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## Ruthenium-catalyzed synthesis of tricyclic 1,5-fused 1,2,3-triazole piperazines

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A double cyclization strategy, involving sequential ruthenium-catalyzed azide alkyne cycloaddition (RuAAC) and hydrogen borrowing, allows the rapid assembly of tricyclic 1,5-fused 1,2,3-triazole piperazines from a proline scaffold. The initial RuAAC-cyclization proceeded in up to 99% yield under mild reaction conditions, while cyclative hydrogen borrowing afforded the desired fused triazole piperazines in up to 75% yield. Both reaction steps are highly atom economic and we envisage that the tricyclic products can find applications in asymmetric transformations, as well as in the synthesis of products of biological interest.

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## Introduction

1,2,3-Triazoles are appealing structures in drug discovery,<sup>1</sup> with three nitrogen atoms that can potentially bind to different receptors in a variety of biological systems. Molecules containing this heterocycle display a wide range of biological properties,<sup>2</sup> including antiviral,<sup>3</sup> antimalarial,<sup>4</sup> anticancer<sup>5</sup> and antitubercular activity<sup>6</sup> (Fig. 1).

Focus to date has mainly been on 1,4-disubstituted 1,2,3-triazoles, easily accessible *via* the copper-catalyzed azide alkyne cycloaddition (CuAAC).<sup>7,8</sup> While this copper-catalyzed cycloaddition has been employed in a wide range of applications,<sup>9–11</sup> it is limited to terminal alkynes as substrates. However, in 2005 Fokin, Jia and co-workers showed that use of a [Cp\*RuCl]-based catalyst allows the selective formation of 1,5-disubstituted as well as 1,4,5-trisubstituted 1,2,3-triazole derivatives, thus broadening the scope of 1,2,3-triazoles available *via* catalytic cycloaddition reactions.<sup>12</sup> With an impressive functional group tolerance,<sup>13</sup> the ruthenium-catalyzed azide alkyne cycloaddition (RuAAC) has been used to synthesize a wide range of target molecules,<sup>14–18</sup> providing access to biologically relevant triazoles.<sup>19,20</sup>

1,2,3-Triazoles fused with other ring systems,<sup>21</sup> such as piperazines or diketopiperazines,<sup>22</sup> are also of interest and

have been studied as potential therapeutics for Alzheimer's disease.<sup>23</sup> In addition, structurally related 1,2,4-triazoles fused to a piperazine ring display antimalarial activity.<sup>24</sup> By starting from a proline-derivative, this structure can potentially be expanded to a tricyclic ring system. There are few synthetic studies towards this latter class of molecules, however. Mohapatra,<sup>25</sup> as well as Tong,<sup>26</sup> have reported a single example each of a tricyclic compound of this type, *via* the formation of a propargylic proline-azide derivative, followed by a non-catalyzed azide alkyne cycloaddition under thermal conditions or using a reaction time of two days (Scheme 1a and b). In both cases, several steps were needed to obtain the precursor materials, however, and the scope of the reaction was not explored. Three-component reactions catalyzed by Lewis acids (AuBr<sub>3</sub>/MnCl<sub>2</sub>/SnCl<sub>2</sub>) or a polymer-supported Ag-NHC catalyst have been applied by Chen<sup>27–29</sup> as well as by Zhang<sup>30</sup> (Scheme 1c), to form an intermediate propargylic amine, which was subsequently cyclized under thermal conditions. While these methods provide efficient access to the targeted fused triazole piperazines, the prolonged heating under acidic conditions may not be suitable for sensitive substrates, and

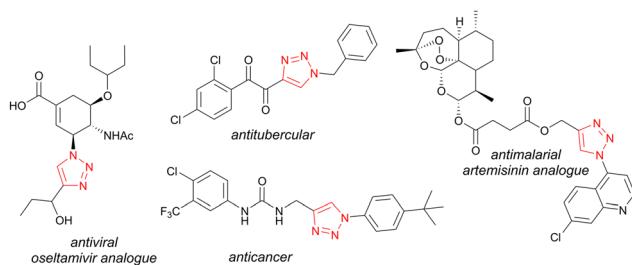


Fig. 1 Biologically active 1,2,3-triazoles.

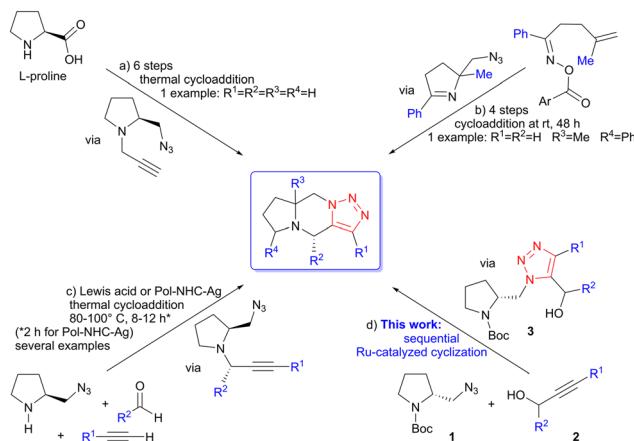
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Scheme 1 Approaches to tricyclic fused triazole piperazines.

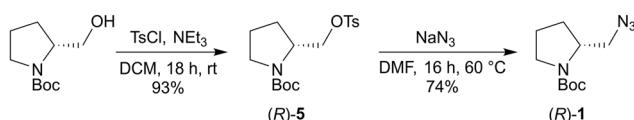
several steps were needed to access the polymer-supported catalyst in the second case. Ruthenium-catalyzed cycloadditions have not been investigated in this context, however, and we were interested if two consecutive ruthenium-catalyzed reactions, in this case RuAAC followed by a hydrogen borrowing reaction, could be used to access tricyclic fused piperazines using easily available commercial catalysts.

The *hydrogen borrowing* reaction provides a convenient catalytic method for connecting an alcohol with an amine or a carbon nucleophile in one reaction step.<sup>31-36</sup> The reaction is generally catalyzed by ruthenium or iridium, and has proven useful in the synthesis of drugs and drug candidates.<sup>37</sup> Furthermore, hydrogen borrowing has earlier been applied towards the preparation of nitrogen-containing heterocycles,<sup>38</sup> such as piperazines,<sup>39</sup> benzodiazepines,<sup>40</sup> and indoles.<sup>41</sup> We thus set out to investigate if the RuAAC reaction between a proline-derived azide (**1**) and internal propargylic alcohols (**2**) to form triazoles **3**, followed by an Ru-catalyzed hydrogen borrowing cyclization, could provide a new route to tricyclic fused triazole piperazines (Scheme 1d). Our results from this study are reported herein.

## Results and discussion

Commercially available proline-derived azide **1**, as the *R* or *S* enantiomer, was initially employed in this project, but due to its high cost and intermittent accessibility, we eventually turned to preparing this derivative ourselves. Azide **1** was thus synthesized from commercial Boc-prolinol in good yield (Scheme 2, exemplified by the *(R)*-enantiomer).

Catalysts for the initial RuAAC reaction were first screened using commercial (*S*)-**1** and propargylic alcohol **2a** on a



Scheme 2 Synthesis of azide (R)-1 from Boc-(R)-prolinol.

Table 1 Catalyst screening for RuAAC reaction<sup>a</sup>

Entry	Catalyst	Mol% catalyst	Solvent	T [°C]	t [h]	Yield 3a <sup>b</sup> [%]
1	[Cp*RuCl] <sub>4</sub>	5	Toluene	40	62	9
2	[Cp*RuCl <sub>2</sub> ] <sub>n</sub>	5	Toluene	40	62	40
3	[Cp*RuCl(PPh <sub>3</sub> ) <sub>2</sub> ]	5	Toluene	40	62	59
4	[Cp*RuCl(cod)]	5	Toluene	40	24	67
5	[Cp*RuCl(cod)]	5	Toluene	40	48	85
6	[Cp*RuCl(cod)]	5	Toluene	50	24	56
7	[Cp*RuCl(cod)]	5	Toluene	25	48	45
8	[Cp*RuCl(cod)]	5	THF	40	41	41
9	[Cp*RuCl(cod)]	5	CH <sub>2</sub> Cl <sub>2</sub>	25	24	51 <sup>c</sup>
10 <sup>d</sup>	[Cp*RuCl(cod)]	10	Toluene	40	1	76

<sup>a</sup> Conditions: alkyne (0.4 mmol), azide (0.4 mmol), catalyst (5 or 10 mol%), and solvent (5 mL) were stirred at 25 or 40 °C under an argon atmosphere for the indicated time. <sup>b</sup> Isolated yield.

<sup>c</sup> Regioisomer **3aa** was also isolated in 10% yield. <sup>d</sup> Reaction performed with (*R*)-**1** enantiomer.

