Asymmetric Synthesis

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Asymmetric Synthesis of 5-(1-Hydroxyalkyl)tetrazoles by Catalytic Enantioselective Passerini-Type Reactions**

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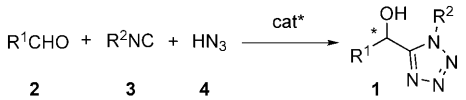
Tetrazoles have long been recognized as carboxylic acid isosteres[1] and are important heterocycles in medicinal chemistry, owing to their increased stability towards metabolic degradation pathways.[2] The acidity of the tetrazole NH group corresponds roughly to that of the carboxylic acid.[3] Consequently, chiral 5-substituted tetrazoles have been investigated as efficient organocatalysts.[4] In addition, the 1,5-disubstituted tetrazole ring has been considered as a surrogate for the *cis*-amide bond, making it a valuable tool in the design of conformationally constrained peptidomimetics.[5] Several methods have been developed for the synthesis of 1,5-disubstituted tetrazoles, including the 5-(1-hydroxyalkyl)tetrazoles (**1**).[6,7] However, to our knowledge, no enantioselective synthesis of **1** has yet been reported. We report herein a [(salen)Al^{III}Me]-catalyzed (salen = *N*,*N*′-bis(salicylidene)ethylenediamine dianion) enantioselective Passerini-type reaction of aldehydes **2**, isocyanides **3** and hydrazoic acid **4**, affording **1** with good-to-excellent enantioselectivity (Scheme 1).[8–11]



Scheme 1. Catalytic enantioselective synthesis of 5-(1-hydroxyalkyl)tetrazole **1** by three-component Passerini reaction (P-3CR).

The three-component Passerini reaction (P-3CR)[12] has seldom been used for the preparation of tetrazoles. Ugi and Meyr reported in 1961 that hydrazoic acid can be used in the Passerini reaction instead of carboxylic acids, for the production of **1** in moderate-to-good yields.[13] Nixey and Hulme have subsequently developed a $TMSN_3$-modified (TMS = trimethylsilyl) P-3CR for the synthesis of *cis*-constrained norstatine-mimetic libraries.[14,15] Recently, we reported that [(salen)Al^{III}Cl][11b–c,16] is an effective catalyst for the enantioselective addition of isocyanides to aldehydes and predicted that using a chiral Lewis acid with a single coordination site was important for the development of enantioselective P-3CR. We subsequently set out to investigate the enantioselective synthesis of 1-(4-methoxyphenyl)-5-(1-hydroxyisobutyl)tetrazole **1a** (Scheme 1) using isobutyraldehyde (**2a**), 4-methoxyphenylisocyanide (**3a**) and $TMSN_3$, as a test reaction. Carrying out the reaction at 0 °C in the presence of catalyst **5a** (Figure 1), **1a** was formed with 52% *ee* (Table 1, entry 1).

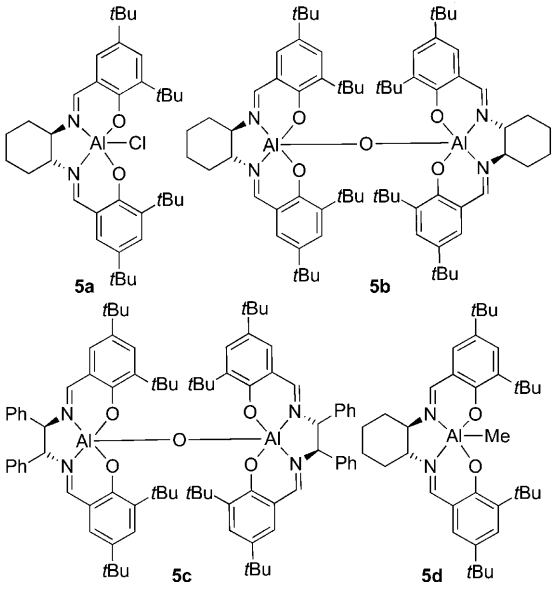


Figure 1. Catalysts screened for enantioselective synthesis of 1-(4-methoxyphenyl)-5-(1-hydroxyisobutyl)tetrazole **1a** by P-3CR.

