The organocatalytic two-step synthesis of diversely functionalized tricyclic tetrazoles†‡

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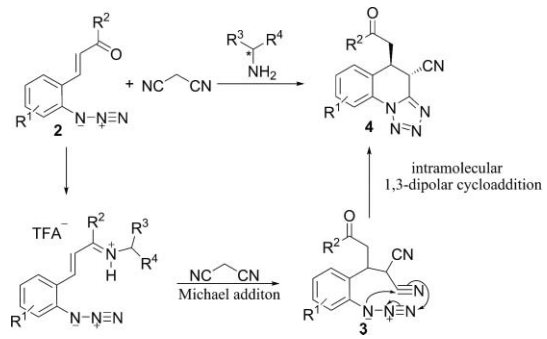
The diversely functionalized tricyclic tetrazoles were synthesised from readily available substrates *via* intramolecular 1,3-dipolar cycloaddition as the key step in good yields (53–78% yield for two steps) with high enantioselectivities (81–99% ee).

Tetrazoles are an increasingly popular functionality with a wide range of applications that are receiving considerable attention. They have been used as a metabolically stable surrogate for a carboxylic acid group.[1] Tetrazoles have also shown valuable properties as precursors of a variety of nitrogen-containing heterocycles[2] and have found use in various material sciences, including photography, information recording systems, and explosives.[3] Thus, the development of new and efficient synthetic routes for the preparation of tetrazoles is of importance in both synthetic organic chemistry and medicinal chemistry. Recently, different approaches towards the synthesis of tetrazoles catalyzed by metal catalyst have been reported.[4–6] To the best of our knowledge, there is no report on the catalytic asymmetric method for the synthesis of chiral tetrazoles derivatives. As such, the development of new and more general catalytic asymmetric methods for their preparation are of significant interest. Herein, we reported for the first time the organocatalytic approach to the asymmetric synthesis of novel and highly functionalized tricyclic tetrazoles *via* Michael addition and 1,3-dipolar cycloaddition.

One goal of our laboratory is to design the novel substrates and develop new chemical and enzymatic strategies and methods for the construction of structurally complex polycyclic natural and non-natural products and biologically active compounds. We have successfully applied the novel chemical and enzymatic strategies and methods for the synthesis optically active polycyclic natural or non-natural products and biologically active compounds, such as a chiral anticoagulant drug, (*S*)-warfarin and 2-amino-2-chromene derivatives, from simple substrates.[7–8] Recently, Deng's group and Lattanzi's group discovered the novel technology of chiral amine catalyzed Michael addition of malononitrile with enones to provide a general route to several diverse Michael adducts in good yields with high enantioselectivity.[9–10] Taking into account recent results,[7–10] we envisaged that the primary aminocatalyst can catalyze a Michael addition of functionalized α,β-unsaturated ketones with malononitrile, followed by intramolecular 1,3-dipolar cycloaddition to give chiral, novel and highly functionalized tricyclic tetrazoles (Scheme 1).



Scheme 1 A proposed mechanism for domino reaction catalyzed by primary aminocatalyst.

We started our original studies on the aminocatalyst- catalyzed reaction between **2a** and malononitrile by screening a series of organic solvents and additives (Table 1). When the reaction was carried out in the presence of **1a** (Fig. 1) (20 mol %) and (*R*)-1,1′-binaphthyo-2,2′-diyl hydrogenphosphate (40%) in THF at ambient temperature, however, the expected intramolecular 1,3-dipolar cycloaddition reaction did not occur at this stage, only Michael adduct **3a** was obtained in 63% yield with excellent enantioselectivity (94% ee, entry 1). A slightly higher ee was received in DCM (entry 2). The ee was dramatically decreased when the reaction was carried out in toluene (entry 3). No main product was obtained when the reaction was carried out in CH_3CN (entries 4, 5). In addition, a variety of acidic additives were further screened (entries 6–8). Gratifyingly, we achieved an excellent enantioselectivity (96% ee) with 78% yield by utilizing the TFA salt of 9-amino-9-deoxyepiquinine **1a** under the same conditions (entry 6). Use of 9-amino-9-deoxyepicinchonine **1b** as the iminium catalyst resulted in a decrease enantioselectivity (Table 1, entry 10).