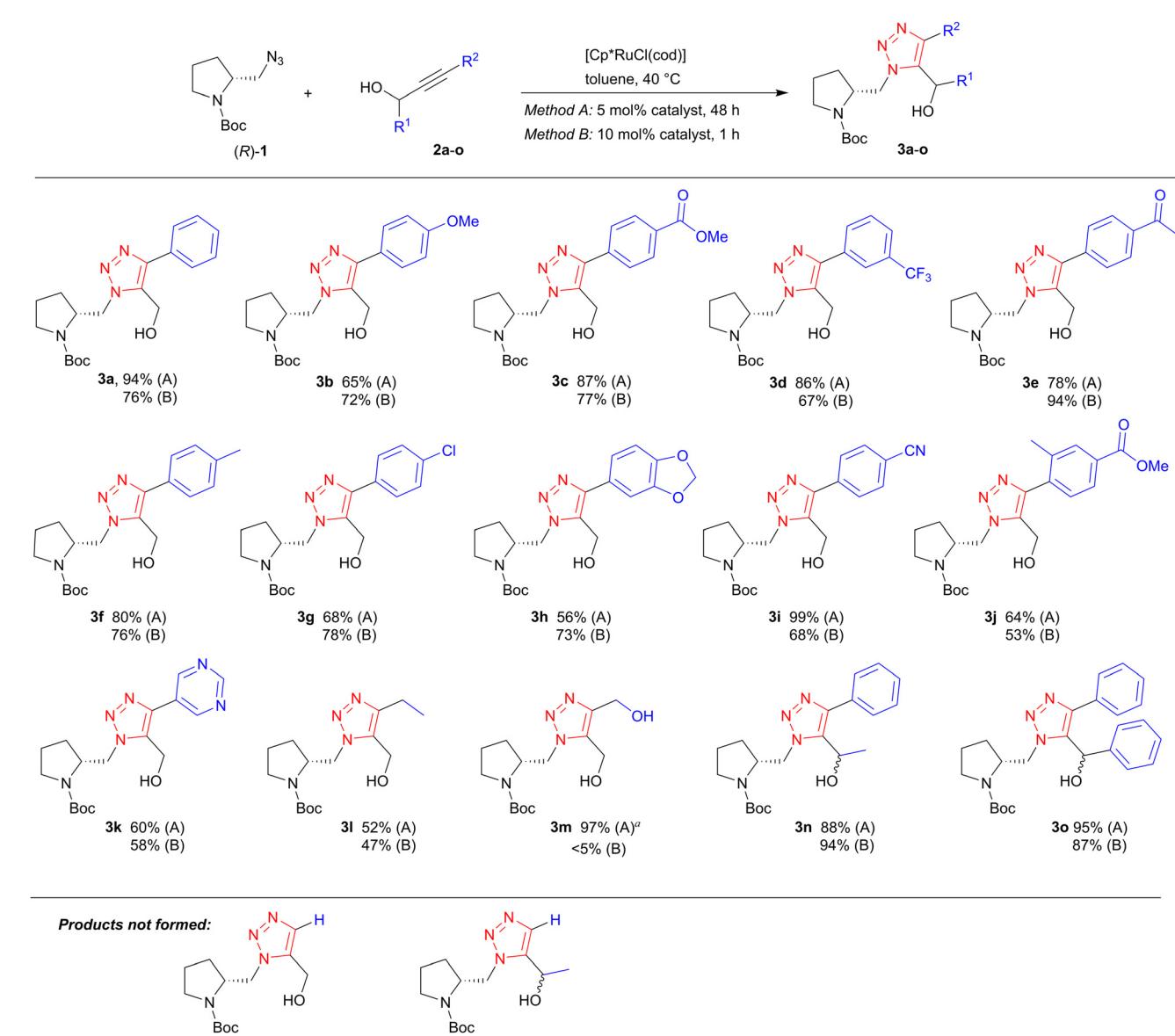
0.4 mmol scale (Table 1). Four different catalysts were examined with toluene as the solvent at 40 °C. The use of [Cp\*RuCl]<sub>4</sub> resulted in a low yield of triazole (*S*)-**3a**, even with a prolonged reaction time of several days (entry 1). Better results were obtained with [Cp\*RuCl<sub>2</sub>]<sub>n</sub> and [Cp\*RuCl(PPh<sub>3</sub>)<sub>2</sub>], albeit still involving slow product formation (entries 2 and 3). Further improvement was seen when switching to [Cp\*RuCl(cod)], which afforded a higher yield after 24 hours (entry 4) and this catalyst was thus selected for further studies. A longer reaction (48 h) time increased the yield of (*S*)-**3a** from 67% to 85% (entry 5), while other changes such as raising or lowering the reaction temperature were not beneficial (entries 6 and 7). In addition to toluene, two other solvents were also investigated. When THF was used as the solvent, the yield dropped to 41% (entry 8). While the reaction in CH<sub>2</sub>Cl<sub>2</sub> was rapid already at 25 °C, around 10% of the regioisomer **3aa** was observed in the crude product (entry 9). While RuAAC reactions involving internal alkynes can give a variable degree of regioselectivity,<sup>13,42</sup> the high selectivity obtained with propargylic alcohols is attributed to H-bond formation between the alcohol and a chloride ligand on the catalyst.<sup>13</sup> However, formation of substantial amounts of the second regioisomer when using CH<sub>2</sub>Cl<sub>2</sub> as the solvent has been reported by others when using propargylic alcohols.<sup>43</sup> While a good yield of (*S*)-**3a** (entry 5) could be obtained under mild reaction conditions and without the need for any extra additives, apart from the catalyst, the reaction time was rather long (48 h). We thus investigated if a higher catalyst loading could lead to a faster reaction and found to our satisfaction that an acceptable yield (76%) could be obtained already after 1 h using 10 mol% [Cp\*RuCl(cod)] (entry 10).

With these results in hand, various propargylic alcohols were then investigated in the RuAAC reaction with azide (*R*)-**1**

(Scheme 3), using the conditions in entries 5 and 10, *i.e.* 5% catalyst for 48 h (Method A) or 10% catalyst for 1 h (Method B).

The (*R*)-1 enantiomer of the proline azide afforded (*R*)-3a in 94% yield when performed on a 0.6 mmol scale using Method A, with a slightly lower yield for Method B (76%). Introducing substituents on the aryl group was unproblematic, and a wide range of substituents in the *meta*- or *para*-position were compatible with the reaction conditions, including methyl, methoxy-, ester-, CF<sub>3</sub>-, acetyl-, dioxole-, chloride-, and nitrile-substituted derivatives. Triazoles 3b–i were isolated in good to excellent yields from these reactions, with no discernable differences in reactivity seen for electron-donating or electron-withdrawing substituents on the 4-aryl group. Looking at more hindered substrates, introduction of a methyl group in the aryl

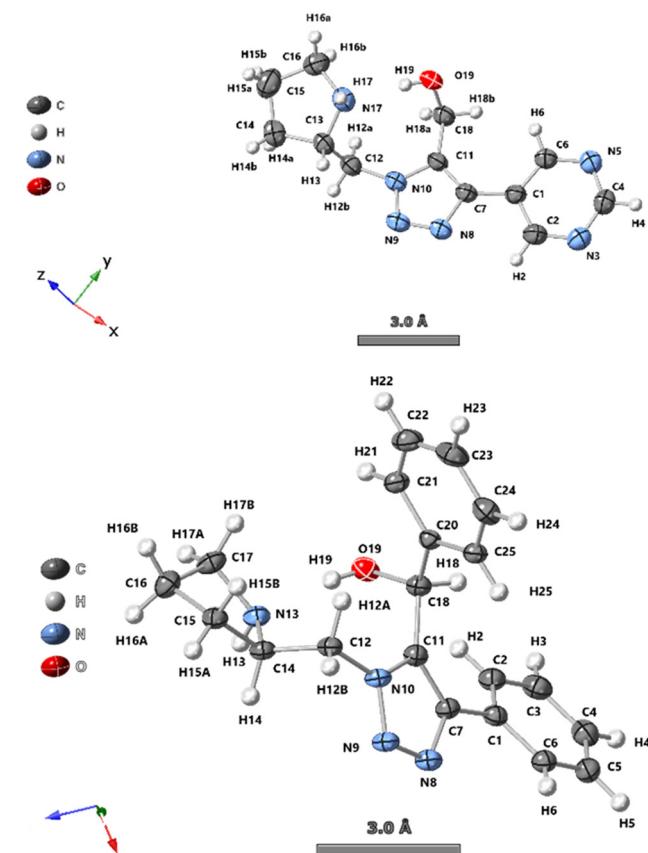
*ortho*-position resulted in a slight reduction in yield, from 87% for 3c to 64% for 3j when using method A, most likely due to steric hindrance which prevents effective coordination of the alkyne to ruthenium. A nitrogen-heterocycle in the form of a pyrimidine unit in the propargylic alcohol was compatible with the reaction conditions, but produced 3k in a slightly lower yield (60%) compared to simpler aromatic substituents. Nitrogen heterocycles are good ligands for ruthenium, and catalyst deactivation may be the reason for the poorer performance for this substrate. Aliphatic propargylic alcohols were also investigated. The reaction of (*R*)-1 with pent-2-yn-1-ol proceeded in a high conversion to the desired cyclized product according to <sup>1</sup>H NMR, but ensuing purification difficulties reduced the yield of 3l to 52%. But-2-yne-1,4-diol as the sub-



**Scheme 3** Triazoles 3 from the RuAAC reaction of azide (*R*)-1 and propargylic alcohols 2. Reagents and conditions: alkyne (0.6 mmol) and (*R*)-1a (0.6 mmol) in toluene (7.5 mL) were stirred under argon at 40 °C using 5 mol% [Cp\*RuCl(cod)] for 48 h (Method A) or 10 mol% [Cp\*RuCl(cod)] for 1 h. Isolated yields. <sup>a</sup> 3 mL dioxane added as co-solvent due to low solubility of alkynol 2m.



strate was more successful, affording **3m** in near quantitative yield. Applying reaction conditions B, using a short reaction time, was not successful in this case, however. The low solubility of this compound, in conjunction with increased possibilities for hydrogen bonding, may be the reason why this substrate requires a longer reaction time. Terminal propargylic alcohols (propargyl alcohol and 3-butyn-2-ol) suffered from competing side reactions and no triazoles could be isolated for these substrates. However, substitution at the propargylic position was unproblematic, exemplified by the use of secondary propargylic alcohols to form **3n** and **3o** in 88% and 95% yields respectively, using method A.



**Fig. 2** Solid state structure of deprotected **3k** and **3o**. Ellipsoids are represented at 50% probability. H atoms are shown as spheres of arbitrary radius. CCDC 2389333 and 2423532.