However, a significant amount of 2-hydroxy-*N*-(4-methoxyphenyl)-3-methylbutanamide **6** was also produced under these conditions. Decreasing the reaction temperature (Table 1, entry 2), adding additives (Na_2SO_4, 4 Å molecular sieves) or using HN_3 did not avoid the formation of **6**.[17] Control experiments indicated that, in the absence of Al catalyst under otherwise identical conditions, formation of **6** did not occur and the yield of **1a** was significantly reduced. These results indicated that the formation of both **1a** and **6** was catalyzed by [(salen)Al^{III}Cl] complex **5a**. Indeed, asymmetric induction also occurred in the formation of compound **6** (55% *ee*). Reasoning that reaction of $TMSN_3$ or HN_3 with

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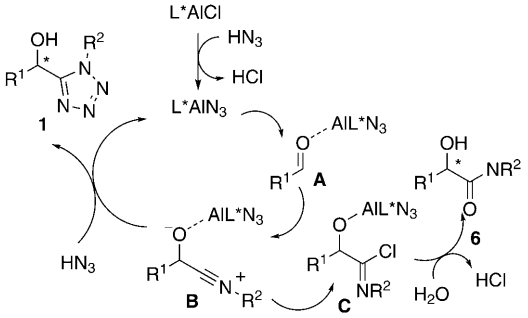
Table 1: Reaction of isobutyraldehyde (**2a**), 4-methoxyphenylisocyanide (**3a**) and $TMSN_3/HN_3$: Screening of reaction conditions.

Entry[a]	Cat* (mol%)	RN_3	T [°C]	Yield [%][b]	*ee* [%][c]
1	**5a** (10)	$TMSN_3$	0	65[d]	52
2	**5a** (10)	$TMSN_3$	−20	80[d]	57
3	**5a** (10)	HN_3	−20	80[d]	57
4	**5b** (10)	HN_3	−20	58	66
5	**5b** (10)	HN_3	−40	50	80
6	**5c** (10)	HN_3	−20	48	60
7	**5d** (10)	HN_3	−20	53	83
8	**5d** (10)	HN_3[e]	−20	97	83
9	**5d** (10)	HN_3[e]	−40	99	85
10	**5d** (10)	HN_3[e]	−60	55	80
11	**5d** (20)	HN_3[e]	−40	95	85
12	**5d** (5)	HN_3[e]	−40	69	86

[a] General conditions: molar ratio **2a**/**3a**/HN_3 = 1.2/1/1, toluene, final concentration 0.2 M. [b] Yields refer to chromatographically pure product. [c] Determined by chiral column (AD stationary phase, eluent: 9:1 hexane/*i*PrOH). [d] Total combined yield of **1a** and **6**; the ratio of **1a**/**6** is approximately 3:1 (determined by NMR spectroscopy). [e] Using 2.5 equivalents HN_3.

5a might produce TMSCl (or HCl), with concurrent generation of an Al–azide complex, a potential mechanism for the formation of **1a** and **6** was proposed (Scheme 2). Herein, nucleophilic addition of isocyanide **3** to the aldehyde–Al complex (**A**) affords the nitrilium ion (**B**), which is trapped by



Scheme 2. Proposed mechanism for the formation of tetrazole **1** and amide byproduct **6**.

hydrazoic acid to provide tetrazole **1**. Concurrently, reaction of **B** with TMSCl or HCl affords the chloroimidate **C**, which, in the presence of adventitious water, is converted into the α-hydroxyamide **6**.

Although the enantioselective preparation of **6** is of interest,[8] our present study focused on the asymmetric synthesis of tetrazole **1**. Since, according to our mechanistic hypothesis, the presence of chloride seemed to be responsible for the formation of **6**, the discrete μ-oxo dimer **5b** was synthesized (Figure 1).[18] Using this catalyst in conjunction with HN_3, formation of **6** was suppressed and compound **1a** was isolated in 58% yield and 66% *ee* (Table 1, entry 4). When the reaction was carried out at −40 °C, the *ee* value of **1a** increased to 80% (Table 1, entry 5). The similar bimetallic catalyst (**5c**), prepared from (1*R*,2*R*)-1,2-diphenyl-1,2-diethanediamine, afforded **1a** with reduced yield and *ee* (Table 1, entry 6). With [(salen)Al^{III}Me] (**5d**), **1a** was isolated in 53% yield a much-improved *ee* value of 83%. By increasing the amount of HN_3 to 2.5 equivalents, **1a** was produced in almost quantitative yield and 83% *ee* (Table 1, entry 8) under otherwise identical conditions. Further decreasing the reaction temperature reduced the yield of **1a** without gain of enantiomeric excess of the product (Table 1, entry 10). Moreover, increasing the loading of catalyst **5d** to 0.2 equivalents did not have significant positive impact on the yield and the *ee* value of the product (Table 1, entry 11). Interestingly, carrying out the reaction with only 0.05 equivalents of catalyst **5d** resulted in similar enantioselectivity, albeit with a reduced yield of **1a** (Table 1, entry 12). Replacing HN_3 with $TMSN_3$ under otherwise identical conditions led to the reduced yield of tetrazole **1a**.

