C_9H_6N_5O_3+H]^+$), 192.2 (100.0, $[C_7H_5N_5O_2+H]^+$). HRMS-APCI (m/z) calcd for $C_{13}H_{15}N_5O_4Na$ $[M+Na]^+$ 328.1016, found 328.1020. HPLC/csp assay (84% ee): Daicel CHIRALPAK IC, 25 cm×4.6 mm i.d., mobile phase 10% IPA/90% Hexanes, flow rate 1 mL/min, detector UV 254 nm, retention time 19.6 min, major and 16.8 min, minor.

(*R*)-1-(5-(4-Methoxyphenyl)-2H-tetrazol-2-yl)ethyl isobutyrate ((*R*)–**12d**). The title compound was obtained as colorless oil (139 mg, 85%) from 5-(4-methoxyphenyl)-1*H*-tetrazole (100 mg, 0.568 mmol, 1.0 equiv), catalyst (*S*,*S*)–**1m** (5.9 mg, 0.011 mmol, 0.04 equiv), isobutyric anhydride (122 µL, 0.738 mmol, 1.3 equiv) and acetaldehyde (35 µL, 0.625 mmol, 1.1 equiv) in accordance with general procedure D. Analytical TLC on silica gel, 1:10 EtOAc/Hexanes, R_f=0.26. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.13-8.07 (2H, m), 7.33 (1H, q, *J*=6.3 Hz), 7.03-6.97 (2H, m), 3.86 (3H, s), 2.60 (1H, qq, *J*=7.0, 7.0 Hz), 1.99 (3H, d, *J*=6.3 Hz), 1.19 (3H, d, *J*=7.0 Hz), 1.15 (3H, d, *J*=7.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 175.0, 165.2, 151.6, 128.7, 119.7, 119.8, 114.4, 80.0, 55.5, 33.8, 19.5, 18.7, 18.7. HRMS-ESI (m/z) calcd for $C_{14}H_{18}N_4O_3Na$ $[M+Na]^+$ 313.1277, found 313.1273. HPLC/csp

assay (92% ee): Daicel CHIRALPAK IC, 25 cm×4.6 mm i.d., mobile phase 10% IPA/90% Hexanes, flow rate 1 mL/min, detector UV 254 nm, retention time 14.2 min, major and 10.8 min, minor.

(*R*)-1-(5-(Pyridin-2-yl)-2*H*-tetrazol-2-yl)ethyl isobutyrate ((*R*)–**12e**). The title compound was obtained as a colorless oil (47 mg, 92%) from 2-(1*H*-tetrazol-5-yl)pyridine (29 mg, 0.197 mmol, 1.0 equiv), catalyst (*S*,*S*)–**1m** (4.1 mg, 0.008 mmol, 0.04 equiv), isobutyric anhydride (43 μL, 0.256 mmol, 1.3 equiv) and acetaldehyde (12 μL, 0.216 mmol, 1.1 equiv) in accordance with general procedure C. Analytical TLC on silica gel, 2:5 EtOAc/Hexanes, R_f=0.2. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.80 (1H, ddd, *J*=4.8, 1.8, 1.0 Hz), 8.27 (1H, ddd, *J*=7.8, 1.0, 1.0 Hz), 7.87 (1H, ddd, *J*=7.8, 7.8, 1.8 Hz), 7.45-7.36 (2H, m), 2.59 (1H, qq, *J*=7.0, 7.0 Hz), 2.03 (3H, d, *J*=6.3 Hz), 1.18 (3H, d, *J*=7.0 Hz), 1.14 (3H, d, *J*=7.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 174.9, 165.0, 150.5, 146.7, 137.3, 125.2, 122.9, 80.5, 33.8, 19.6, 18.7, 18.6. HRMS-ESI (m/z) calcd for $C_{12}H_{15}N_5O_2Na$ $[M+Na]^+$ 284.1123, found 284.1128. HPLC/csp assay (94% ee): Daicel CHIRALPAK IC, 25 cm×4.6 mm i.d., mobile phase 30% IPA/70% Hexanes, flow rate 1 mL/min, detector UV 254 nm, retention time 44.5 min, major and 26.3 min, minor.

(*R*)-1-(5-(2-Bromophenyl)-2H-tetrazol-2-yl)ethyl isobutyrate ((*R*)–**12f).** The title compound was obtained as a colorless oil (294 mg, 97%) from 5-(2-bromophenyl)-1*H*-tetrazole (200 mg, 0.89 mmol, 1.0 equiv), catalyst (*S*,*S*)–**1m** (18.5 mg, 0.04 mmol, 0.04 equiv), isobutyric anhydride (192 μL, 1.16 mmol, 1.3 equiv) and acetaldehyde (55 μL, 0.98 mmol, 1.1 equiv) in accordance with general procedure C. Less than 3% of **13f** was observed by ^{1}H-NMR of the reaction mixture. Analytical TLC on silica gel, 1:10 EtOAc/Hexanes, R_f=0.3. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.87 (1H, ddd, *J*=7.7, 1.8, 0.4 Hz), 7.74 (1H, ddd, *J*=8.0, 7.4, 1.8 Hz), 7.44 (1H, ddd, *J*=7.7, 7.4, 1.3 Hz), 7.39 (1H, q, *J*=6.2 Hz), 7.34 (1H, ddd, *J*=8.0, 7.4, 1.8 Hz), 2.62 (1H, qq, *J*=7.0, 7.0 Hz), 2.03 (3H, d, *J*=6.2 Hz), 1.20 (3H, d, *J*=7.0 Hz), 1.16 (3H, d, *J*=7.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 174.9, 164.4, 134.3, 131.9, 131.6, 128.4, 127.6, 122.3, 80.2, 33.9, 19.5, 18.7, 18.7. HRMS-ESI (m/z) calcd for $C_{13}H_{15}N_4O_2NaBr$ $[M+Na]^+$ 361.0276, found 361.0276. HPLC/csp assay (92% ee): Daicel

CHIRALPAK IB, 25 cm × 4.6 mm i.d., mobile phase 1% IPA/99% Hexanes, flow rate 1 mL/min, detector UV 254 nm, retention time 10.4 min, major and 9.8 min, minor.

(*R*)-1-(5-([1,1'-Biphenyl]-2-yl)-2*H*-tetrazol-2-yl)ethyl isobutyrate ((*R*)-**12g**) **and 1-(5-([1,1'-Biphenyl]-2-yl)-1*H*-tetrazol-1-yl)ethyl isobutyrate (13g).** Title compounds (*R*)–**12g** and **13g** were obtained as colorless oils in 53 mg (84%) and 5 mg (8%) yields, respectively, from 5-([1,1'-biphenyl]-2-yl)-2*H*-tetrazole (42 mg, 0.19 mmol, 1.0 equiv), catalyst (*S*,*S*)-**1m** (3.9 mg, 0.008 mmol, 0.04 equiv), isobutyric anhydride (41 μL, 0.25 mmol, 1.3 equiv) and acetaldehyde (11 μL, 0.21 mmol, 1.1 equiv) in accordance with general procedure C.