**Table 2** Catalyst screening for hydrogen borrowing reaction<sup>a</sup>

Entry	Catalyst (mol%)	L (mol%)	Base (mol%)	T [°C]	t [h]	Yield <b>4a</b> <sup>b</sup> [%]
1	[Ru( <i>p</i> -cymene)Cl <sub>2</sub> ] <sub>2</sub> (2.5)	DPEphos (5)	Et <sub>3</sub> N (5)	130	24	50
2	[Ru( <i>p</i> -cymene)Cl <sub>2</sub> ] <sub>2</sub> (5)	DPEphos (10)	Et <sub>3</sub> N (10)	130	24	75
3 <sup>c</sup>	[Ru( <i>p</i> -cymene)Cl <sub>2</sub> ] <sub>2</sub> (5)	DPEphos (10)	Et <sub>3</sub> N (10)	130	24	71
4	—	DPEphos (10)	Et <sub>3</sub> N (10)	130	24	0
5	—	—	Et <sub>3</sub> N (10)	130	24	0
6	[Cp*IrCl <sub>2</sub> ] <sub>2</sub> (3)	—	NaHCO <sub>3</sub> (6)	110	17	14
7	[Cp*IrCl <sub>2</sub> ] <sub>2</sub> (3)	—	KOAc (6)	110	17	5

<sup>a</sup> Conditions – Step 1: 3 M HCl in MeOH, 40 °C, 1 h; step 2: deprotected triazole (0.2–0.45 mmol), catalyst (3–10 mol%), ligand (0–10 mol%), base (5–10 mmol), toluene (10 mL mmol<sup>-1</sup> substrate) 110 °C or 130 °C, 17 or 24 h. <sup>b</sup> Entries 1–5: isolated yield. Entries 6 and 7: conversion, determined by <sup>1</sup>H NMR. <sup>c</sup> Performed on 1 mmol scale.



tive catalyst, but these conditions afforded low product yields (entries 6 and 7).  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$  in conjunction with DPEphos and  $\text{Et}_3\text{N}$  as base was used for further experiments.

Selected substrates from Scheme 3 were then explored in hydrogen borrowing-type cyclizations (Scheme 4). The cyclized products displayed a strong coordination to the catalyst, most likely due to the piperazine nitrogens, and isolating the desired compounds with sufficient purity proved challenging. A combination of different purification techniques were pursued (ion exchange resins, use of metal scavengers, flash chromatography). However, adsorbing the crude product on amine-functionalized silica gel prior to purification by automated flash chromatography allowed for isolation in higher yields. Cyclization of phenyl-substituted triazole  $(R)$ -3a afforded tricyclic 4a in 75% yield. Functional groups such as methoxy and  $\text{CF}_3$  on the aromatic ring were well tolerated and the corresponding fused triazoles 4b and 4d were isolated 65% and 74% yield respectively. Triazole 3e, with an acetyl group in the *para* position of the phenyl ring, was also cyclized successfully to 4e. Concomitant transfer hydrogenation of the ketone is a potential side reaction here, but no such byproduct was seen. Substrate 3g containing a chlorine-substituted phenyl ring was found to be compatible with the reaction conditions, affording 4g in a moderate yield. The more sterically hindered alcohol 3j, with an *ortho*-substituted aromatic, afforded 4j in

35% yield, while alkyl-substituted 4l was produced in 39% yield. Cyclization of secondary alcohol 3n was not successful, affording only trace amounts of product. Reasoning that a benzylic alcohol might be more easily dehydrogenated in the hydrogen borrowing reaction, we thus attempted cyclization of 3o, but with similar results. Given the strong binding to ruthenium, we envisage that products of type 4 could find applications as chiral ligands in transition metal-catalyzed transformations.

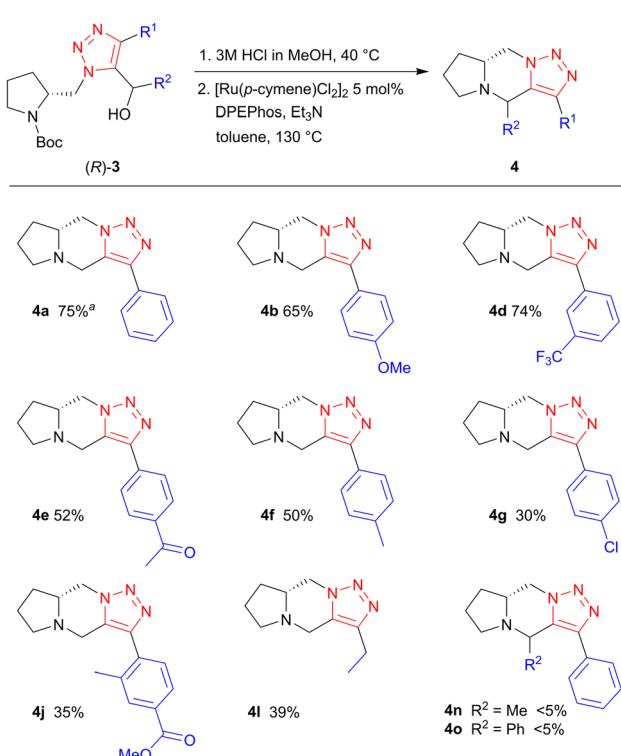
## Conclusion

In conclusion, we have shown that sequential ruthenium-catalyzed reactions can be employed to access fused triazole piperazines in a facile and atom economic manner. Boc-protected prolinol was converted to a proline–azide derivative, which was reacted with a wide range of propargylic alcohols *via* a ruthenium-catalyzed azide alkyne cycloaddition under mild reaction conditions, affording 1,4,5-trisubstituted triazoles 3 with a pendant alcohol in up to 99% yield. Amine deprotection, followed by an intramolecular ruthenium-catalyzed hydrogen borrowing reaction, afforded a selection of fused triazole piperazines (4) in up to 75% yield. We envisage that both derivatives 3 and 4 could find applications in the synthesis of new chiral ligands and organocatalysts for asymmetric transformations. In addition, the developed methodology could potentially be exploited in the synthesis of fused tricyclic compounds of medicinal or biological interest in the future.

## Experimental section

### General

All chemicals, including propargylic alcohols 2a, 2l, 2m, 2n and 2o, were purchased from commercial sources and used without further purification. Solvents were received and used as anhydrous grade. MP-carbonate (MP = macroporous polystyrene, capacity 3 mmol g<sup>-1</sup>) was purchased from Biotage. All glassware was oven-dried before use and all reactions were performed under a nitrogen or argon atmosphere. Flash chromatography was performed using a Biotage Isolera One or Biotage Selekt instrument. <sup>1</sup>H and <sup>13</sup>C NMR spectra were obtained on a Varian MR 400 MHz instrument, a Varian VNMR-S 500 MHz instrument, or an Oxford 800 MHz Bruker Avance III HD spectrometer in  $\text{CDCl}_3$  using the solvent residual peak as reference. The abbreviations used were: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, app = apparent, br = broad. HRMS was performed on an Agilent 1290 infinity LC system equipped with an autosampler tandem to an Agilent 6520 Accurate Mass Q-TOF LC/MS. Melting points were measured on either a Mettler FP90 with a FP82HT hot stage or a Büchi Melting Point B-545 and are uncorrected. IR spectra were obtained with a PerkinElmer Spectrum One FT-IR Spectrometer. FT-ATR-IR spectra were recorded on a PerkinElmer Spectrum Frontier infrared spectro-



**Scheme 4** Formation of fused triazole piperazines 4. Reagents and conditions: (1) 3 M HCl in MeOH, 40 °C, 1 h; (2)  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$  (5 mol%), DPEphos (10 mol%),  $\text{Et}_3\text{N}$  (10 mol%), toluene, 130 °C, 24–48 h. Isolated yields for the 2-step process. <sup>a</sup>The corresponding enantiomer (*S*)-4a was also prepared in 58% yield from (*S*)-3a.



meter with pike-GladiATR module. Optical rotations were measured on samples dissolved in DCM with a PerkinElmer 341 LC polarimeter with a sodium lamp (D-line, wavelength = 589 nm). For previously reported compounds, only  $^1\text{H}$  and  $^{13}\text{C}$  NMR data is provided.

### Single crystal X-ray diffraction (ScXRD)

Single whiteish colourless block-shaped crystals of **3k** and **3o** were obtained by recrystallisation from MeOH. Suitable crystals were selected and placed on a mounted cryo loop and mounted on an XtaLAB Synergy R, HyPix diffractometer. During data collection, the crystals were kept at a steady temperature of 293(2) K for **3k** and  $T = 107.02$  (10) K for **3o**. The structure was solved with the ShelXT 2016/6<sup>44</sup> structure solution program using the dual solution method and by using Olex2<sup>45</sup> as the graphical interface. The model was refined with version 2016/6 of ShelXL 2016/6 using Least Squares minimisation.<sup>44</sup>

### Synthetic procedures

**tert-Butyl (R)-2-(tosyloxymethyl)pyrrolidine-1-carboxylate ((R)-5).** Triethylamine (10 mmol, 1.39 mL) was added dropwise to a solution of *N*-Boc-(*R*)-prolinol (2 mmol, 402 mg) in anhydrous  $\text{CH}_2\text{Cl}_2$  (1 mL) in 20 mL Biotage reaction vial under nitrogen. An ice bath was then placed under the flask and the  $\text{TsCl}$  (3 mmol, 572 mg) was added to the mixture. After stirring for 18 h at room temperature, 40 mL of diethyl ether was added and the organic phase was washed with 5 M HCl ( $2 \times 15$  mL). The aqueous phase was extracted with diethyl ether ( $2 \times 20$  mL) and the combined organic phases were washed with brine (10 mL) and water (10 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and evaporated *in vacuo*, affording 683 mg (93%) of (*R*)-5 as a brownish oil. Spectral data for this product were in accordance to earlier reported data for (*R*)-5, prepared *via* a slightly different reaction procedure.<sup>46</sup>

**tert-Butyl (R)-2-(azidomethyl)pyrrolidine-1-carboxylate ((R)-1).** This compound was prepared following a procedure reported for the corresponding mesylate.<sup>47</sup> To a solution of (*R*)-5 (1 mmol, 367 mg) in anhydrous DMF (6 mL) in 20 mL Biotage reaction vial under nitrogen,  $\text{NaN}_3$  (2.5 mmol, 162 mg, *Caution!  $\text{NaN}_3$  is toxic, potentially explosive and should be handled with care*) was added and the solution was stirred for 5 min at room temperature, then overnight (16 h) at 60 °C. After this time, 5 mL of water were added to the mixture and the aqueous phase was extracted with ethyl acetate ( $2 \times 20$  mL). The combined organic phases were washed with a saturated solution of  $\text{NaHCO}_3$  (10 mL), water ( $2 \times 10$  mL) and brine (10 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and evaporated under a flow of nitrogen to give 166 mg (74%) of azide (*R*)-1 as a transparent liquid. This compound was found to be sufficiently pure to be used without further purification. Spectral data for this product were in accordance to earlier reported data.<sup>47</sup>

### General procedure for the RuAAC reaction

Method A:  $[\text{Cp}^*\text{RuCl}(\text{cod})]$  (5 mol%) was added to a sealed Biotage® 10–20 mL MW-vial. The vial was purged with argon

and toluene (6 mL) was added. A mixture of the alkyne (0.6 mmol) and the azide (0.6 mmol) in toluene (1.5 mL) was added dropwise to the catalyst solution and the vial was heated in an oil bath at 40 °C with stirring for 48 h. The reaction mixture was cooled to room temperature, concentrated and directly purified by flash chromatography using a gradient of petroleum ether/ethyl acetate (0–60%), followed by a gradient of dichloromethane/methanol (0–30%).