The absolute configuration of **1a** was determined according to Trost's empirical model.[19] Esterification of **1a** with (*S*)- and (*R*)-*O*-methylmandelic acid afforded esters **7** and **8**, respectively, in excellent yields (Figure 2). The calculated chemical shift difference for the proton H_a (see Figure 2, $\Delta\delta_{H_a(\mathbf{7}-\mathbf{8})} = 0.18$) allowed us to tentatively attribute the (*S*) configuration to tetrazole **1a**.

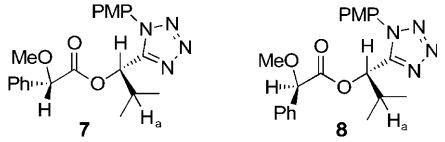
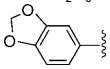
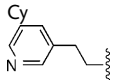


Figure 2. (*S*)- and (*R*)-*O*-methylmandelic acid-derived esters, used for determination of absolute configuration of **1a**. PMP = *p*-methoxyphenyl.

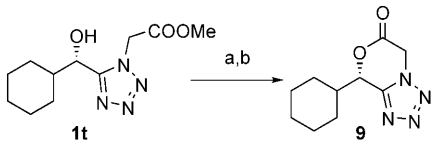
Having optimized conditions and stoichiometries for the reaction (**2a**/**3a**/HN_3/**5d** = 1.2:1:2.5:0.1), we next examined the generality of this catalytic enantioselective process by varying the structure of the aldehyde **2** and isocyanide **3**. A range of linear and α-branched aliphatic aldehydes were effective substrates for this reaction. The presence of a potentially coordinating pyridine ring was also tolerated although the reaction yield was significantly reduced (Table 2, entry 21). Aromatic isocyanides with electron-donating (OMe, Me, NMe_2) or electronic-withdrawing groups (Br) were both effective reaction partners. However, the sterically encumbered 2,6-dimethylphenylisocyanide **3j** afforded the corresponding adduct **1r** with diminished yield and enantioselectivity (Table 2, entry 18). Aliphatic isocyanides (**3b**, **3c**, **3l**) were equally acceptable substrates (Table 2, entries 2, 5, 10, 11, and 20). The use of α-isocyanoacetate is of particular interest since it afforded directly the dipeptide mimic **1t** (Table 2, entry 20). In addition, the adduct **1t** can easily be converted, in 82% yield, into bicyclic compound **9**, following a standard hydrolysis/lactonization sequence (Scheme 3). When 5-isocyanobenzo[*d*][1,3]dioxole **3i** was used, the corresponding adduct **1q** was isolated in 88% yield with 97% *ee* (Table 2, entry 17).

Salen–Al complexes are known to catalyze the nucleophilic addition of azide to α,β-unsaturated imides and to α,β-unsaturated ketones. We investigated the possibility of

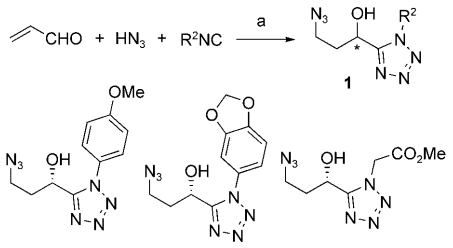
Table 2: Catalytic enantioselective three-component synthesis of a range of chiral 5-(1-hydroxyalkyl)tetrazoles (**1**).

Entry[a]	R^1[b]	Aldehyde	R^2	Isocyanide	Yield [%][c]	*ee* [%][d]
1	*i*Pr	**2a**	4-$MeOC_6H_4$	**3a**	99 (**1a**)	85
2	*i*Pr	**2a**	Cy	**3b**	90 (**1b**)	95
3	Et	**2b**	4-$MeOC_6H_4$	**3a**	88 (**1c**)	87
4	Cy	**2c**	4-$MeOC_6H_4$	**3a**	90 (**1d**)	91
5	*i*Pr	**2a**	Bn	**3c**	76 (**1e**)	92
6	Bn	**2d**	4-$MeOC_6H_4$	**3a**	97 (**1f**)	64
7	$PhCH_2CH_2$	**2e**	4-$MeOC_6H_4$	**3a**	92 (**1g**)	87
8	*n*-hexyl	**2f**	4-$MeOC_6H_4$	**3a**	88 (**1h**)	85
9	*i*Bu	**2g**	4-$MeOC_6H_4$	**3a**	96 (**1i**)	84
10	Cy	**2c**	Bn	**3c**	91 (**1j**)	83
11	Cy	**2c**	Cy	**3b**	93 (**1k**)	84
12	Cy	**2c**	Ph	**3d**	68 (**1l**)	92
13	Cy	**2c**	4-MeC_6H_4	**3e**	80 (**1m**)	95
14	Cy	**2c**	3-MeC_6H_4	**3f**	70 (**1n**)	85
15	Cy	**2c**	4-BrC_6H_4	**3g**	60 (**1o**)	87
16	Cy	**2c**	4-$NMe_2C_6H_4$	**3h**	95 (**1p**)	94
17	Cy	**2c**		**3i**	88 (**1q**)	97
18	Cy	**2c**	2,6-$(Me)_2C_6H_3$	**3j**	53 (**1r**)	51
19	Cy	**2c**	4-MeO-2-$NO_2C_6H_3$	**3k**	48 (**1s**)	62
20	Cy	**2c**	$MeOOCCH_2$	**3l**	93 (**1t**)	75
21		**2h**	4-$MeOC_6H_4$	**3a**	45 (**1u**)	80

