Asymmetric Catalysis

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Catalytic Enantioselective Synthesis of N,C$^{\alpha}$,C$^{\alpha}$-Trisubstituted α-Amino Acid Derivatives Using 1*H*-Imidazol-4(5*H*)-ones as Key Templates**

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Abstract: *1H-Imidazol-4(5H)-ones are introduced as novel nucleophilic α-amino acid equivalents in asymmetric synthesis. These compounds not only allow highly efficient construction of tetrasubstituted stereogenic centers, but unlike hitherto known templates, provide direct access to N-substituted (alkyl, allyl, aryl) α-amino acid derivatives.*

Because of the continuous interest in α,α-disubstituted (quaternary) α-amino acids,[1] many methods for their stereoselective preparation have been reported,[1,2] but catalytic approaches still remain underdeveloped.[2d–f,3] A major catalytic, enantioselective entry to quaternary NH α-amino acids consists of the α-functionalization of a nucleophilic template, for example, either an α-iminoester or azlactone, and subsequent hydrolysis (Figure 1a).[4] However, the majority of these methods are unable to afford the N-substituted analogues directly,[5] and an additional N-alkylation process is required.[6] This limitation is unfortunate since N-methyl (or superior N-alkyl) α-amino-acid-derived compounds are potential therapeutic candidates owing to their comparatively higher lipophilicity and membrane permeability.[7] We hypothesized that 1*H*-imidazol-4(5*H*)-ones might serve as appropriate templates for addressing this deficiency (Figure 1b): 1) the NR^2 group would be easily pre-installed, 2) base-catalyzed enolization appears suitable (aromatic enolate formation), and 3) unlike azlactones and related heterocycles, the new template would not present the Cα/Cγ selectivity complication.[8] However, this realization would require effective control of the stereochemistry of the C–C bond-forming step and, to the best of our knowledge, asymmetric reactions of 1*H*-imidazol-4(5*H*)-ones are unprecedented.

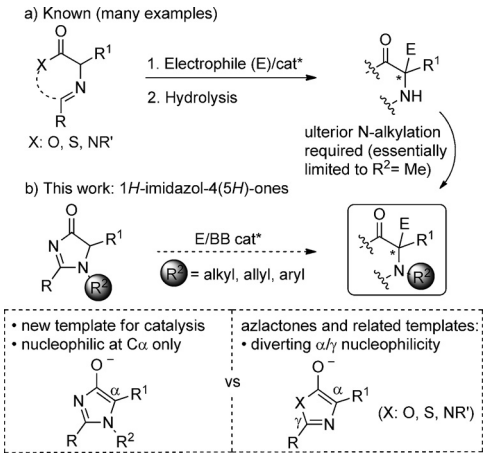
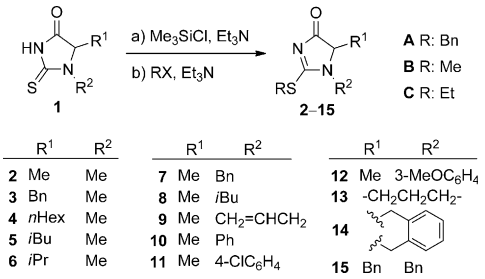


Figure 1. Enantioselective approaches to N,C$^{\alpha}$,C$^{\alpha}$-trisubstituted α-amino acid units. BB = Brønsted base.

For validation of the idea we selected the readily available 2-thio-1*H*-imidazol-4(5*H*)-ones **2**–**15** (Scheme 1)[9] whose base-catalyzed conjugate addition reaction[10] to nitroolefins[11] was evaluated first (Table 1). After examining several chiral Brønsted bases,[9] it was gratifying to find that by using the Rawal catalyst **C1**[12] the reactions of the N-methyl imidazolones **2A**–**6A** with nitroolefins (**16**) proceeded effectively in terms of yield and stereocontrol, regardless of the electron-neutral, electron-rich, and electron-poor character of either the β-aryl or heteroaryl substituent in **16** (entries 1–3 and 7–10). The reactions with β-alkyl-substituted nitroolefins (**16h**–**j**) using **C1** proceeded with poorer diastereocontrol, but it was improved by changing to the catalyst **C2**[13] (compare entries 4 and 6, 12 and 13, and 18 and 19), and the enantioselectivity for the major diastereomer was excellent in all the cases. The imidazolones **7A**–**12A**, bearing N-substituents other than methyl, for example, benzyl, allyl, isobutyl, phenyl, *p*-chlorophenyl, and *m*-methoxyphenyl,



Scheme 1. 1*H*-Imidazol-4(5*H*)-ones employed in this study.