Method B: Same procedure as for method A, but using  $[\text{Cp}^*\text{RuCl}(\text{cod})]$  (10 mol%) and a reaction time of 1 h.

**tert-Butyl (S)-2-((5-(hydroxymethyl)-4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)pyrrolidine-1-carboxylate ((S)-3a).** Method A: 220 mg (0.72 mmol scale), 85%, white solid; mp = 47–49 °C; IR (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$  3198, 2984, 2926, 1687, 1382, 1170, 1118, 1041, 782;  $[\alpha]_D^{20} = +52.8$  (4.29,  $\text{CH}_2\text{Cl}_2$ );  $\delta_{\text{H}}$  NMR (400 MHz,  $\text{CDCl}_3$ ) 1.43 (s, 9H), 1.85–2.07 (m, 3H), 2.13–2.27 (m, 1H), 3.21–3.35 (m, 1H), 3.39–3.52 (m, 1H), 4.17 (app bs, 1H), 4.36 (dd,  $J = 8.7$  Hz, 13.7 Hz, 1H), 4.56 (dd,  $J = 3.7$  Hz, 13.7 Hz, 1H), 4.77–4.91 (m, 2H), 5.33 (app bs, 1H), 7.34–7.39 (m, 1H), 7.45 (br t,  $J = 7.1$  Hz, 2H), 7.74 (br d,  $J = 7.0$  Hz, 2H);  $\delta_{\text{C}}$  NMR (100 MHz,  $\text{CDCl}_3$ ) 23.3, 28.5, 28.8, 46.9, 50.6, 52.3, 57.4, 81.0, 127.9, 128.2, 128.8, 131.1, 132.9, 146.4, 155.6; HRMS (ESI<sup>+</sup>)  $m/z$  calcd for  $\text{C}_{19}\text{H}_{27}\text{N}_4\text{O}_3$  ( $[\text{M} + \text{H}]^+$ ) 359.2083, found 359.2076.

**tert-Butyl (R)-2-((5-(hydroxymethyl)-4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)pyrrolidine-1-carboxylate ((R)-3a).** Method A: 201 mg (0.60 mmol scale), 94%; method B: 138 mg (0.50 mmol scale), 76%, white solid;  $[\alpha]_D^{20} = -47.0$  (0.48,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$  and  $^{13}\text{C}$ -NMR were identical to the *S*-enantiomer. This reaction was also performed on 1 mmol scale, affording 297 mg (83%) of (*R*)-3a.

**tert-Butyl (R)-2-((5-(hydroxymethyl)-4-(4-methoxyphenyl)-1*H*-1,2,3-triazol-1-yl)methyl)pyrrole-dine-1-carboxylate ((R)-3b).** Method A: 155 mg (0.61 mmol scale), 65%; method B: 143 mg (0.50 mmol scale), 72%, white solid; mp = 57–58 °C; IR (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$  3404, 2974, 1692, 1510, 1395, 1395, 1252, 1176;  $[\alpha]_D^{20} = -48.0$  (2.66,  $\text{CH}_2\text{Cl}_2$ );  $\delta_{\text{H}}$  NMR (400 MHz,  $\text{CDCl}_3$ ) 1.39 (s, 9H), 1.82–2.05 (m, 3H), 2.12–2.24 (m, 1H), 3.18–3.34 (m, 1H), 3.37–3.51 (m, 1H), 3.79 (s, 3H), 4.15 (app bs, 1H), 4.34 (dd,  $J = 8.7$ , 13.7 Hz, 1H), 4.54 (dd,  $J = 3.6$ , 13.7 Hz, 1H), 4.75–4.90 (m, 2H), 5.31 (bs, 1H), 6.89–6.98 (m, 2H), 7.59–7.68 (m, 2H);  $\delta_{\text{C}}$  NMR (100 MHz,  $\text{CDCl}_3$ ) 23.2, 28.4, 28.8, 46.8, 50.5, 52.2, 55.3, 57.3, 80.8, 114.2, 123.6, 129.1, 132.2, 146.1, 155.5, 159.6; HRMS (ESI<sup>+</sup>)  $m/z$  calcd for  $\text{C}_{20}\text{H}_{29}\text{N}_4\text{O}_4$  ( $[\text{M} + \text{H}]^+$ ) 389.2189, found 389.2193.

**tert-Butyl (R)-2-((5-(hydroxymethyl)-4-(4-methoxycarbonyl)-phenyl)-1*H*-1,2,3-triazol-1-yl)methyl)pyrrolidine-1-carboxylate ((R)-3c).** Method A: 222 mg (0.61 mmol scale), 87%; method B: 159 mg (0.50 mmol scale), 77%, yellowish solid; mp = 50–52 °C; IR (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$  3419, 2975, 1722, 1692, 1394, 1280, 1112;  $[\alpha]_D^{20} = -54.1$  (1.42,  $\text{CH}_2\text{Cl}_2$ );  $\delta_{\text{H}}$  NMR (400 MHz,  $\text{CDCl}_3$ ) 1.39 (s, 9H), 1.82–2.05 (m, 3H), 2.06–2.21 (m, 1H), 3.19–3.34 (m, 1H), 3.35–3.50 (m, 1H), 3.90 (s, 3H), 4.08–4.21 (m, 1H), 4.35 (dd,  $J = 8.7$ , 13.8 Hz, 1H), 4.54 (dd,  $J = 3.4$ , 13.8 Hz, 1H), 4.77–4.91 (m, 2H), 5.38 (bs, 1H), 7.79–7.86 (m, 2H), 8.01–8.13 (m, 2H);  $\delta_{\text{C}}$  NMR (100 MHz,  $\text{CDCl}_3$ ) 23.3, 28.4, 28.7, 46.8, 50.7, 52.2, 57.3, 81.0, 127.5, 129.5, 130.1, 133.6, 135.5,



145.2, 155.6, 166.9; HRMS (ESI<sup>+</sup>) *m/z* calcd for C<sub>21</sub>H<sub>29</sub>N<sub>4</sub>O<sub>5</sub> ([M + H]<sup>+</sup>) 417.2138, found 417.2128.

**tert-Butyl (R)-2-((5-(hydroxymethyl)-4-(trifluoromethyl)-phenyl)-1*H*-1,2,3-triazol-1-yl)methyl)pyrrolidine-1-carboxylate ((R)-3d).** Method A: 226 mg (0.62 mmol scale); 86%; method B: 144 mg (0.50 mmol scale), 67%, off-white solid; mp = 51–53 °C; IR (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$  3404, 2979, 2888, 1694, 1396, 1313, 1168, 1125, 702;  $[\alpha]_{\text{D}}^{20} = -58.9$  (1.50, CH<sub>2</sub>Cl<sub>2</sub>);  $\delta_{\text{H}}$  NMR (400 MHz, CDCl<sub>3</sub>) 1.40 (s, 9H), 1.83–2.06 (m, 3H), 2.07–2.22 (m, 1H), 3.19–3.34 (m, 1H), 3.36–3.51 (m, 1H), 4.07–4.22 (m, 1H), 4.36 (dd, *J* = 8.7, 13.7 Hz, 1H), 4.55 (dd, *J* = 3.9, 13.7 Hz, 1H), 4.75–4.92 (m, 2H), 5.39 (bs, 1H), 7.49–7.63 (m, 2H), 7.92 (d, *J* = 7.5 Hz, 1H), 8.04 (s, 1H);  $\delta_{\text{C}}$  NMR (100 MHz, CDCl<sub>3</sub>) 23.3, 28.4, 28.8, 46.9, 50.8, 52.2, 57.4, 81.1, 124.2 (q, *J* = 272 Hz), 124.7 (q, *J* = 3.7 Hz), 124.8 (q, *J* = 3.7 Hz), 129.4, 131.0, 131.3 (q, *J* = 32.4 Hz), 132.0, 133.5, 145.1, 155.7;  $\delta_{\text{F}}$  NMR (376 MHz, CDCl<sub>3</sub>) –62.69; HRMS (ESI<sup>+</sup>) *m/z* calcd for C<sub>20</sub>H<sub>26</sub>F<sub>3</sub>N<sub>4</sub>O<sub>3</sub> ([M + H]<sup>+</sup>) 427.1957, found 427.1970.

**tert-Butyl (R)-2-((4-acetylphenyl)-5-(hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)methyl)pyrrolidine-1-carboxylate ((R)-3e).**

Method A: 189 mg (0.60 mmol scale), 78%; method B: 188 mg (0.50 mmol scale), 94%, off-white solid; mp = 45–50 °C; IR (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$  3400, 2976, 1685, 1395, 1269, 1168, 1114;  $[\alpha]_{\text{D}}^{20} = -47.9$  (1.54, CH<sub>2</sub>Cl<sub>2</sub>);  $\delta_{\text{H}}$  NMR (400 MHz, CDCl<sub>3</sub>) 1.41 (s, 9H), 1.85–2.06 (m, 3H), 2.10–2.24 (m, 1H), 2.61 (s, 3H), 3.19–3.35 (m, 1H), 3.39–3.52 (m, 1H), 4.09–4.23 (m, 1H), 4.30–4.43 (m, 1H), 4.56 (dd, *J* = 3.5, 13.7 Hz, 1H), 4.77–4.94 (m, 2H), 5.39 (bs, 1H), 7.83–7.90 (m, 2H), 7.98–8.05 (m, 2H);  $\delta_{\text{C}}$  NMR (100 MHz, CDCl<sub>3</sub>) 23.3, 26.8, 28.4, 28.8, 46.9, 50.7, 52.2, 57.4, 81.1, 127.8, 128.9, 133.7, 135.7, 136.4, 145.2, 155.6, 197.9; HRMS (ESI<sup>+</sup>) *m/z* calcd for C<sub>21</sub>H<sub>29</sub>N<sub>4</sub>O<sub>4</sub> ([M + H]<sup>+</sup>) 401.2189, found 401.2190.