In order to get the desired product **4a**, we next investigated the intramolecular 1,3-dipolar cycloaddition of **3a**. Although several solvents, such as toluene, CH_2Cl_2, and THF were tested, no reaction occurred at ambient temperature or reflux. Gratifyingly, the desired product **4a** was formed in an excellent yield without loss of the enantiomeric purity when the product **3a** was refluxed in CH_3CN for 12 h, but the diastereoselectivity was poor (Table 2,

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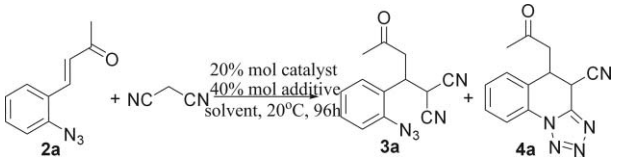
‡ Crystal data for **4g** $C_{18}H_{12}BrN_5O$ (394.24), Triclinic, space group *P*1, a = 6.760(3) Å, b = 7.753(4) Å, c = 15.097(7) Å, U = 766.8(6) Å^3, Z = 2, specimen 0.268 × 0.104 × 0.054 mm^3, T = 296(2) K, SIEMENS P4 diffractometer, absorption coefficient 2.698 mm^{-1}, reflections collected 9543, independent reflections 3590 [R(int) = 0.1178], refinement by Full-matrix least-squares on F^2, data/restraints/parameters 3590/0/227, goodness-of-fit on F^2 = 1.018, final R indices [$I > 2\sigma(I)$] R_1 = 0.0714, wR_2 = 0.1543, R indices (all data) R_1 = 0.2236, wR_2 = 0.1976, largest diff. peak and hole 0.982 and −1.097 e Å^{-3}. Crystallographic data for the structure 4 g have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-773011.

Table 1 Enantioselective Michael Addition of **2a** and Malononitrile with **3a** Catalyzed by **1**[a]



Entry	Catalyst	Solvent/additive	Yield[b] **3a**	ee[c] **3a**
1	**1a**	THF/(*R*)-**1c**[d]	63%	94%
2	**1a**	DCM/(*R*)-**1c**[d]	71%	95%
3	**1a**	Toluene/(*R*)-**1c**[d]	35%	87%
4	**1a**	CH_3CN/(*R*)-**1c**[d]	—	—
5	**1a**	DCM–CH_3CN(1 : 1)/(*R*)-**1d**[d]	—	—
6	**1a**	DCM/TFA	78%	96%
7	**1a**	DCM/HCl	—	—
8[e]	**1a**	DCM/TFA	41%	95%
9	**1b**	DCM/TFA	71%	75%
10	**1c**	DCM/—	45%	0

[a] Unless otherwise noted, reactions performed with 0.1 mmol of **2a**, 0.2 mmol malononitrile, 20 mol% catalyst **1a** and 40 mol% additive, in 1 mL solvent at 20 °C for 96 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] (*R*)-**1d** = (*R*)-1,1′-Binaphthyo-2,2′-diyl Hydrogenphosphate. [e] At 0 °C.

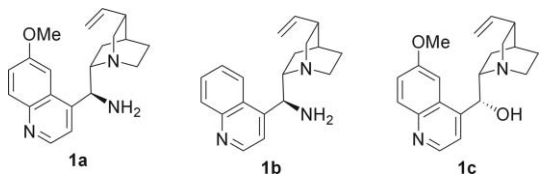


Fig. 1 The structure of catalysts **1**.

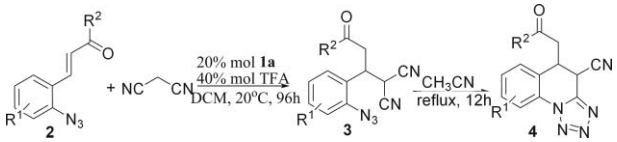
entry 1, dr = 56 : 44). The structure of the class of compounds **4** was also confirmed by crystallographic study of racemic **4g**, as illustrated by the ORTEP diagram depicted in Fig. 2. In the hope of enhancing the diastereoselectivity, the reaction was carried out in CH_3CN at 25 °C catalyzed by zinc salts or TABF, unfortunately, the reaction became complicated.

We successfully obtained the desired product **4** when the product **3** was refluxed in CH_3CN for 12 h. We then examined a range of functionalized α,β-unsaturated ketones and malononitrile to explore the generality of this new methodology. The reaction scope proved to be broad with respect to functionalized α,β-unsaturated ketones (Table 2). As illustrated in Table 2, for the reactions of malononitrile, excellent ees were achieved with functionalized benzalacetone 2 bearing various β-aryl substituents (entries 1–3). High enantioselectivities (**3**: 94%–97% ee; **4**: 88%–99% ee) were obtained in the reactions of malononitrile and electron-withdrawing substituent on aryl ring of functionalized benzalacetone substrates **2b–2c** (entries 2, 3). The diastereoselectivities also improved, slightly (dr = 62 : 38, entry 2). Our organocatalytic protocol also confirms its efficiency in activating aromatic ketones such as chalcone **2d–2m** (Table 2, entries 4–13). It turned out that the substituents on the phenyl group of chalcone had little influence on the reactions. Good yields and high enantioselectivities were also obtained with our organocatalytic protocol (Table 2, entries 4–13).