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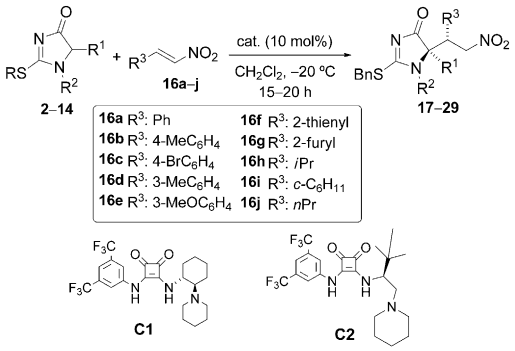
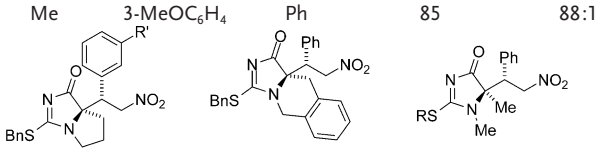
Table 1: Catalytic reaction between imidazolones **2–14** and nitroolefins **16**.[a]



Entry	Prod.	R^1	R^2	R^3	Yield [%][b]	d.r. [%][c]	*ee* [%][d]
1	**17a**	Me	Me	Ph	97	93:7	99
2	**17b**	Me	Me	4-MeC_6H_4	91	90:10	96
3	**17c**	Me	Me	4-BrC_6H_4	82	94:6	98
4	**17h**	Me	Me	*i*Pr	66[e]	60:40	96
5					77[e,f]	50:50	−90
6					58[e,g]	80:20	−90
7	**18d**	Bn	Me	3-MeC_6H_4	82	92:8	95
8	**19a**	*n*Hex	Me	Ph	81	98:2	98
9	**20f**	*i*Bu	Me	2-thienyl	84	92:8	86
10	**21g**	*i*Pr	Me	2-furyl	75	93:7	92
11	**22a**	Me	Bn	Ph	85	98:2	98
12	**22i**	Me	Bn	*c*-C_6H_{11}	40[e]	75:25	94
13					40[e,f]	80:20	−90
14	**23a**	Me	*i*Bu	Ph	78	98:2	93
15	**24a**	Me	$CH_2CH{=}CH_2$	Ph	77	92:8	94
16					65[h]	90:10	95
17	**25a**	Me	Ph	Ph	65	93:7	92
18	**25j**	Me	Ph	*n*Pr	51[e]	50:50	94
19					51[e,g]	80:20	−90
20	**26b**	Me	4-ClC_6H_4	4-MeC_6H_4	83	98:2	98
21	**27a**	Me	3-$MeOC_6H_4$	Ph	85	88:12	95



[a] Reactions conducted on a 0.3 mmol scale in 0.5 mL CH_2Cl_2 (mol ratio of imidazolone/nitroolefin/**C1** catalyst 1:2:0.1) unless otherwise stated. [b] Yield of the isolated major diastereomer. [c] Determined by ^{1}H NMR (300 MHz) analysis of the crude reaction mixture. [d] Determined by HPLC analysis using a chiral stationary phase. [e] Reaction run at 50 °C in 1,2-dichloroethane. [f] Using *ent*-**C1**. [g] Using **C2**. [h] Reaction run at 4 mmol scale using 5 mol% catalyst (reaction time 30 h).

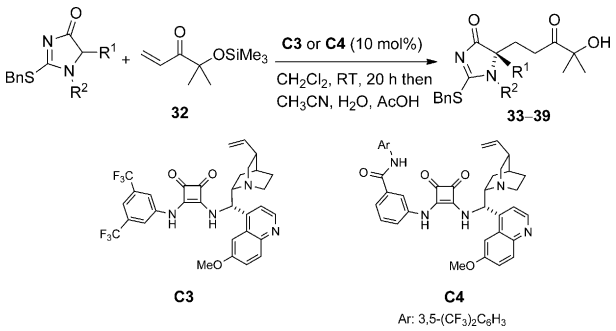
were all tolerated (entries 11–17, 20, and 21). Also bicyclic imidazolones, such as **13A** and **14A**, provided the corresponding adducts (**28a**, **28e**, **29a**) with equal effectiveness. These latter products represent quaternary proline and related derivatives which cannot be accessed directly through established catalytic methodologies.[14] Of practical interest, the catalyst loading may be reduced from 10 to 5 mol% without affecting the results (entry 15 versus 16). In contrast, the nature of the S-substituent group appears to have limited impact on stereoselectivity as results obtained from the imidazolones **2B** and **2C**, to produce **30a** and **31a**, respectively, are comparable to those obtained with **2A**.