**tert-Butyl (R)-2-((5-(hydroxymethyl)-4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)methyl)pyrrolidine-1-carboxylate ((R)-3f).** Method A: 136 mg (0.46 mmol scale), 80%; method B: 85 mg (0.30 mmol scale), 76%, off-white solid; mp = 51–54 °C; IR (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$  3395, 2976, 1694, 1394, 1169, 1114, 826;  $[\alpha]_{\text{D}}^{20} = -74.4$  (0.17, CH<sub>2</sub>Cl<sub>2</sub>);  $\delta_{\text{H}}$  NMR (400 MHz, CDCl<sub>3</sub>) 1.42 (s, 9H), 1.82–2.07 (m, 3H), 2.10–2.27 (m, 1H), 2.37 (s, 3H), 3.20–3.33 (m, 1H), 3.36–3.51 (m, 1H), 4.15 (app bs, 1H), 4.34 (dd, *J* = 8.7, 13.7 Hz, 1H), 4.54 (dd, *J* = 3.7, 13.7 Hz, 1H), 4.76–4.90 (m, 2H), 5.34 (bs, 1H), 7.24 (m, 2H), 7.60–7.63 (m, 2H);  $\delta_{\text{C}}$  NMR (100 MHz, CDCl<sub>3</sub>) 21.4, 23.3, 28.4, 28.8, 46.9, 50.6, 52.3, 57.4, 80.9, 127.8, 128.2, 129.5, 132.6, 137.9, 146.3, 155.6; HRMS (ESI<sup>+</sup>) *m/z* calcd for C<sub>20</sub>H<sub>29</sub>N<sub>4</sub>O<sub>3</sub> ([M + H]<sup>+</sup>) 373.2240, found 373.2245.

**tert-butyl (R)-2-((4-(4-chlorophenyl)-5-(hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)methyl)pyrrole-dine-1-carboxylate ((R)-3g).**

Method A: 160 mg (0.60 mmol scale), 68%; method B: 154 mg (0.50 mmol scale), 78%, off-white solid; mp = 48–49 °C; IR (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$  3401, 2976, 1693, 1493, 1394, 1168, 1092, 1007, 837;  $[\alpha]_{\text{D}}^{20} = -47.7$  (2.15, CH<sub>2</sub>Cl<sub>2</sub>);  $\delta_{\text{H}}$  NMR (400 MHz, CDCl<sub>3</sub>) 1.42 (s, 9H), 1.84–2.05 (m, 3H), 2.09–2.24 (m, 1H), 3.21–3.35 (m, 1H), 3.38–3.52 (m, 1H), 4.06–4.21 (m, 1H), 4.28–4.40 (m, 1H), 4.49–4.57 (m, 1H), 4.73–4.89 (m, 2H), 5.36 (bs, 1H), 7.37–7.44 (m, 2H), 7.66–7.72 (m, 2H);  $\delta_{\text{C}}$  NMR (100 MHz, CDCl<sub>3</sub>) 23.3, 28.4, 28.8, 46.9, 50.7, 52.2, 57.4, 81.0, 129.1, 129.6, 133.0, 134.2,

145.3, 155.6; HRMS (ESI<sup>+</sup>) *m/z* calcd for C<sub>19</sub>H<sub>26</sub>ClN<sub>4</sub>O<sub>3</sub> ([M + H]<sup>+</sup>) 393.1693, found 393.1676.

**tert-Butyl (R)-2-((4-(benzo[d][1,3]dioxol-5-yl)-5-(hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)methyl)pyrrolidine-1-carboxylate ((R)-3h).** Method A: 115 mg (0.51 mmol scale), 56%; method B: 146 mg (0.50 mmol scale), 73%, beige amorphous solid; (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$  3394, 2976, 1693, 1505, 1395, 1236, 1168, 1117, 1038;  $[\alpha]_{\text{D}}^{20} = -59.3$  (0.80, CH<sub>2</sub>Cl<sub>2</sub>);  $\delta_{\text{H}}$  NMR (400 MHz, CDCl<sub>3</sub>) 1.41 (s, 9H), 1.81–2.04 (m, 3H), 2.09–2.24 (m, 1H), 3.19–3.34 (m, 1H), 3.37–3.49 (m, 1H), 4.07–4.21 (m, 1H), 4.27–4.38 (m, 1H), 4.47–4.58 (m, 1H), 4.71–4.88 (m, 2H), 5.27 (bs, 1H), 5.97 (s, 2H), 6.86 (dd, *J* = 8.0, 2.6, 1H), 7.18 (dt, *J* = 8.0, 2.2 Hz, 1H), 7.22–7.25 (m, 1H);  $\delta_{\text{C}}$  NMR (100 MHz, CDCl<sub>3</sub>) 23.3, 28.4, 28.8, 46.9, 50.6, 52.2, 57.4, 80.9, 101.2, 108.4, 108.7, 121.7, 125.1, 132.4, 146.1, 147.7, 148.1, 155.6; HRMS (ESI<sup>+</sup>) *m/z* calcd for C<sub>20</sub>H<sub>27</sub>N<sub>4</sub>O<sub>5</sub> ([M + H]<sup>+</sup>) 403.1981, found 403.1984.

**tert-Butyl (R)-2-((4-(4-cyanophenyl)-5-(hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)methyl)pyrrolidine-1-carboxylate ((R)-3i).**

Method A: 228 mg (0.60 mmol scale), 99%, method B: 79 mg (0.30 mmol scale), 68%, off-white solid; mp = 46–47 °C; IR (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$  3430, 2922, 2229, 1599, 1416, 1121;  $[\alpha]_{\text{D}}^{20} = -58.1$  (1.34, CH<sub>2</sub>Cl<sub>2</sub>);  $\delta_{\text{H}}$  NMR (400 MHz, CDCl<sub>3</sub>) 1.41 (s, 9H), 1.90–2.07 (m, 3H), 2.12–2.24 (m, 1H), 3.21–3.36 (m, 1H), 3.40–3.52 (m, 1H), 4.10–4.22 (m, 1H), 4.38 (dd, *J* = 8.5, 13.6 Hz, 1H), 4.55 (dd, *J* = 3.6, 13.6 Hz, 1H), 4.76–4.92 (m, 2H), 5.39 (bs, 1H), 7.72–7.76 (m, 2H), 7.90–7.94 (m, 2H);  $\delta_{\text{C}}$  NMR (100 MHz, CDCl<sub>3</sub>) 23.3, 28.4, 28.9, 46.9, 50.9, 52.1, 57.4, 81.2, 111.6, 119.0, 128.2, 132.7, 134.0, 135.7, 144.6, 155.7; HRMS (ESI<sup>+</sup>) *m/z* calcd for C<sub>20</sub>H<sub>26</sub>N<sub>5</sub>O<sub>3</sub> ([M + H]<sup>+</sup>) 384.2036, found 384.2036.

**tert-Butyl (R)-2-((5-(hydroxymethyl)-4-(methoxycarbonyl)-2-methylphenyl)-1*H*-1,2,3-triazol-1-yl)methyl)pyrrolidine-1-carboxylate ((R)-3j).** Method A: 164 mg (0.67 mmol scale), 64%; method B: 98 mg (0.43 mmol scale), 53%, yellowish solid; mp = 49–50 °C; IR (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$  3435, 2923, 1723, 1399;  $[\alpha]_{\text{D}}^{20} = -92.2$  (0.83, CH<sub>2</sub>Cl<sub>2</sub>);  $\delta_{\text{H}}$  NMR (400 MHz, CDCl<sub>3</sub>) 1.41 (s, 9H), 1.83–2.05 (m, 3H), 2.15–2.26 (m, 1H), 2.36 (s, 3H), 3.20–3.33 (m, 1H), 3.38–3.49 (m, 1H), 3.89 (s, 3H), 4.12–4.23 (m, 1H), 4.35 (m, 1H), 4.51–4.63 (m, 2H), 4.68 (m, 1H), 5.41 (bs, 1H), 7.36 (d, *J* = 7.5 Hz, 1H), 7.86 (d, *J* = 7.5, 1H), 7.93 (s, 1H);  $\delta_{\text{C}}$  NMR (100 MHz, CDCl<sub>3</sub>) 20.4, 23.2, 28.4, 28.7, 46.9, 50.6, 52.1, 52.2, 57.3, 81.0, 126.9, 130.0, 130.8, 131.7, 134.2, 134.7, 138.0, 145.2, 155.6, 167.0; HRMS (ESI<sup>+</sup>) *m/z* calcd for C<sub>22</sub>H<sub>31</sub>N<sub>4</sub>O<sub>5</sub> ([M + H]<sup>+</sup>) 431.2294, found 431.2303.