From a synthetic point of view, one-pot procedures beginning with simple, readily available substrates provide ideal strategies for the regioselective formation of highly functionalized tricyclic tetrazoles. We found that the Michael addition and 1,3-dipolar cycloaddition products can be processed in one pot and tricyclic tetrazoles can be obtained with satisfactory yields with excellent enantioselectivities in some cases (Scheme 2).

In summary, the novel and highly functionalized tricyclic tetrazoles were constructed *via* intramolecular 1,3-dipolar cycloaddition as the key step. The reaction scopes were quite broad and excellent enantioselectivity (81–99% ee) were achieved employing readily available 9-amino-9-deoxy-epiquinine **1a** as the iminium organocatalysts. Further work is in progress to utilize chiral tricyclic tetrazoles as intermediates for the bioactive molecules synthesis.

Table 2 Asymmetric Michael addition and intramolecular 1,3-dipolar cycloaddition of functionalized α,β-unsaturated ketones **2** to malononitrile[a]



Entry	R^1	R^2	(**2**)	Yield(%)[b]/ee(%)[c]	**3**	Yield (%)[b]	**4**	dr[c]	ee (%)[c]
1	H	CH_3	(**2a**)	85/96	**3a**	92	**4a**	56/44	96/96
2	5-Cl	CH_3	(**2b**)	72/94	**3b**	83	**4b**	62/38	94/99
3	5-Br	CH_3	(**2c**)	82/97	**3c**	81	**4c**	53/47	88/98
4	H	Ph	(**2d**)	73/93	**3d**	94	**4d**	60/40	—/90
5	H	*p*-$CH_3C_6H_4$	(**2e**)	76/93	**3e**	93	**4e**	63/37	99/99
6	H	*p*-ClC_6H_4	(**2f**)	81/91	**3f**	87	**4f**	61/39	92/93
7	H	*p*-BrC_6H_4	(**2g**)	80/90	**3g**	88	**4g**	57/43	90/92
8[e]	5-Cl	*p*-$CH_3C_6H_4$	(**2h**)	69/90	**3h**	86	**4h**	62/38	86/83
9	5-Cl	*p*-BrC_6H_4	(**2i**)	61/83	**3i**	85	**4i**	60/40	82/81
10	5-Cl	*p*-ClC_6H_4	(**2j**)	62/84	**3j**	89	**4j**	55/45	81/88
11	5-Br	*p*-$CH_3C_6H_4$	(**2k**)	60/95	**3k**	91	**4k**	58/42	92/95
12	5-Br	*p*-BrC_6H_4	(**2l**)	68/91	**3l**	79	**4l**	60/40	—/90
13	5-Br	*p*-ClC_6H_4	(**2m**)	66/93	**3m**	88	**4m**	61/39	—/92

[a] Unless otherwise noted, reactions were performed with 0.1 mmol of **2**, 0.2 mmol malononitrile, 20 mol% **1a** and 20 mol% TFA in 1 mL DCM at 20 °C for 96 h, then **3** was isolated and refluxed in CH_3CN for 12 h. [b] Isolated yield. [c] Determined by ^1H NMR or HPLC analysis.

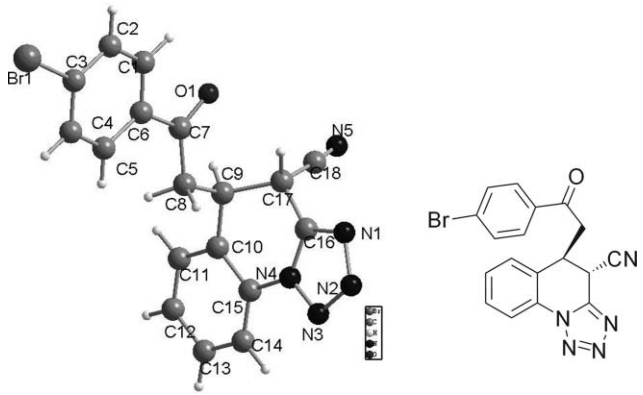
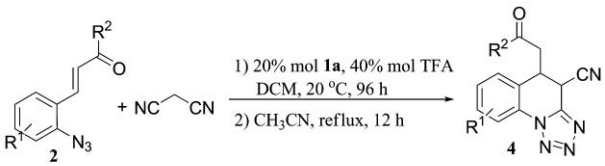


Fig. 2 Molecular structure of **4g**.



	4	yield%	dr	ee%
R_1 = H, R_2 = *p*-$CH_3C_6H_4$;	**4e**	58	57/43	95/95
R_2 = 5-Cl, R_2 = *p*-$CH_3C_6H_4$;	**4h**	71	63/37	96/91
R_3 = 5-Br, R_2 = *p*-$CH_3C_6H_4$;	**4k**	52	59/41	94/93

Scheme 2 Synthesis of functionalized tricyclic tetrazoles, using one-pot tandem reaction.

Acknowledgements

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