(*R*)-1-(5-([1,1'-Biphenyl]-2-yl)-2*H*-tetrazol-2-yl)ethyl isobutyrate ((*R*)–**12g**). Analytical TLC on silica gel, 1:10 EtOAc/Hexanes, R_f=0.3. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.87 (1H, ddd, *J*=7.6, 1.5, 0.6 Hz), 7.55 (1H, ddd, *J*=7.6, 7.6, 1.5 Hz), 7.51-7.44 (2H, m), 7.30-7.23 (3H, m), 7.22-7.14 (3H, m), 2.51 (1H, qq, *J*=7.0, 7.0 Hz), 1.77 (3H, d, *J*=6.3 Hz), 1.14 (3H, d, *J*=7.0 Hz), 1.10 (3H, d, *J*=7.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 174.8, 165.5, 142.4, 140.9, 130.9, 130.5, 130.3, 129.3, 128.0, 127.6, 127.2, 126.1, 79.9, 33.8, 19.3, 18.9, 18.7, 18.6. HRMS-ESI (m/z) calcd for $C_{19}H_{20}N_4O_2Na$ $[M+Na]^+$ 359.1484, found 359.1478. HPLC/csp assay (92% ee): Daicel CHIRALPAK IC, 25 cm × 4.6 mm i.d., mobile phase 10% IPA/90% Hexanes, flow rate 1 mL/min, detector UV 254 nm, retention time 11.3 min, major and 8.3 min, minor.

1-(5-([1,1'-Biphenyl]-2-yl)-1*H*-tetrazol-1-yl)ethyl isobutyrate (13g). Analytical TLC on silica gel, 1:10 EtOAc/Hexanes, R_f=0.1. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.68 (1H, ddd, *J*=8.0, 6.8, 1.8 Hz), 7.61-7.52 (3H, m), 7.35-7.28 (3H, m), 7.18-7.12 (2H, m), 6.08 (1H, q, *J*=6.2 Hz), 2.33 (1H, qq, *J*=7.0, 7.0 Hz), 1.01 (3H, d, *J*=6.2 Hz), 0.99 (3H, d, *J*=7.0 Hz), 0.94 (3H, d, *J*=7.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 174.9, 154.9, 141.5, 139.1, 132.0, 130.4, 129.2, 129.1, 128.2, 128.1, 122.5, 75.6, 33.6, 18.5, 18.5, 18.4. HRMS-ESI (m/z) calcd for $C_{19}H_{20}N_4O_2Na$ $[M+Na]^+$ 359.1484, found 359.1476. HPLC/csp assay (70% ee): Daicel CHIRALPAK IB, 25 cm × 4.6 mm i.d., mobile phase 10% IPA/90% Hexanes, flow rate 1 mL/min, detector UV 254 nm, retention time 6.1 min, major and 7.2 min, minor.

(*R*)-1-(5-Isopropyl-2*H*-tetrazol-2-yl)ethyl isobutyrate ((*R*)–**12h**) **and 1-(5-isopropyl-1*H*-tetrazol-1-yl)ethyl isobutyrate (13h).** Title compounds (*R*)–**12h** and **13**h were obtained as colorless oils in 78 mg (77%) and 7 mg (6%) yields, respectively, from 5-isopropyl-2*H*-tetrazole (50 mg, 0.446 mmol, 1.0 equiv), catalyst (*S*,*S*)–**1m** (9.3 mg, 0.018 mmol, 0.04 equiv), isobutyric anhydride (96 µL, 0.580 mmol, 1.3 equiv) and acetaldehyde (28 µL, 0.491 mmol, 1.1 equiv) in accordance with general procedure C.

(*R*)-1-(5-Isopropyl-2*H*-tetrazol-2-yl)ethyl isobutyrate ((*R*)–**12h**). Analytical TLC on silica gel, 1:10 EtOAc/Hexanes, R_f=0.64. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.25 (1H, q, *J*=6.2 Hz), 3.26 (1H, hept, *J*=7.0 Hz), 2.57 (1H, qq, *J*=7.0, 7.0 Hz), 1.93 (3H, d, *J*=6.2 Hz), 1.38 (6H, d, *J*=7.0 Hz), 1.17 (3H, d, *J*=7.0 Hz), 1.12 (3H, d, *J*=7.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 175.0, 171.9, 79.8, 33.8, 26.3, 19.4, 18.7, 18.7. HRMS-ESI (m/z) calcd for $C_{10}H_{18}N_4O_2Na$ $[M+Na]^+$ 249.132, found 249.1325. Chiral GC assay (92% ee): Astec CHIRALDEX B-DM, length: 50 m., diameter: 250.00 µm, init. temp. 90 °C, init. temp. time 0.0 min, ramp 4 °C/min, final temp. 180 °C, final temp. time 7.5 min, retention time 19.0 min, major and 19.1 min, minor.

1-(5-Isopropyl-1*H*-tetrazol-1-yl)ethyl isobutyrate (13h) Analytical TLC on silica gel, 1:10 EtOAc/Hexanes, R_f=0.32. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 6.85 (1H, q, *J*=6.2 Hz), 3.37 (1H, qq, *J*=7.0, 7.0 Hz), 2.56 (1H, qq, *J*=7.0, 7.0 Hz), 1.94 (3H, d, *J*=6.2 Hz), 1.44 (3H, d, *J*=7.0 Hz), 1.35 (3H, d, *J*=7.0 Hz), 1.15 (3H, d, *J*=7.0 Hz), 1.10 (3H, d, *J*=7.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 175.6, 159.7, 74.9, 33.8, 24.1, 22.1, 20.8, 20.2, 18.7, 18.6. HRMS-ESI (m/z) calcd for $C_{10}H_{18}N_4O_2Na$ $[M+Na]^+$ 249.1327, found 249.1327. Chiral GC assay (74% ee): Astec CHIRALDEX B-DM, length: 50 m., diameter: 250.00 µm, init. temp. 90 °C, init. temp. time 0.0 min, ramp 4 °C/min, final temp. 180 °C, final temp. time 7.5 min, retention time 24.2 min, major and 24.3 min, minor.

(*R*)-1-(5-Methyl-2*H*-tetrazol-2-yl)ethyl isobutyrate ((*R*)–**12i**) **and 1-(5-methyl-1*H*-tetrazol-1-yl)ethyl isobutyrate (13i).** Title compounds (*R*)–**12i** and **13**i were obtained as colorless oils in 29 mg (65%) and 12 mg (27%) yields, respectively, from 5-methyl-1*H*-tetrazole (22 mg, 0.196 mmol, 1.0 equiv), catalyst (*S*,*S*)–**1m** (4.1 mg, 0.008 mmol, 0.04 equiv), isobutyric anhydride (42 µL, 0.255

mmol, 1.3 equiv) and acetaldehyde (12 μL, 0.215 mmol, 1.1 equiv) in accordance with general procedure C.