**tert-Butyl (R)-2-((5-(hydroxymethyl)-4-(pyrimidin-5-yl)-1*H*-1,2,3-triazol-1-yl)methyl)pyrrolidine-1-carboxylate ((R)-3k).**

Method A: 103 mg (0.48 mmol scale), 60%; method B: 104 mg (0.50 mmol scale), 58%, off-white solid; mp = 118–119 °C; IR (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$  3401, 2976, 1692, 1396, 1168, 1116, 725;  $[\alpha]_{\text{D}}^{20} = -68.8$  (0.62, CH<sub>2</sub>Cl<sub>2</sub>);  $\delta_{\text{H}}$  NMR (400 MHz, CDCl<sub>3</sub>) 1.38 (s, 9H), 1.84–2.05 (m, 3H), 2.06–2.18 (m, 1H), 3.18–3.33 (m, 1H), 3.36–3.50 (m, 1H), 4.07–4.22 (m, 1H), 4.38 (dd, *J* = 13.7, 8.2 Hz, 1H), 4.56 (dd, *J* = 13.7, 4.3 Hz, 1H), 4.75–4.93 (m, 2H), 5.42 (bs, 1H), 9.12 (s, 2H), 9.17 (s, 1H);  $\delta_{\text{C}}$  NMR (100 MHz, CDCl<sub>3</sub>) 23.2, 28.4, 28.7, 46.8, 50.8, 51.8, 57.1, 81.0, 125.6, 134.4, 140.1, 155.2, 155.5, 157.9; HRMS (ESI<sup>+</sup>) *m/z* calcd for C<sub>17</sub>H<sub>25</sub>N<sub>6</sub>O<sub>3</sub> ([M + H]<sup>+</sup>) 361.1988, found 361.1985.



**tert-Butyl (R)-2-((4-ethyl-5-(hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)methyl)pyrrolidine-1-carboxylate ((*R*)-3*l*). Method A: 81 mg (0.60 mmol scale), 52%; method B: 117 mg (0.08 mmol scale), 47% brown solid; mp = 102–103 °C; IR (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$  3395, 2975, 1694, 1395, 1171, 1029, 773;  $[\alpha]_{\text{D}}^{20} = -0.8$  (0.31,  $\text{CH}_2\text{Cl}_2$ );  $\delta_{\text{H}}$  NMR (400 MHz,  $\text{CDCl}_3$ ) 1.28 (t,  $J = 7.6$  Hz, 3H), 1.45 (s, 9H), 1.81–2.06 (m, 3H), 2.12–2.26 (m, 1H), 2.71 (q,  $J = 7.6$  Hz, 2H) 3.19–3.32 (m, 1H), 3.37–3.51 (m, 1H), 4.05–4.17 (m, 1H), 4.26 (dd,  $J = 9.2$ , 13.6 Hz, 1H), 4.47 (dd,  $J = 3.4$ , 13.6 Hz, 1H), 4.63–4.77 (m, 2H), 5.21 (t,  $J = 6.5$  Hz, 1H);  $\delta_{\text{C}}$  NMR (100 MHz,  $\text{CDCl}_3$ ) 14.6, 18.5, 23.3, 28.5, 28.7, 46.9, 50.4, 51.8, 57.2, 80.9, 132.5, 147.5, 155.6; HRMS (ESI $^{+}$ )  $m/z$  calcd for  $\text{C}_{15}\text{H}_{27}\text{N}_4\text{O}_3$  ( $[\text{M} + \text{H}]^{+}$ ) 311.2083, found 311.2090.**

**tert-Butyl (R)-2-((4,5-bis(hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)methyl)pyrrolidine-1-carboxylate ((*R*)-3*m*). Reactants were dissolved in toluene/dioxane 1 : 1 (2.5 mL). Method A: 181 mg (0.60 mmol), 97%; method B: <5%, brown sticky oil; IR (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$  3397, 2976, 1695, 1399, 1169, 1118, 1026, 774;  $[\alpha]_{\text{D}}^{20} = -38.3$  (1.1,  $\text{CH}_2\text{Cl}_2$ );  $\delta_{\text{H}}$  NMR (400 MHz,  $\text{CDCl}_3$ ) 1.45 (s, 9H), 1.78–1.97 (m, 3H), 2.03–2.18 (m, 1H), 3.18–3.31 (m, 1H), 3.36–3.48 (m, 1H), 4.05–4.16 (m, 1H), 4.31 (dd,  $J = 8.7$ , 13.6 Hz, 1H); 4.50 (dd,  $J = 3.0$ , 13.6 Hz, 1H), 4.67–4.89 (m, 4H), 5.14 (bs, 1H), one –OH group not visible;  $\delta_{\text{C}}$  NMR (100 MHz,  $\text{CDCl}_3$ ) 23.3, 28.5, 47.0, 50.4, 52.0, 55.8, 57.0, 80.7, 134.8, 145.3, 155.4; HRMS (ESI $^{+}$ )  $m/z$  calcd for  $\text{C}_{14}\text{H}_{25}\text{N}_4\text{O}_4$  ( $[\text{M} + \text{H}]^{+}$ ) 313.1876, found 313.1869.**

**tert-Butyl (2*R*)-2-((5-(1-hydroxyethyl)-4-phenyl-1*z*-1,2,3-triazol-1-yl)methyl)pyrrolidine-1-carboxylate ((*R*)-3*n*). Method A: 197 mg, 88% (0.60 mmol scale); method B: 106 mg (0.30 mmol scale), 94% white solid, ~1 : 1 mixture of diastereomers; mp = 60–61 °C; IR (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$  3394, 2978, 1694, 1394, 1250, 1169, 1105, 116, 700;  $[\alpha]_{\text{D}}^{20} = -68.6$  (0.18,  $\text{CH}_2\text{Cl}_2$ );  $\delta_{\text{H}}$  NMR (400 MHz,  $\text{CDCl}_3$ ) 1.31 (s) overlapping with 1.39 (s, 9H, two diastereomers), 1.59 (s, 3H), 1.75–2.02 (m, 3H), 2.04–2.24 (m, 1H), 3.20–3.35 (m, 1H), 3.36–3.52 (m, 1H), 4.27–4.39 (m, 1H), 4.40–4.57 (m) and 4.58–4.70 (m, 2H, two diastereomers), 5.19–5.35 (m, 1H), 5.42 (bs, 1H), 7.30–7.37 (m, 1H), 7.37–7.45 (m, 2H), 7.57 (br d,  $J = 6.6$  Hz, 1H), 7.62–7.72 (m, 1H);  $\delta_{\text{C}}$  NMR (100 MHz,  $\text{CDCl}_3$ , mixture of diastereomers) 21.5, 22.2, 23.1, 23.2, 28.4, 28.4, 28.6, 29.1, 46.5, 46.8, 51.0, 52.1, 55.9, 56.8, 60.4, 60.6, 80.4, 80.8, 128.0, 128.0, 128.5, 128.5, 128.8, 131.5, 131.6, 136.4, 136.5, 144.4, 145.2, 155.4, 155.5; HRMS (ESI $^{+}$ )  $m/z$  calcd for  $\text{C}_{20}\text{H}_{29}\text{N}_4\text{O}_3$  ( $[\text{M} + \text{H}]^{+}$ ) 373.2240, found 373.2260.**

**tert-Butyl (2*R*)-2-((5-(hydroxy(phenyl)methyl)-4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)pyrrolidine-1-carboxylate ((*R*)-3*o*). (Method A: 412 mg (1.0 mmol scale), 95%; method B: 151 mg (0.4 mmol), 87%, off-white solid, ~1 : 1 mixture of diastereomers); mp = 56–58 °C; FTIR–ATR  $\nu_{\text{max}}/\text{cm}^{-1}$  3317, 2974, 2931, 2870, 1689, 1658, 1392, 1164, 1114, 1045, 771;  $[\alpha]_{\text{D}}^{20} = -10.2$  (1.2,  $\text{CH}_2\text{Cl}_2$ );  $\delta_{\text{H}}$  NMR (400 MHz,  $\text{CDCl}_3$ , mixture of diastereomers) 1.26 (s) and 1.45 (s, 9H), 1.85–1.97 (m, 3H), 2.00–2.11 (m, 1H), 3.15–3.24 (m, 0.5H), 3.25–3.38 (m, 1H); 3.42–3.51 (app t,  $J = 8$  Hz, 0.5H), 3.79 (dd,  $J = 5.7$ , 13.9 Hz, 0.5H), 3.94–4.18 (m, 2H), 4.56–4.64 (m, 0.5H), 6.32 (br s) overlapping with 6.34 (br s, 1H), 7.32–7.46 (m, 5H), 7.24–7.31 (m, 3H), 7.67 (br t,  $J =$**

7.0 Hz, 2H);  $\delta_{\text{C}}$  NMR (100 MHz,  $\text{CDCl}_3$ , mixture of diastereomers) 22.8, 23.0, 28.2, 28.3, 28.6, 46.0, 46.6, 50.4, 52.2, 54.9, 57.3, 64.6, 65.4, 89.48, 89.91, 125.7, 125.6, 127.6, 127.6, 128.0, 128.0, 128.1, 128.2, 128.4, 128.5, 128.5, 128.6, 130.6, 130.8, 131.0, 134.3, 134.4, 140.1, 140.2, 146.4, 155.0, 155.4; HRMS (ESI $^{+}$ )  $m/z$  calcd for  $\text{C}_{25}\text{H}_{30}\text{N}_4\text{O}_3\text{Na}$  ( $[\text{M} + \text{Na}]^{+}$ ) 457.2216, found 457.2213.

#### General procedure for the Boc-deprotection and hydrogen borrowing reaction

Reactions were generally performed on a 0.2–0.45 mmol scale. The Boc-amine was treated with HCl (conc. aq., 5 mL  $\text{mmol}^{-1}$  substrate) in methanol (15 mL  $\text{mmol}^{-1}$  substrate) at 40 °C, and monitored by TLC (typical reaction time was 1 h). After completion of the reaction, the solvent and excess acid were removed under reduced pressure. The remaining HCl-salt was neutralized with one of the following methods: (1) vigorous stirring in a mixture of dichloromethane and 2 M aqueous NaOH for approximately 30 min. The layers were separated with a TELOS® phase separator and the aqueous layer was extracted with dichloromethane five times. The combined organic layers were concentrated to yield the free amine, or (2) the HCl-salt was treated with 6 equiv. of MP-carbonate in methanol at 40 °C for 48 h. The MP-carbonate was then filtered off and washed with dichloromethane and methanol and the filtrate was concentrated *in vacuo*. The freshly prepared amino alcohol was added to a Biotage® 10–20 mL vial, together with  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$  (5 mol%) and DPEphos (10 mol%). The vial was purged with argon and toluene (10 mL  $\text{mmol}^{-1}$  substrate) was added, followed by triethylamine (10 mol%). The reaction mixture was stirred at room temperature for 5 min, and then at 130 °C for 24–64 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure and the crude was directly analysed by  $^1\text{H}$  NMR to confirm product formation. The product was then applied on a Biotage® amine functionalised silica samplet (KP-NH) and then purified by standard flash chromatography on silica gel, eluting with a slow gradient of 0–60% ethyl acetate in petroleum ether, followed by 0–30% methanol in dichloromethane.