[a] General conditions: molar ratio **2a**/**3a**/HN_3/**5d** = 1.2/1/2.5/0.1, toluene, final concentration 0.2 M, −40 °C. [b] Cy = cyclohexyl. [c] Yields refer to chromatographically pure product. [d] Determined by chiral column (AD stationary phase, eluent: hexane/*i*PrOH = 9:1).



Scheme 3. Lactonization of dipeptide mimic **1t**: a) potassium hydroxide, methanol, room temperature, 6 h; b) dicyclohexylcarbodiimide/4-dimethylaminopyridine, N,N-dimethylformamide/dichloromethane, room temperature, 24 h, 82%.



1v (80%, 80% *ee*) **1w** (71%, 81% *ee*) **1x** (72%, 63% *ee*)

Scheme 4. Tandem Michael addition/enantioselective P-3CR to functionalized tetrazoles: a) **5d** (0.1 equiv), toluene, −40 °C.

performing a tandem Michael addition/enantioselective P-3CR using an α,β-unsaturated aldehyde as the carbonyl substrate, if the Michael addition took place faster than the P-3CR. Indeed, reaction of acrolein with hydrazoic acid and 4-methoxyphenylisocyanide occurred in an ordered manner, to afford the 1-(4′-methoxyphenyl)-5-(1′-hydroxy-3-azidopropyl)tetrazole (**1v**) in 80% yield with 80% *ee*. Compounds **1w** and **1x** were similarly prepared using 5-isocyanobenzo[*d*]-[1,3]dioxole (**3i**) and isocyanoacetate (**3l**) as isocyanide inputs (Scheme 4).

The complex **5d** most probably acts as a precatalyst in this transformation, as it is known that **5d** reacts rapidly with hydrazoic acid to afford the corresponding azide complex.[20] Two additional control experiments were performed in order to gain some mechanistic insights. Reaction of a stoichiometric amount of [(salen)$Al^{III}N_3$] complex with aldehyde **2a** in the absence of HN_3 afforded only a trace amount of adduct **1a**, indicating that the azide group is directly transferred from hydrazoic acid rather than from the Al-bound azide. Furthermore, premixing [(salen)Al^{III}Me], with 0.1 equivalents of enantioenriched tetrazole **1a** and subsequent addition of aldehyde **2a**, isocyanide **3a**, and HN_3 under otherwise standard conditions afforded the adduct **1a** with a similar *ee* value, indicating that the tetrazole itself does not significantly modify the catalytic properties of the aluminum complex.[21]

In summary, we have developed the first catalytic enantioselective synthesis of 5-(1-hydroxyalkyl)tetrazoles by a [(salen)Al^{III}Me]-catalyzed three-component Passerini reaction (P-3CR) of aldehydes, isocyanides, and hydrazoic acid. The reaction is applicable to a wide range of aliphatic aldehydes and to both aromatic and aliphatic isocyanides, affording the corresponding tetrazoles in good-to-excellent yields and enantiomeric excesses. By using acrolein as a substrate, a tandem Michael addition/enantioselective P-3CR provided the highly functionalized tetrazoles **1v**–**1x**. In light of the wide-ranging applicability of isocyanide-based multicomponent reactions,[22] the possibility to develop chiral enantioselective versions tremendously broadens their synthetic utility.[23]

Experimental Section

1a: In a flame-dried round-bottom flask equipped with a stirrer bar, a mixture of [(salen)Al^{III}Me] (0.025 mmol, 15.0 mg) and dry toluene (0.3 mL) was stirred at room temperature until the catalyst had completely dissolved. Isobutyraldehyde (0.3 mmol, 27.7 μL) was then introduced and the resulting mixture was stirred at room temperature for a further 30 min. The mixture was cooled to −40 °C, and a solution of 1-isocyano-4-methoxybenzene (0.25 mmol, 33.0 mg) in toluene (0.4 mL) was added, followed by hydrazoic acid[17] (0.5 mL, 1.3 M in

toluene). After being stirred at −40 °C for 48 h, the reaction mixture was purified by flash chromatography on silica gel (eluent: 2:1 petroleum ether/ethyl acetate) to afford the tetrazole **1a** (61.4 mg, 0.248 mmol, 99 %, 85 % *ee*).

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