(*R*)-1-(5-Methyl-2*H*-tetrazol-2-yl)ethyl isobutyrate ((*R*)–**12i**). Analytical TLC on silica gel, 3:7 EtOAc/Hexanes, R_f=0.52. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.25 (1H, q, *J*=6.3 Hz), 2.56 (1H, qq, *J*=7.0, 7.0 Hz), 2.54 (3H, s), 1.92 (3H, d, *J*=6.3 Hz), 1.16 (3H, d, *J*=7.0 Hz), 1.12 (3H, d, *J*=7.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 174.9, 163.3, 79.7, 33.8, 19.4, 18.7, 18.6, 11.0. GC–MS m/z (% relative intensity, ion): 128.0 (9.8, $C_4H_8N_4O^+$), 113.0 (6.3, $C_6H_9O_2^+$), 100.0 (14.9, $C_5H_8O_2^+$), 83.0 (35.4, $C_2H_3N_4^+$), 71.0 (100.0, $C_4H_7O^+$). HRMS-ESI (m/z) calcd for $C_8H_{14}N_4O_2Na$ $[M+Na]^+$ 221.1014, found 221.1017. Chiral GC assay (94% ee): Astec CHIRALDEX B-DM, length: 50 m., diameter: 250.00 μm, init. temp. 90 °C, init. temp. 0.0 min, ramp 4 °C/min, final temp. 180 °C, final temp. time 7.5 min, retention time 15.5 min, major and 15.7 min, minor.

1-(5-Methyl-1*H*-tetrazol-1-yl)ethyl isobutyrate (13i). Analytical TLC on silica gel, 3:7 EtOAc/Hexanes, R_f=0.2. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 6.79 (1H, q, *J*=6.3 Hz), 2.64 (3H, s), 2.55 (1H, qq, *J*=7.0, 7.0 Hz), 1.93 (3H, d, *J*=6.3 Hz), 1.14 (3H, d, *J*=7.0 Hz), 1.08 (3H, d, *J*=7.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 175.6, 151.8, 75.1, 33.7, 19.9, 18.6, 9.1. GC–MS m/z (% relative intensity, ion): 115.0 (15.3, $C_6H_{11}O_2^+$), 111.0 (25.1, $C_4H_7N_4^+$), 100.0 (14.9, $C_5H_8O_2^+$), 83.0 (83.6, $C_2H_3N_4^+$), 71.0 (100.0, $C_4H_7O^+$). HRMS-ESI (m/z) calcd for $C_8H_{14}N_4O_2Na$ $[M+Na]^+$ 221.1014, found 221.1013. Chiral GC assay (70% ee): Astec CHIRALDEX B-DM, length: 50 m., diameter: 250.00 μm, init. temp. 90 °C, init. temp. time 0.0 min, ramp 4 °C/min, final temp. 180 °C, final temp. time 7.5 min, retention time 23.3 min, major and 24.0 min, minor.

(*R*)-1-(2*H*-Tetrazol-2-yl)ethyl isobutyrate ((*R*)–**12j**) **and 1-(1*H*-tetrazol-1-yl)ethyl isobutyrate (13j).** Title compounds (*R*)–**12j** and **13**j were obtained as colorless oils in 21 mg (39%) and 30 mg (57%) yields, respectively, from 1*H*-tetrazole (20 mg, 0.29 mmol, 1.0 equiv), catalyst (*S*,*S*)–1m (5.9 mg, 0.01 mmol, 0.04 equiv), isobutyric anhydride (62 μL, 0.37 mmol, 1.3 equiv) and acetaldehyde (18 μL, 0.32 mmol, 1.1 equiv) in accordance with general procedure C.

(*R*)-1-(2*H*-Tetrazol-2-yl)ethyl isobutyrate ((*R*)–**12j**). Analytical TLC on silica gel, 3:7 EtOAc/Hexanes, R_f=0.64. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.55 (1H, s), 7.35 (1H, q, *J*=6.3 Hz),

2.58 (1H, qq, *J*=7.0, 7.0 Hz), 1.97 (3H, d, *J*=6.3 Hz), 1.17 (3H, d, *J*=7.0 Hz), 1.13 (3H, d, *J*=7.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 174.9, 153.1, 80.0, 33.8, 19.4, 18.7, 18.7. GC–MS m/z (% relative intensity, ion): 115.0 (15.8, $C_6H_{11}O_2^+$), 71.0 (100.0, $C_4H_7O^+$), 69.0 (25.4, CHN_4^+). HRMS-ESI (m/z) calcd for $C_7H_{12}N_4O_2Na$ $[M+Na]^+$ 207.0858, found 207.0859. Chiral GC assay (84% ee): Astec CHIRALDEX B-DM, length: 50 m., diameter: 250.00 μm, 160 °C for 25 min, retention time 6.2 min, major and 6.3 min, minor.

1-(1*H*-Tetrazol-1-yl)ethyl isobutyrate (13j). Analytical TLC on silica gel, 3:7 EtOAc/Hexanes, R_f=0.32. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.82 (1H, s), 7.01 (1H, q, *J*=6.3 Hz), 2.55 (1H, qq, *J*=7.0, 7.0 Hz), 2.00 (3H, d, *J*=6.3 Hz), 1.15 (3H, d, *J*=7.0 Hz), 1.08 (3H, d, *J*=7.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 175.7, 142.9, 76.1, 33.7, 19.3, 18.6, 18.5. GC–MS m/z (% relative intensity, ion): 115.0 (10.2, $C_6H_{11}O_2^+$), 97.0 (33.6, $C_3H_5N_4^+$), 71.0 (100.0, $C_4H_7O^+$), 69.0 (79.5, CHN_4^+). HRMS-ESI (m/z) calcd for $C_7H_{12}N_4O_2Na$ $[M+Na]^+$ 207.0858, found 207.0854. Chiral GC assay (28% ee): Astec CHIRALDEX B-DM, length: 50 m., diameter: 250.00 μm, 160 °C for 25 min, retention time 12.5 min, major and 13.8 min, minor.

1-(2-Phenyl-1*H*-imidazol-1-yl)ethyl isobutyrate (12k). The title compound was obtained as a colorless oil (34 mg, 68%) from 2-phenyl-1*H*-imidazole (28 mg, 0.194 mmol, 1.0 equiv), catalyst (*S*,*S*)–**1m** (4.0 mg, 0.008 mmol, 0.04 equiv), isobutyric anhydride (42 μL, 0.253 mmol, 1.3 equiv) and acetaldehyde (12 μL, 0.214 mmol, 1.1 equiv) in accordance with general procedure C. Analytical TLC on silica gel, 2:5 EtOAc/Hexanes, R_f=0.4. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.59-7.53 (2H, m), 7.49-7.41 (3H, m), 7.24-7.16 (2H, m), 6.74 (1H, q, *J*=6.2 Hz), 2.53 (1H, qq, *J*=7.2, 7.2 Hz), 1.69 (3H, d, *J*=6.2 Hz), 1.19-1.10 (6H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 175.2, 147.8, 130.2, 129.4, 129.4, 129.2, 128.8, 116.6, 76.2, 33.9, 21.6, 19.2, 18.8, 18.7. HRMS-ESI (m/z) calcd for $C_{15}H_{19}N_2O_2$ $[M+H]^+$ 259.1447, found 259.1453. HPLC/csp assay (88% ee): Daicel CHIRALPAK IC, 25 cm × 4.6 mm i.d., mobile phase 10% IPA/90% Hexanes, flow rate 1 mL/min, detector UV 254 nm, retention time 20.4 min, major and 31.8 min, minor.