**(*R*)-3-Phenyl-7,8,8a,9-tetrahydro-4*H*,6*H*-pyrrolo[1,2-*a*][1,2,3]triazolo[1,5-*d*]pyrazine ((*R*)-4*a*). Prepared from (*R*)-3*a* (129 mg, 0.360 mmol), with a reaction time of 24 h for hydrogen borrowing, affording (*R*)-4*a* as an off-white solid (65 mg, 75%);  $[\alpha]_{\text{D}}^{20} = -57.8$  (0.77,  $\text{CH}_2\text{Cl}_2$ );  $\delta_{\text{H}}$  NMR (500 MHz,  $\text{CD}_2\text{Cl}_2$ ) 1.63–1.75 (m, 1H), 1.93–2.11 (m, 2H), 2.11–2.23 (m, 1H), 2.44 (app q,  $J = 8.9$  Hz, 1H), 2.68–2.77 (m, 1H), 3.31 (br t,  $J = 8.5$  Hz, 1H), 3.61 (d,  $J = 14.8$  Hz, 1H), 4.02 (t,  $J = 11.5$  Hz, 1H), 4.47 (d,  $J = 14.8$  Hz, 1H), 4.71 (dd,  $J = 8.1$ , 2.5 Hz, 1H), 7.33 (t,  $J = 5.0$  Hz, 1H), 7.44 (app t,  $J = 5.1$  Hz, 2H), 7.70 (d,  $J = 4.7$  Hz, 2H);  $\delta_{\text{C}}$  NMR (125 MHz,  $\text{CDCl}_3$ ) 22.8, 28.0, 48.8, 52.2, 54.0, 59.6, 126.3, 127.7, 128.9, 128.9, 131.5, 141.4. Analytical data were in accordance with published data for this compound.<sup>30</sup> This reaction was also performed on 1 mmol scale, affording 171 mg (71%) of (*R*)-4*a*. Reactions performed in the absence of catalyst or in the absence of both catalyst and ligand did not**



afford any product. A reaction performed on 0.33 mmol scale, using  $[\text{Cp}^*\text{IrCl}_2]_2$  (3.3 mol%) as the catalyst, afforded 11.5 mg (14%) of **(R)-4a**.

**(S)-3-Phenyl-7,8,8a,9-tetrahydro-4H,6H-pyrrolo[1,2-a][1,2,3]triazolo[1,5-d]pyrazine ((S)-4a).** Prepared from **(S)-3a** (183 mg, 0.51 mmol), with a reaction time of 24 h for hydrogen borrowing, affording **(S)-4a** as a white solid (71 mg, 58%);  $[\alpha]_{\text{D}}^{20} +52.3$  (0.63,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$  and  $^{13}\text{C}$  NMR were identical to the *(R)*-enantiomer and in accordance with published data for this compound.<sup>30</sup>

**(R)-3-(4-methoxyphenyl)-7,8,8a,9-tetrahydro-4H,6H-pyrrolo[1,2-a][1,2,3]triazolo[1,5-d]pyrazine ((R)-4b).** Prepared from **(R)-3b** (104 mg, 0.268 mmol), with a 48 h reaction time for hydrogen borrowing, affording **(R)-4b** as a white solid (47 mg, 65%); mp = 153–163 °C; IR (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$  3059, 2936, 2797, 1512, 1254, 1165, 998, 838;  $[\alpha]_{\text{D}}^{20} -53.1$  (0.55,  $\text{CH}_2\text{Cl}_2$ );  $\delta_{\text{H}}$  NMR (400 MHz,  $\text{CDCl}_3$ ) 1.60–1.73 (m, 1H), 1.91–2.09 (m, 2H), 2.09–2.20 (m, 1H), 2.43 (app q,  $J = 8.9$  Hz, 1H), 2.67–2.78 (m, 1H), 3.30 (dt,  $J = 2.4$ , 8.6 Hz, 1H), 3.57 (d,  $J = 14.7$  Hz, 1H), 3.83 (s, 3H), 4.02 (t,  $J = 11.5$  Hz, 1H), 4.44 (d,  $J = 14.7$  Hz, 1H), 4.72 (dd,  $J = 3.7$ , 12.2 Hz, 1H), 6.94–7.00 (m, 2H), 7.59–7.65 (m, 2H);  $\delta_{\text{C}}$  NMR (100 MHz,  $\text{CDCl}_3$ ) 22.8, 28.0, 48.7, 52.2, 53.9, 55.4, 59.6, 114.3, 124.2, 127.5, 128.0, 141.2, 159.2; HRMS (ESI+)  $m/z$  calcd for  $\text{C}_{15}\text{H}_{19}\text{N}_4\text{O}$  ( $[\text{M} + \text{H}]^+$ ) 255.1609, found 255.1600.

**(R)-3-(4-Chlorophenyl)-7,8,8a,9-tetrahydro-4H,6H-pyrrolo[1,2-a][1,2,3]triazolo[1,5-d]pyrazine ((R)-4g).** Prepared from **(R)-3g** (114 mg, 0.289 mmol), with a reaction time of 48 h for hydrogen borrowing, affording **(R)-4g** (24 mg, 30%) as a red solid; an analytical sample was prepared by purifying the product a second time using standard flash chromatography with the same gradient; mp = 184–187 °C; IR (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$  3070, 2961, 2930, 2815, 1497, 1317, 1164, 1090, 1005, 840;  $[\alpha]_{\text{D}}^{20} -58.4$  (0.31,  $\text{CH}_2\text{Cl}_2$ );  $\delta_{\text{H}}$  NMR (400 MHz,  $\text{CDCl}_3$ ) 1.61–1.73 (m, 1H), 1.92–2.10 (m, 2H), 2.11–2.21 (m, 1H), 2.44 (app q,  $J = 8.9$ , 1H), 2.68–2.79 (m, 1H), 3.32 (dt,  $J = 2.8$ , 8.3 Hz, 1H), 3.58 (d,  $J = 14.8$  Hz, 1H), 4.02 (t,  $J = 11.5$  Hz, 1H), 4.43 (d,  $J = 14.8$  Hz, 1H), 4.74 (dd,  $J = 3.5$ , 12.2 Hz, 1H), 7.35–7.43 (m, 2H), 7.59–7.65 (m, 2H);  $\delta_{\text{C}}$  NMR (100 MHz,  $\text{CDCl}_3$ );  $\delta$  22.8, 28.0, 48.7, 52.2, 53.9, 59.5, 127.5, 129.0, 129.1, 130.0, 133.6, 140.4; HRMS (ESI+)  $m/z$  calcd for  $\text{C}_{14}\text{H}_{16}\text{ClN}_4$  ( $[\text{M} + \text{H}]^+$ ) 275.1063, found 275.1052.

**(R)-3-(3-(Trifluoromethyl)phenyl)-7,8,8a,9-tetrahydro-4H,6H-pyrrolo[1,2-a][1,2,3]triazolo[1,5-d]pyrazine ((R)-4d).** Prepared from **(R)-4d** (186 mg, 0.436 mmol), with a 48 h reaction time for hydrogen borrowing, affording **(R)-4d** (99 mg, 74%) as an off-white solid; mp = 145–146 °C; IR (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$  2947, 2802, 1323, 1132, 1070, 701;  $[\alpha]_{\text{D}}^{20} = -42.2$  (1.6,  $\text{CH}_2\text{Cl}_2$ );  $\delta_{\text{H}}$  NMR (400 MHz,  $\text{CDCl}_3$ ) 1.62–1.76 (m, 1H, overlapping with  $\text{H}_2\text{O}$ ), 1.94–2.12 (m, 2H), 2.12–2.24 (m, 1H), 2.46 (app q,  $J = 8.9$  Hz, 1H), 2.71–2.82 (m, 1H), 3.34 (dt,  $J = 2.6$ , 8.5 Hz, 1H), 3.64 (d,  $J = 14.8$  Hz, 1H), 4.05 (t,  $J = 11.5$  Hz, 1H), 4.47 (d,  $J = 14.8$  Hz, 1H), 4.73 (dd,  $J = 3.8$ , 12.3 Hz, 1H), 7.52–7.61 (m, 2H), 7.85–7.91 (m, 1H), 7.96 (s, 1H);  $\delta_{\text{C}}$  NMR (100 MHz,  $\text{CDCl}_3$ ) 22.8, 27.9, 48.5, 52.3, 53.9, 59.5, 122.9 (q,  $J = 3.8$  Hz), 124.2 (q,  $J = 272$  Hz), 124.1 (q,  $J = 3.8$  Hz), 129.3, 129.4, 129.5, 131.3 (q,  $J = 32.3$  Hz), 132.3, 140.0;  $\delta_{\text{F}}$  NMR (376 MHz,  $\text{CDCl}_3$ ) –62.71; HRMS (ESI+)  $m/z$  calcd for  $\text{C}_{15}\text{H}_{16}\text{F}_3\text{N}_4$  ( $[\text{M} + \text{H}]^+$ ) 309.1327, found 309.1328.