1-(4-Phenyl-1*H*-imidazol-1-yl)ethyl isobutyrate (12l). The title compound was obtained as a colorless oil (43 mg, 86%) from 4-phenyl-1*H*-imidazole (28 mg, 0.194 mmol, 1.0 equiv), catalyst (*S*,*S*)–**1m** (4.0 mg, 0.008 mmol, 0.04 equiv), isobutyric anhydride (42 μL, 0.253 mmol, 1.3 equiv) and acetaldehyde (12 μL, 0.214 mmol, 1.1 equiv) in accordance with general procedure C. Analytical TLC on silica gel, 2:5 EtOAc/Hexanes, R_f=0.2. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.88-7.71 (3H, m), 7.45-7.31 (3H, m), 7.31-7.19 (1H, m), 6.73 (1H, q, *J*=6.3 Hz), 2.53 (1H, qq, *J*=7.0, 7.0 Hz), 1.83 (3H, d, *J*=6.3 Hz), 1.16 (3H, d, *J*=7.0 Hz), 1.11 (3H, d, *J*=7.0 Hz). ^{1}H NMR spectra is in agreement with that in the literature.[31] HPLC/csp assay (82% ee): Daicel CHIRALPAK IC, 25 cm × 4.6 mm i.d., mobile phase 30% IPA/70% Hexanes, flow rate 1 mL/min, detector UV 254 nm, retention time 32.7 min, major and 18.6 min, minor.

1-(3-Phenyl-1*H*-pyrazol-1-yl)ethyl isobutyrate (12m). The title compound was obtained as a colorless oil (44 mg, 88%) from 3-phenyl-1*H*-pyrazole (28 mg, 0.194 mmol, 1.0 equiv), catalyst (*S*,*S*)–**1m** (4.0 mg, 0.008 mmol, 0.04 equiv), isobutyric anhydride (42 μL, 0.253 mmol, 1.3 equiv) and acetaldehyde (12 μL, 0.214 mmol, 1.1 equiv) in accordance with general procedure C. Analytical TLC on silica gel, 1:10 EtOAc/Hexanes, R_f=0.5. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.86-7.80 (2H, m), 7.64 (1H, d, *J*=2.5 Hz), 7.44-7.36 (2H, m), 7.35-7.27 (1H, m), 6.82 (1H, q, *J*=6.2 Hz), 6.58 (1H, d, *J*=2.5 Hz), 2.55 (1H, qq, *J*=7.0, 7.0 Hz), 1.91 (3H, d, *J*=6.2 Hz), 1.16 (3H, d, *J*=7.0 Hz), 1.10 (3H, d, *J*=7.0 Hz). ^{1}H NMR spectra is in agreement with that in the literature.[31] HPLC/csp assay (88% ee): Daicel CHIRALPAK IB, 25 cm × 4.6 mm i.d., mobile phase 10% IPA/90% Hexanes, flow rate 1 mL/min, detector UV 254 nm, retention time 4.3 min, major and 6 min, minor.

1-(3-Phenyl-1*H*-1,2,4-triazol-1-yl)ethyl isobutyrate (12n). The title compound was obtained as a colorless oil (9 mg, 59%) from 3-phenyl-1,2,4-triazole (8 mg, 0.055 mmol, 1.0 equiv), catalyst (*S*,*S*)–**1m** (1.2 mg, 0.002 mmol, 0.04 equiv), isobutyric anhydride (12 μL, 0.072 mmol, 1.3 equiv) and acetaldehyde (3 μL, 0.06 mmol, 1.1 equiv) in accordance with general procedure D. Analytical TLC on silica gel, 2:5 EtOAc/Hexanes, R_f=0.61. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.31 (1H, s), 8.17-8.09 (2H, m), 7.49-7.36 (3H, m), 6.86 (1H, q, *J*=6.3 Hz), 2.56 (1H, qq, *J*=7.0, 7.0 Hz), 1.93 (3H, d,

J=6.3 Hz), 1.17 (3H, d, *J*=7.0 Hz), 1.11 (3H, d, *J*=7.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 176.1, 162.8, 144.8, 130.8, 129.6, 128.7, 126.7, 76.9, 33.9, 19.2, 18.8, 18.7. HRMS-ESI (m/z) calcd for $C_{14}H_{18}N_3O_2$ $[M+H]^+$260.1399, found 260.1387. HPLC/csp assay (74% ee): Daicel CHIRALPAK IA, 25 cm × 4.6 mm i.d., mobile phase 10% IPA/90% Hexanes, flow rate 1 mL/min, detector UV 254 nm, retention time 6.4 min, major and 9.7 min, minor.

1-(4-Phenyl-2*H*-1,2,3-triazol-2-yl)ethyl isobutyrate (12o) and 1-(4-phenyl-1*H*-1,2,3-triazol-1-yl)ethyl isobutyrate (13o). Title compounds **12o** and **13o** were obtained as colorless oils, 31 mg (62%) yield and 4 mg (8%), respectively, from phenyltriazole (28 mg, 0.193 mmol, 1.0 equiv), catalyst (*S*,*S*)–**1m** (4.0 mg, 0.008 mmol, 0.04 equiv), isobutyric anhydride (42 μL, 0.251 mmol, 1.3 equiv) and acetaldehyde (12 μL, 0.212 mmol, 1.1 equiv) in accordance with general procedure C.

1-(4-Phenyl-2*H*-1,2,3-triazol-2-yl)ethyl isobutyrate (12o). Analytical TLC on silica gel, 1:10 EtOAc/Hexanes, R_f=0.5. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.92 (1H, s), 7.85-7.79 (2H, m), 7.47-7.41 (2H, m), 7.40-7.33 (1H, m), 7.15 (1H, q, *J*=6.2 Hz), 2.57 (1H, qq, *J*=7.0, 7.0 Hz), 1.95 (3H, d, *J*=6.2 Hz), 1.18 (3H, d, *J*=7.0 Hz), 1.13 (3H, d, *J*=7.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 175.43, 148.61, 132.19, 130.09, 129.01, 128.92, 126.27, 81.56, 33.94, 19.34, 18.85, 18.76. HRMS-ESI (m/z) calcd for $C_{14}H_{17}N_3O_2Na$ $[M+Na]^+$ 282.1218, found 282.1221. HPLC/csp assay (86% ee): Daicel CHIRALPAK IC, 25 cm × 4.6 mm i.d., mobile phase 1% IPA/99% Hexanes, flow rate 1 mL/min, detector UV 254 nm, retention time 10.1 min, major and 11 min, minor.

1-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)ethyl isobutyrate (13o). Analytical TLC on silica gel, 1:10 EtOAc/Hexanes, R_f=0.2. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.97 (1H, s), 7.88-7.80 (2H, m), 7.47-7.38 (2H, m), 7.39-7.29 (1H, m), 7.06 (1H, q, *J*=6.3 Hz), 2.57 (1H, qq, *J*=7.0, 7.0 Hz), 1.99 (3H, d, *J*=6.3 Hz), 1.18 (3H, d, *J*=7.0 Hz), 1.13 (3H, d, *J*=7.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 175.7, 147.8, 130.4, 129.0, 128.5, 126.0, 119.5, 77.9, 33.9, 19.7, 18.8, 18.7. HRMS-ESI (m/z) calcd for $C_{14}H_{17}N_3O_2Na$ $[M+Na]^+$ 282.1218, found 282.1219. HPLC/csp assay (60% ee): Daicel CHIRALPAK IC, 25 cm × 4.6 mm i.d., mobile phase 10% IPA/90% Hexanes, flow rate 1 mL/min, detector UV 254 nm, retention time 26.6 min, major and 21 min, minor.

1-(1*H*-Benzo[*d*]imidazol-1-yl)ethyl isobutyrate (12p). The title compound was obtained as a colorless oil (34 mg, 75%) from 1*H*-benzo[*d*]imidazole (23 mg, 0.194 mmol, 1.0 equiv), catalyst (*S*,*S*)–**1m** (4.0 mg, 0.008 mmol, 0.04 equiv), isobutyric anhydride (42 μL, 0.253 mmol, 1.3 equiv) and acetaldehyde (12 μL, 0.214 mmol, 1.1 equiv) in accordance with general procedure C. Analytical TLC on silica gel, 2:5 EtOAc/Hexanes, R_f=0.1. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.11 (1H, s), 7.84-7.77 (1H, m), 7.63-7.53 (1H, m), 7.37-7.27 (2H, m), 7.02 (1H, q, *J*=6.3 Hz), 2.53 (1H, qq, *J*=7.0, 7.0 Hz), 1.94 (3H, d, *J*=6.3 Hz), 1.15 (3H, d, *J*=7.0 Hz), 1.07 (3H, d, *J*=7.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 175.8, 141.2, 137.9, 132.5, 123.7, 123.0, 120.7, 111.0, 75.0, 34.0, 20.1, 18.8. HRMS-ESI (m/z) calcd for $C_{13}H_{17}N_2O_2$ $[M+H]^+$ 233.1290, found 233.1289. HPLC/csp assay (56% ee): Daicel CHIRALPAK IC, 25 cm × 4.6 mm i.d., mobile phase 30% IPA/70% Hexanes, flow rate 1 mL/min, detector UV 254 nm, retention time 18.4 min, major and 11.7 min, minor.

1-(1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7*H*-purin-7-yl)ethyl isobutyrate (12q). The title compound was obtained as a colorless oil (44 mg, 88%) from 1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (35 mg, 0.194 mmol, 1.0 equiv), catalyst (*S*,*S*)–**1m** (4.0 mg, 0.008 mmol, 0.04 equiv), isobutyric anhydride (42 μL, 0.253 mmol, 1.3 equiv) and acetaldehyde (12 μL, 0.214 mmol, 1.1 equiv) in accordance with general procedure C. Analytical TLC on silica gel, 2:5 EtOAc/Hexanes, R_f=0.21. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.80 (1H, s), 7.18 (1H, q, *J*=6.2 Hz), 3.58 (3H, s), 3.41 (3H, s), 2.57 (1H, qq, *J*=7.0, 7.0 Hz), 1.87 (3H, d, *J*=6.2 Hz), 1.16 (3H, d, *J*=7.0 Hz), 1.13 (3H, d, *J*=7.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 175.2, 154.7, 151.7, 149.1, 139.0, 106.4, 76.6, 33.9, 30.0, 28.3, 21.1, 18.8, 18.7. HRMS-ESI (m/z) calcd for $C_{13}H_{19}N_4O_4$ $[M+H]^+$ 295.1406, found 295.1405. HPLC/csp assay (22% ee): Daicel CHIRALPAK IA, 25 cm × 4.6 mm i.d., mobile phase 25% IPA/75% Hexanes, flow rate 1 mL/min, detector UV 254 nm, retention time 10.1 min, major and 12.9 min, minor.

(*R*)-1-(5-Phenyl-2*H*-tetrazol-2-yl)ethyl propionate ((*R*)–**12r**). The title compound was obtained as a colorless oil (44 mg, 87%) from 5-phenyl-1*H*-tetrazole (30 mg, 0.205 mmol, 1.0 equiv), catalyst (*S*,*S*)–**1m** (4.3 mg, 0.008 mmol, 0.04 equiv), propanoic acid (20 μL, 0.267 mmol, 1.3 equiv), pivalic

anhydride (54 μL, 0.267 mmol, 1.3 equiv) and acetaldehyde (12 μL, 0.225 mmol, 1.1 equiv) in accordance with general procedure E. Analytical TLC on silica gel, 1:10 EtOAc/Hexanes, R_f=0.26. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.23-8.13 (2H, m), 7.52-7.44 (3H, m), 7.39 (1H, q, *J*=6.3 Hz), 2.41 (2H, dq, *J*=7.6, 2.0 Hz), 2.02 (3H, d, *J*=6.3 Hz), 1.15 (3H, t, *J*=7.6 Hz). ^{1}H NMR spectra is in agreement with that in the literature.[31] HPLC/csp assay (90% ee): Daicel CHIRALPAK IB, 25 cm × 4.6 mm i.d., mobile phase 10% IPA/90% Hexanes, flow rate 1 mL/min, detector UV 254 nm, retention time 10.7 min, major and 8.7 min, minor.

(*R*)-1-(5-Phenyl-2H-tetrazol-2-yl)ethyl cyclopentanecarboxylate ((*R*)–**12s**). The title compound was obtained as colorless oil (44 mg, 87%) from 5-phenyl-1-*H*-tetrazole (30 mg, 0.205 mmol, 1.0 equiv), catalyst (*S*,*S*)–**1m** (4.3 mg, 0.008 mmol, 0.04 equiv), pivalic anhydride (54 μL, 0.267 mmol, 1.3 equiv), cyclopentanecarboxylic acid (29 μL, 267 mmol, 1.3 equiv) and acetaldehyde (12 μL, 0.214 mmol, 1.1 equiv) in accordance with general procedure E. Analytical TLC on silica gel, 1:10 EtOAc/Hexanes, R_f=0.3. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.21-8.15 (2H, m), 7.53-7.46 (3H, m), 7.36 (1H, d, *J*=6.2 Hz), 2.79 (1H, tt, *J*=8.6, 7.2 Hz), 2.01 (3H, d, *J*=6.2 Hz), 1.96-1.50 (8H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 174.6, 165.3, 130.7, 127.2, 127.1, 80.1, 43.5, 29.9, 29.9, 25.9, 25.9, 19.5. HRMS-ESI (m/z) calcd for $C_{15}H_{18}N_4O_2Na$ $[M+Na]^+$ 309.1327, found 309.1317. HPLC/csp assay (80% ee): Daicel CHIRALPAK IC, 25 cm × 4.6 mm i.d., mobile phase 5% IPA/95% Hexanes, flow rate 1 mL/min, detector UV 254 nm, retention time 12.9 min, major and 9.4 min, minor.

(*R*)-1-(5-Phenyl-2H-tetrazol-2-yl)ethyl 2-phenylacetate ((*R*)–12t). The title compound was obtained as a colorless oil (60 mg, 95%) from 5-phenyl-1-*H*-tetrazole (30 mg, 0.205 mmol, 1.0 equiv), catalyst (*S*,*S*)–**1m** (4.3 mg, 0.008 mmol, 0.04 equiv), pivalic anhydride (54 μL, 0.267 mmol, 1.3 equiv), 2-phenylacetic acid (36 mg, 0.267 mmol, 1.3 equiv) and acetaldehyde (12 μL, 0.214 mmol, 1.1 equiv) in accordance with general procedure E. Analytical TLC on silica gel, 1:10 EtOAc/Hexanes, R_f=0.2. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.19-8.15 (2H, m), 7.53-7.48 (3H, m), 7.38 (1H, q, *J*=6.3 Hz), 7.33-7.21 (5H, m), 3.69 (2H, s), 2.02 (3H, d, *J*=6.3 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 169.5, 165.4, 132.8, 130.7, 129.3, 129.0, 128.8, 127.6, 127.2, 127.1, 80.4, 40.9, 19.4. HRMS-ESI (m/z) calcd

for $C_{17}H_{16}N_4O_2Na$ $[M+Na]^+$ 331.1171, found 331.1168. HPLC/csp assay (66% ee): Daicel CHIRALPAK IC, 25 cm × 4.6 mm i.d., mobile phase 5% IPA/95% Hexanes, flow rate 1 mL/min, detector UV 254 nm, retention time 17.5 min, major and 18.5 min, minor.