**(R)-1-(4-(7,8,8a,9-Tetrahydro-4H,6H-pyrrolo[1,2-a][1,2,3]triazolo[1,5-d]pyrazin-3-yl)phenyl)eth-an-1-one ((R)-4e).** Prepared from **(R)-3e** (153 mg, 0.382 mmol), with a 64 h reaction time for hydrogen borrowing, affording **(R)-4e** (57 mg, 52%) as an off white solid; mp = 181–187 °C; IR (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$  3058, 2959, 2801, 1674, 1607, 1360, 1271, 1002, 844;  $[\alpha]_{\text{D}}^{20} -31.8$  (0.72,  $\text{CH}_2\text{Cl}_2$ );  $\delta_{\text{H}}$  NMR (400 MHz,  $\text{CDCl}_3$ ) 1.62–1.76 (m, 1H), 1.94–2.12 (m, 2H), 2.12–2.23 (m, 1H), 2.46 (app q,  $J = 8.8$  Hz, 1H) 2.62 (s, 3H), 2.71–2.81 (m, 1H), 3.33 (dt,  $J = 2.7$ , 8.5 Hz, 1H), 3.64 (d,  $J = 14.8$  Hz, 1H), 4.04 (t,  $J = 11.6$  Hz, 1H), 4.50 (d,  $J = 14.8$  Hz, 1H), 4.75 (dd,  $J = 3.7$ , 12.3 Hz, 1H), 7.77–7.82 (m, 2H), 7.99–8.05 (m, 2H);  $\delta_{\text{C}}$  NMR (100 MHz,  $\text{CDCl}_3$ ) 22.8, 26.8, 28.0, 48.8, 52.3, 53.9, 59.5, 126.0, 129.1, 130.0, 136.0, 136.0, 140.3, 197.7; HRMS (ESI+)  $m/z$  calcd for  $\text{C}_{16}\text{H}_{19}\text{N}_4\text{O}$  ( $[\text{M} + \text{H}]^+$ ) 283.1559, found 283.1538.

**(R)-3-(p-Tolyl)-7,8,8a,9-tetrahydro-4H,6H-pyrrolo[1,2-a][1,2,3]triazolo[1,5-d]pyrazine ((R)-4f).** Prepared from **(R)-3f** (147 mg, 0.394 mmol), with a reaction time of 64 h for hydrogen borrowing, affording **(R)-4f** as a white solid (50 mg, 50%); mp = 166 °C; IR (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$  2978, 2795, 1510, 1444, 1317, 1160, 1005, 826;  $[\alpha]_{\text{D}}^{20} -57.3$  (0.78,  $\text{CH}_2\text{Cl}_2$ );  $\delta_{\text{H}}$  NMR (400 MHz,  $\text{CDCl}_3$ ) 1.61–1.73 (m, 1H), 1.92–2.10 (m, 2H), 2.10–2.20 (m, 1H), 2.38 (s, 3H), overlapping with 2.44 (app q,  $J = 8.9$  Hz, 1H), 2.68–2.79 (m, 1H), 3.31 (dt,  $J = 2.5$ , 8.6 Hz, 1H), 3.59 (d,  $J = 14.8$  Hz, 1H), 4.02 (t,  $J = 11.5$  Hz, 1H), 4.45 (d,  $J = 14.8$  Hz, 1H), 4.72 (dd,  $J = 3.7$ , 12.2 Hz, 1H), 7.21–7.26 (m, 2H), 7.55–7.61 (m, 2H);  $\delta_{\text{C}}$  NMR (100 MHz,  $\text{CDCl}_3$ ) 21.4, 22.7, 27.9, 48.7, 52.1, 53.9, 59.6, 126.2, 128.5, 128.6, 129.6, 137.5, 141.4; HRMS (ESI+)  $m/z$  calcd for  $\text{C}_{15}\text{H}_{19}\text{N}_4$  ( $[\text{M} + \text{H}]^+$ ) 255.1609, found 255.1600.

**(R)-3-(4-Chlorophenyl)-7,8,8a,9-tetrahydro-4H,6H-pyrrolo[1,2-a][1,2,3]triazolo[1,5-d]pyrazine ((R)-4g).** Prepared from **(R)-3g** (114 mg, 0.289 mmol), with a reaction time of 48 h for hydrogen borrowing, affording **(R)-4g** (24 mg, 30%) as a red solid; an analytical sample was prepared by purifying the product a second time using standard flash chromatography with the same gradient; mp = 184–187 °C; IR (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$  3070, 2961, 2930, 2815, 1497, 1317, 1164, 1090, 1005, 840;  $[\alpha]_{\text{D}}^{20} -58.4$  (0.31,  $\text{CH}_2\text{Cl}_2$ );  $\delta_{\text{H}}$  NMR (400 MHz,  $\text{CDCl}_3$ ) 1.61–1.73 (m, 1H), 1.92–2.10 (m, 2H), 2.11–2.21 (m, 1H), 2.44 (app q,  $J = 8.9$ , 1H), 2.68–2.79 (m, 1H), 3.32 (dt,  $J = 2.8$ , 8.3 Hz, 1H), 3.58 (d,  $J = 14.8$  Hz, 1H), 4.02 (t,  $J = 11.5$  Hz, 1H), 4.43 (d,  $J = 14.8$  Hz, 1H), 4.74 (dd,  $J = 3.5$ , 12.2 Hz, 1H), 7.35–7.43 (m, 2H), 7.59–7.65 (m, 2H);  $\delta_{\text{C}}$  NMR (100 MHz,  $\text{CDCl}_3$ );  $\delta$  22.8, 28.0, 48.7, 52.2, 53.9, 59.5, 127.5, 129.0, 129.1, 130.0, 133.6, 140.4; HRMS (ESI+)  $m/z$  calcd for  $\text{C}_{14}\text{H}_{16}\text{ClN}_4$  ( $[\text{M} + \text{H}]^+$ ) 275.1063, found 275.1052.

**Methyl (R)-3-methyl-4-(7,8,8a,9-tetrahydro-4H,6H-pyrrolo[1,2-a][1,2,3]triazolo[1,5-d]pyrazin-3-yl)benzoate ((R)-4j).** Prepared from **(R)-3j** (68 mg, 0.159 mmol), using a 48 h reaction time, affording **(R)-4j** as a pale brown oil (17 mg, 35%); IR (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$  2953, 2801, 1719, 1612, 1437, 1299, 1260, 1200, 1119, 1005, 774;  $[\alpha]_{\text{D}}^{20} -16.9$  (0.78,  $\text{CH}_2\text{Cl}_2$ );  $\delta_{\text{H}}$  NMR (400 MHz,  $\text{CDCl}_3$ ) 1.63–1.76 (m, 1H), 1.92–2.10 (m, 2H), 2.12–2.23 (m, 1H), 2.38 (app q,  $J = 8.9$  Hz, 1H) overlapping with 2.45 (s, 3H), 2.69–2.85 (m, 1H), 3.20–3.31 (m, 1H), 3.44 (d,  $J = 14.8$  Hz, 1H), 3.92 (s, 3H), 4.06 (t,  $J = 11.6$  Hz, 1H), 4.19 (d,  $J = 14.8$  Hz, 1H), 4.77 (dd,  $J = 3.8$ , 12.3 Hz, 1H), 7.27 (d,  $J = 8.0$  Hz, 1H), 7.88 (d,  $J = 8.0$  Hz, 1H), 7.97 (s, 1H);  $\delta_{\text{C}}$  NMR (200 MHz,  $\text{CDCl}_3$ ) 20.7, 22.8, 28.0, 48.1, 52.1, 52.3, 53.9, 60.0, 127.0, 129.6, 129.8, 130.3, 132.1, 134.8, 137.9, 141.2, 167.1; HRMS (ESI+)  $m/z$  calcd for  $\text{C}_{17}\text{H}_{21}\text{N}_4\text{O}_2$  ( $[\text{M} + \text{H}]^+$ ) 313.1664, found 313.1650.

**(R)-3-Ethyl-7,8,8a,9-tetrahydro-4H,6H-pyrrolo[1,2-a][1,2,3]triazolo[1,5-d]pyrazine ((R)-4l).** Prepared from **(R)-3l** (99 mg, 0.317 mmol), with a reaction time of 48 h for hydrogen borrowing. The product still contained impurities after a first chromatography, and a consecutive flash chromatography (DCM/MeOH 1 : 0 → 9 : 1 over 40 column volumes) was used to separate the remaining impurities, but also with some loss of product, affording **(R)-4l** as a white solid (24 mg, 39%); mp = 118–123 °C; IR (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$  2969, 2933, 2876, 2802, 1581,

1464, 1317, 1227, 1170, 1015, 807;  $[\alpha]_D^{20} -75.2$  (0.22,  $\text{CH}_2\text{Cl}_2$ );  $\delta_{\text{H}}$  NMR (400 MHz,  $\text{CDCl}_3$ ) 1.24 (t,  $J = 7.6$  Hz, 3H), 1.59–1.70 (m, 1H), 1.89–2.19 (m, 3H), 2.39 (app q,  $J = 9.1$  Hz, 1H), 2.57–2.74 (m, 3H), 3.23–3.39 (m, 2H), 3.94 (t,  $J = 11.3$  Hz, 1H), 4.22 (d,  $J = 14.5$  Hz, 1H), 4.64 (dd,  $J = 12.3, 3.9$  Hz, 1H);  $\delta_{\text{C}}$  NMR (100 MHz,  $\text{CDCl}_3$ ) 13.6, 18.5, 22.7, 27.9, 47.2, 51.6, 53.9, 60.0, 128.1, 143.2; HRMS (ESI $^+$ )  $m/z$  calcd for  $\text{C}_{10}\text{H}_{17}\text{N}_4$  ([M + H] $^+$ ) 193.1453, found 193.1446.

## Author contributions

A. S. S.: conceptualization, investigation, methodology, validation, writing – original draft. F. F.: investigation, methodology, validation, writing – review & editing. A. E. and A. R.: investigation, validation. M. G.: investigation, formal analysis, writing – review & editing. J. R. J.: methodology. P.-O. N.: methodology, supervision. N. K.: conceptualization, methodology, supervision, funding acquisition, resources, writing – original draft.

## Conflicts of interest

There are no conflicts to declare.

## Data availability

The  $^1\text{H}$  and  $^{13}\text{C}$  NMR data supporting this article has been included as part of the SI, together with experimental procedures for the precursor alkynols and crystal structure data for Boe-deprotected **3k** and **3o**. See DOI: <https://doi.org/10.1039/d5ob01137j>.

CCDC 2389333 and 2423532 contains the supplementary crystallographic data for this paper.<sup>48a,b</sup>

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