(*R*)-1-(5-Phenyl-2H-tetrazol-2-yl)ethyl (*tert*-butoxycarbonyl)glycinate ((*R*)–**12u**). The title compound was obtained as colorless oil (56 mg, 79%) from 5-phenyl-1-*H*-tetrazole (30 mg, 0.205 mmol, 1.0 equiv), catalyst (*S*,*S*)–**1m** (4.3 mg, 0.008 mmol, 0.04 equiv), pivalic anhydride (54 μL, 0.267 mmol, 1.3 equiv), (*tert*-butoxycarbonyl)glycine (47 mg, 0.267 mmol, 1.3 equiv) and acetaldehyde (12 μL, 0.214 mmol, 1.1 equiv) in accordance with general procedure E. Analytical TLC on silica gel, 2:5 EtOAc/Hexanes, R_f=0.58. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.19-8.15 (2H, m), 7.52-7.46 (3H, m), 7.41 (1H, q, *J*=6.3 Hz), 5.04-4.94 (1H, br s), 4.07 (1H, dd, *J*=18.5, 6.0 Hz), 3.88 (1H, dd, *J*=18.5, 6.0 Hz), 2.05 (3H, d, *J*=6.3 Hz), 1.43 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 168.7, 165.5, 155.7, 130.8, 129.0, 127.2, 127.0, 80.6, 80.5, 42.4, 28.4, 19.4. HRMS-ESI (m/z) calcd for $C_{16}H_{21}N_5O_4Na$ $[M+Na]^+$ 370.1491, found 370.1491. HPLC/csp assay (86% ee): Daicel CHIRALPAK IC, 25 cm × 4.6 mm i.d., mobile phase 20% IPA/80% Hexanes, flow rate 1 mL/min, detector UV 254 nm, retention time 14.3 min, major and 12.4 min, minor.

(*R*)-1-(5-Phenyl-2H-tetrazol-2-yl)ethyl N-(*tert*-butoxycarbonyl)-N-methylglycinate ((*R*)–**12v**). The title compound was obtained as a colorless oil (54 mg, 73%) from 5-phenyl-1-*H*-tetrazole (30 mg, 0.205 mmol, 1.0 equiv), catalyst (*S*,*S*)–**1m** (4.3 mg, 0.008 mmol, 0.04 equiv), pivalic anhydride (54 μL, 0.267 mmol, 1.3 equiv), *N*-(*tert*-butoxycarbonyl)-*N*-methylglycine (51 mg, 0.267 mmol, 1.3 equiv) and acetaldehyde (12 μL, 0.214 mmol, 1.1 equiv) in accordance with general procedure E. Analytical TLC on silica gel, 2:5 EtOAc/Hexanes, R_f=0.58. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.24-8.11 (2H, m), 7.53-7.47 (3H, m), 7.43 (0.51H, q, *J*=6.3 Hz), 7.40 (0.49H, q, *J*=6.3 Hz), 4.19 (0.51H, d, *J*=18.0 Hz), 3.95 (1H, s), 3.89 (0.49H, d, *J*=18.0 Hz), 2.93 (1.53H, s), 2.89 (1.47H, s), 2.07-2.02 (3H, m), 1.46 (4.41H, s), 1.35 (4.59H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 168.1, 165.5, 165.5, 156.1, 155.3, 130.8, 130.8, 129.0, 127.2, 80.7, 80.6, 80.4, 51.0, 50.3, 35.8, 28.4, 28.3, 27.2, 19.52, 19.46. HRMS-ESI (m/z) calcd for $C_{17}H_{23}N_5O_4Na$ $[M+Na]^+$ 384.1648, found 384.1642. HPLC/csp

assay (70% ee): Daicel CHIRALPAK IC, 25 cm × 4.6 mm i.d., mobile phase 20% IPA/80% Hexanes, flow rate 1 mL/min, detector UV 254 nm, retention time 11 min, major and 9.9 min, minor.

(*R*)-**1-(5-(4-Nitrophenyl)-2*H*-tetrazol-2-yl)ethyl 2-phenylacetate** ((*R*)–**12w**). The title compound was obtained as a colorless oil (115 mg, 77%) from 5-(4-nitrophenyl)-2*H*-tetrazole (81 mg, 0.424 mmol, 1.0 equiv), catalyst (*S*,*S*)–**1m** (13.2 mg, 0.025 mmol, 0.06 equiv), pivalic anhydride (95 μL, 0.466 mmol, 1.1 equiv), phenylacetic acid (63 mg, 0.466 mmol, 1.1 equiv) and acetaldehyde (28 μL, 0.509 mmol, 1.2 equiv) in accordance with general procedure E. Analytical TLC on silica gel, 1:10 EtOAc/Hexanes, R_f=0.11. Crystalline material was obtained by initial dissolving the purified oily material (after column chromatography; 140 mg) in Et_2O (6 mL), followed by addition of hexane (6 mL). The resulting solution was allowed to evaporate. Formation of crystalline material (elongated plates) of (*R*)–**12**w (mp 106–107 °C (96% ee, HPLC/csp)) was observed when ca. 1/4 volume of solvents had been evaporated. When ca. 2/5 volume of solvent had been evaporated, the solid crop was filtered and washed with hexane (4 mL). Filtrate contains almost racemic **12w** (8% ee, HPLC/csp). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.46-8.20 (4H, m), 7.40 (1H, q, *J*=6.2 Hz), 7.35-7.21 (5H, m), 3.70 (2H, s), 2.03 (3H, d, *J*=6.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 169.5, 163.5, 149.2, 133.0, 132.6, 129.3, 128.8, 128.0, 127.7, 124.3, 80.6, 40.9, 19.5. Anal. Calcd for $C_{17}H_{15}N_5O_4$: C, 57.79; H, 4.28; N, 19.82 Found: C, 57.80; H, 4.24; N, 19.73. Optical rotation (96% ee, HPLC/csp) $[\alpha]^{20}_D$ +157.7 (*c* 0.74, CH_2Cl_2). HPLC/csp assay (96% ee): Daicel CHIRALPAK IC, 25 cm × 4.6 mm i.d., mobile phase 20% IPA/80% Hexanes, flow rate 1 mL/min, detector UV 254 nm, retention time 17.6 min, major and 19.2 min, minor.

(*R*)-1-(5-(4-nitrophenyl)-2*H*-tetrazol-2-yl)ethyl 2-(4-bromophenyl)acetate ((*R*)–**12x**). The title compound was obtained as a colorless oil (63 mg, 40%) from 5-(4-nitrophenyl)-2*H*-tetrazole (70 mg, 0.37 mmol, 1.0 equiv), catalyst (*S*,*S*)–**1m** (7.6 mg, 0.015 mmol, 0.04 equiv), pivalic anhydride (81 μL, 0.40 mmol, 1.1 equiv), 2-(4-bromophenyl)acetic acid (87 mg, 0.40 mmol, 1.1 equiv) and acetaldehyde (24 μL, 0.44 mmol, 1.2 equiv) in accordance with general procedure C. Analytical TLC on silica gel, 2:5 EtOAc/Hexanes, R_f=0.5.

Crystalline material was obtained by initial dissolving the purified oily material (after column chromatography) in Et_2O (5 mL), followed by addition of hexane (5 mL). The resulting solution was allowed to evaporate. Formation of crystalline material (needle clusters) of **12x** (mp 76–79 °C (6% ee, HPLC/csp)) was observed when ca. 1/4 volume of solvents had been evaporated. When ca. 2/5 volume of solvent had been evaporated, the solid crop was filtered and washed with hexane (4 mL). Filtrate was concentrated and the residue was recrystallized from E_2O to obtain enantiomerically enriched (*R*)–**12x** as colorless plates (mp 40–42 °C, 98% ee, HPLC/csp). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.40 – 8.30 (m, 4H), 7.46 – 7.41 (m, 2H), 7.38 (q, *J* = 6.2 Hz, 1H), 7.17 – 7.09 (m, 2H), 3.65 (s, 2H), 2.03 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 169.0, 163.6, 149.3, 132.9, 132.0, 131.5, 131.1, 128.0, 124.4, 121.8, 80.7, 40.3, 19.5. Anal. Calcd for $C_{17}H_{14}N_5O_4Br$: C, 47.24; H, 3.26; N, 16.2 Found: C, 47.41; H, 3.26; N, 15.93. Optical rotation (98% ee, HPLC/csp) [α] +124.0 (*c* 0.50, CH_2Cl_2). HPLC/csp assay (98% ee): Daicel CHIRALPAK IC, 25 cm × 4.6 mm i.d., mobile phase 20% IPA/80% Hexanes, flow rate 1 mL/min, detector UV 254 nm, retention time 17.1 min, major and 14.5 min, minor.

(*R*)-1-(5-(4-Nitrophenyl)-2*H*-tetrazol-2-yl)ethyl *N*-(*tert*-butoxycarbonyl)-*N*-methylglycinate ((*R*)–**12y**). The title compound (*R*)–**12y** was obtained as a colorless oil (76 mg, 61%) from 5-(4-nitrophenyl)-2*H*-tetrazole (60 mg, 0.32 mmol, 1.0 equiv), catalyst (*S*,*S*)–**1m** (10 mg, 0.018 mmol, 0.06 equiv), pivalic anhydride (69 μL, 0.35 mmol, 1.1 equiv), *N*-(*tert*-butoxycarbonyl)-*N*-methylglycine (66 mg, 0.35 mmol, 1.1 equiv) and acetaldehyde (21 μL, 0.35 mmol, 1.1 equiv) following general procedure C. Analytical TLC on silica gel, 2:5 EtOAc/Hexanes, R_f=0.58.

Solid material was obtained by initial dissolving the purified oily material (after column chromatography) in Et_2O (4 mL), followed by addition of hexane (4 mL). The resulting solution was allowed to evaporate. Formation of colorless needles **12y** (mp 86–88 °C (6% ee, HPLC/csp)) was observed when ca. 1/4 volume of solvents had been evaporated. When ca. 2/5 volume of solvent had been evaporated, the solid crop was filtered and washed with hexane (4 mL). Filtrate was concentrated to obtain enantiomerically enriched (*R*)–**12y** as amorphous solid (92% ee, HPLC/csp). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.41-8.31 (4H, m), 7.45 (0.47H, q, *J*=6.3 Hz), 7.42 (0.53H, q,

J=6.3 Hz), 4.16 (0.47H, d, *J*=18.0 Hz), 3.96 (1H, s), 3.93 (0.53H, d, *J*=18.0 Hz), 2.93 (1.41H, s), 2.90 (1.59H, s), 2.07 (1.41H, d, *J*=6.3 Hz), 2.05 (1.59H, d, *J*=6.3 Hz), 1.45 (4.77H, s), 1.35 (4.23H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 168.1, 163.7, 163.6, 156.1, 155.2, 149.3, 133.0, 128.1, 124.4, 80.7, 80.6, 50.9, 50.3, 35.8, 28.4, 28.3, 19.6, 19.5. HRMS-ESI (m/z) calcd for $C_{17}H_{22}N_6O_6Na$ $[M+Na]^+$ 429.1499, found 429.1492. HPLC/csp assay (88% ee): Daicel CHIRALPAK IC, 25 cm × 4.6 mm i.d., mobile phase 20% IPA/80% Hexanes, flow rate 1 mL/min, detector UV 254 nm, retention time 31.5 min, major and 27.5 min, minor.

(*R*)-1-(5-(4-Nitrophenyl)-2*H*-tetrazol-2-yl)ethyl (*tert*-butoxycarbonyl)glycinate ((*R*)–**12z**). The title compound was obtained as a colorless oil (66 mg, 53%) from 5-(4-nitrophenyl)-2*H*-tetrazole (60 mg, 0.32 mmol, 1.0 equiv), catalyst (*S*,*S*)–**1m** (10 mg, 0.018 mmol, 0.06 equiv), pivalic anhydride (69 μL, 0.35 mmol, 1.1 equiv), (*tert*-butoxycarbonyl)glycine (60 mg, 0.345 mmol, 1.1 equiv) and acetaldehyde (21 μL, 0.35 mmol, 1.1 equiv) following general procedure C. Analytical TLC on silica gel, 2:5 EtOAc/Hexanes, R_f=0.58.

Solid material was obtained by initial dissolving the purified oily material (after column chromatography) in Et_2O (4 mL), followed by addition of hexane (4 mL). The resulting solution was allowed to evaporate. Formation of colorless plates of **12z** (mp 116–118 °C (1% ee, HPLC/csp)) was observed when ca. 1/4 volume of solvents had been evaporated. After ca. 2/5 volume of solvent had been evaporated, the formation of needle cluster (mp 127-128 °C (98% ee, HPLC/csp)) was also observed. At this point all solids were removed by filtration and the filtrate was concentrated to afford enantiomerically enriched (*R*)–**12z** (94% ee, HPLC/csp). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.41-8.31 (4H, m), 7.44 (1H, q, *J*=6.3 Hz), 5.04-4.92 (1H, br s), 4.06 (1H, dd, *J*=18.6, 6.3 Hz), 3.91 (1H, dd, *J*=18.6, 5.6 Hz), 2.07 (3H, d, *J*=6.3 Hz), 1.43 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 168.7, 163.7, 155.7, 149.3, 132.9, 128.1, 124.4, 80.8, 80.6, 42.4, 28.4, 19.5. HRMS-ESI (m/z) calcd for $C_{16}H_{20}N_6O_6Na$ $[M+Na]^+$ 415.1342, found 415.1338. Optical rotation (94% ee, HPLC/csp) $[\alpha]^{20}_D$ +83.2 (*c* 0.11, CH_2Cl_2). HPLC/csp assay (94% ee): Daicel CHIRALPAK IC, 25 cm × 4.6 mm i.d., mobile phase 20% IPA/80% Hexanes, flow rate 1 mL/min, detector UV 254 nm, retention time 39 min, major and 29.4 min, minor.

(*R*)-1-(5-(4-Nitrophenyl)-2*H*-tetrazol-2-yl)ethyl (*S*)-2-fluoro-2-phenylacetate ((*R*,*S*)–**14**). TMS-Cl (35.9 μL, 0.283 mmol, 1.0 equiv) was added to a colorless solution of hemiaminal (*R*)–**12w** (100 mg, 0.28 mmol, 1.0 equiv) and *N*-fluorobenzenesulfonimide (89 mg, 0.283 mmol, 1.0 equiv) in anhydrous THF (4.3 mL) under argon atmosphere. The solution was cooled to –100 °C and LiHMDS (1M solution in THF, 300 μL, 0.30 mmol, 1.05 equiv) was added at a rate to maintain the reaction temperature below -98 °C (drops the LiHMDS solution were allowed to drain off the walls of the flask). The resulting pale yellow solution was stirred at –100 °C for 1 h, then gradually warmed to –60 °C and was quenched with aqueous saturated NH_4Cl solution (2 mL). Resulting suspension was diluted with H_2O (10 mL) and washed with EtOAc (20 mL). Organic layer was washed with aqueous 1M KI solution (20 mL) (organic phase became yellow) and aqueous 1M $Na_2S_2O_3$ solution (20 mL) (organic phase became colorless) then dried over Na_2SO_4. ^{19}F NMR of the crude reaction mixture showed product with d.r. 94:6. Purification of the crude product by HPLC column chromatography using isocratic elution (10% EtOAc/Hexanes) afforded product as a colorless needle-like crystals (74 mg, 70% yield, d.r. >99:1 by ^{19}F NMR); Pure material was obtained by recrystallization from Et_2O/Hexanes: mp 125-127 °C. ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.40 – 8.31 (m, 4H), 7.50 – 7.34 (m, 6H), 5.83 (d, J = 47.2 Hz, 1H), 1.99 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 166.6 (d, *J* = 29.1 Hz), 163.7, 149.3, 133.2 (d, *J* = 20.2 Hz), 132.8, 130.3 (d, *J* = 2.3 Hz), 129.2, 128.1, 126.9, 126.9, 124.4, 89.0 (d, *J* = 188.1 Hz), 81.0, 19.1. ^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ -180.2 (d, *J* = 47.2 Hz). HRMS-APCI (m/z) calcd for $C_{17}H_{14}FN_5O_4Na$ $[M+Na]^+$ 394.0922, found 394.0927. Optical rotation $[\alpha]^{20}_D$ +7.8 (*c* 0.58, CH_2Cl_2).

(*S*)-2-Fluoro-2-phenylacetic acid ((*S*)–**15**). LiOH (0.1M aqueous solution, 14 mL, 10 equiv) was added to a solution of hemiaminal (*R*,*S*)–**14** (50 mg, 0.135 mmol, 1.0 equiv) in 1,4-dioxane (12 mL). The colorless solution was stirred at room temperature until UPLC-MS analysis showed full conversion of hemiaminal (*R*,*S*)–**14** (usually, 30 min). Then it was acidified to pH 1 by aqueous 1M HCl and extracted with EtOAc (2x20 mL). Combined organic extracts were dried over Na_2SO_4 and solvent was removed under reduced pressure. The semi-solid white residue was suspended in $CHCl_3$

(1 mL), precipitate was filtered and washed with $CHCl_3$ (1 mL). Concentration of filtrate under reduced pressure yielded 19 mg (90%) of acid (*S*)–**15** as a white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.52 – 7.46 (m, 2H), 7.46 – 7.40 (m, 3H), 5.83 (d, *J* = 47.5 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ -180.4 (d, J = 47.5 Hz). $[\alpha]^{20}_D$ +86.1 (*c* 0.16, CH_2Cl_2). ^{1}H NMR and ^{19}F NMR data is consistent with that in the literature.[54,55]

Ethyl (*S*)-2-fluoro-2-phenylacetate ((*S*)–**16**). A white suspension of K_2CO_3 (60 mg, 0.431 mmol, 4.0 equiv; oven-dried at 120 °C for 12 h) and hemiaminal (*R*,*S*)–**14** (40 mg, 0.108 mmol, 1.0 equiv) in anhydrous EtOH (1 mL) was stirred at room temperature under argon atmosphere until UPLC-MS analysis showed full conversion of the starting hemiaminal (*R*,*S*)–**14** (usually 30 min). Solid was removed by filtration and filter cake was washed with EtOAc (20 mL). Filtrate was extracted with aqueous saturated $NaHCO_3$ solution (2x20 mL). Organic layer was dried over Na_2SO_4 and all volatiles were removed under reduced pressure to afford 19 mg (97%) of ethyl (*S*)-2-fluoro-2-phenylacetate ((*S*)–**16**). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.50 – 7.44 (m, 2H), 7.43 – 7.39 (m, 3H), 5.77 (d, *J* = 47.8 Hz, 1H), 4.33 – 4.17 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 168.7 (d, *J* = 27.5 Hz), 134.5 (d, *J* = 20.3 Hz), 129.73, 129.71 , 128.9, 126.8, 126.7, 89.5 (d, *J* = 185.4 Hz), 62.0, 14.2. ^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ -179.9 (d, *J* = 47.8 Hz). Optical rotation (99% ee, HPLC/csp) $[\alpha]^{20}_D$ +66.0 (*c* 0.65, MeOH). HPLC/csp assay (99% ee): Daicel CHIRALPAK OJ, 25 cm × 4.6 mm i.d., mobile phase 10% IPA/90% Hexanes, flow rate 1 mL/min, detector UV 210 nm, retention time 10.4 min, major and 8.4 min, minor. ^{1}H NMR, ^{19}F NMR, ^{13}C NMR and chiral HPLC data is consistent with that in the literature.[56,57]

Associated Content

Supporting Information

The following files are available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.XXXXXXX.

Experimental details, characterization data, and NMR spectra (PDF)

X-ray crystallographic data for hemiaminal esters (*R*)–**12x** and (*R,S*)–**14** (CIF)

Author Information

Corresponding Authors

E-mail: edgars@osi.lv

E-mail: david.w.piotrowski@pfizer.com

Notes

The authors declare no competing financial interest.

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(41) The propensity for DMAP catalysts (*S*,*S*)–**1a,e,m** to form intramolecular hydrogen bonds in the ground state has been observed, and may be correlated to the enantiocontrol in the DKR. NMR studies showed that the less selective DMAP species (*S*,*S*)–**1a,e** form stronger intramolecular hydrogen bonds compared to the most selective catalyst (*S*,*S*)–**1m** (for NMR studies, see page S54 in Supporting Information). Presumably, the H-bond stabilizes the ground state conformation of the catalyst (*S*,*S*)–**1a,e** by forming an intramolecular H-bond between the amide N–H and *O*-acetyl group. In contrast, catalyst (*S*,*S*)–**1m** may be able to better stabilize the transition state for the acyl transfer reaction via intermolecular H-bond donation. For influence of hydrogen bonding in the design of chiral DMAP catalysts, see: Gleeson, O.; Gun'ko, Y.; Connon, S. *Synlett* **2013**, *24*, 1728–1734.
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