In addition to these observations, it was also found that Michael acceptors, which are less reactive than nitroolefins, may participate in these reactions with equal effectiveness (Table 2). For example, the reaction of **2A** with the acrylate surrogate **32**,[15] promoted by catalyst **C1**, provided, after desilylation of the intermediate adduct, the product **33** in good yield (74%), albeit with moderate enantioselectivity (84% *ee*).[16] Improved selectivity (91% *ee*) was observed using **C2**, and even better selectivity was obtained with **C3**[17] (94% *ee*) and the new catalyst **C4** (96% *ee*, Table 2, entry 1). Under these latter conditions, the enone **32** also reacted efficiently with other imidazolones (entries 2–7).[18]

The chemical manipulation of adducts was briefly investigated to illustrate the synthetic potential of this approach (Scheme 2). Thus, nucleophilic displacement of the thioether group served to establish concise routes to various classes of heterocycles of interest in medicinal chemistry,[19] that is, imidazolidinones (**40**, **41**), 2-aryl imidazolones (**43**), 2-amino imidazolones (**44**), and hydantoins (**45–47**). Eventually, acid hydrolysis of **41** afforded the amino amide **42** with all the above reactions proceeding in good yields. Similarly, the hydantoins **48–50** could be obtained upon smooth hydrolysis of the corresponding adducts **33–35**. Further oxidative elaboration of the ketol moiety in these products[9,15] led to the corresponding carboxylic acids **51**/**52**, the aldehyde **53**, and ketone **54**. The present catalytic approach thus facilitates a novel entry for the rapid construction of functionalized 5,5-disubstituted hydantoins, a well-recognized scaffold for drug discovery.[20] Finally, the X-ray structure analyses of hydantoins **46** and **51** served to establish the configuration of the adducts.[21]

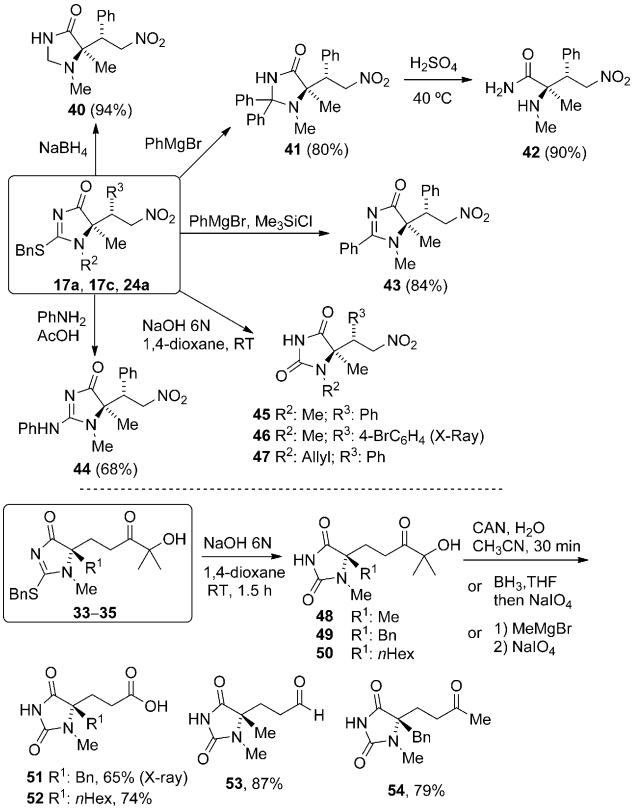
On the other hand, given that the new template allows direct access to N-substituted quaternary α-amino acid derivatives, additional ways for the elaboration of adducts can be envisaged in which the NR^2 moiety plays a strategic role. For instance (Scheme 3), from the common adduct **47**, the densely functionalized bi- (**55**) and tricyclic (**56**) compounds were prepared in two and four steps, respectively.[9]

Table 2: 1,4-Addition of 1*H*-imidazolo-4(5*H*)ones to the α′-silyloxy enone **32**.[a]

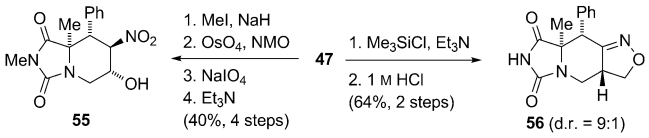


Entry	Imidazolone	R^1	R^2	Prod.	Yield [%][b]	*ee* [%][c]
1	**2A**	Me	Me	**33**	82	96[d]
2	**3A**	Bn	Me	**34**	75	96
3	**4A**	*n*Hex	Me	**35**	81	94
4	**5A**	*i*Bu	Me	**36**	71	96
5	**7A**	Me	Bn	**37**	78	96
6	**9A**	Me	CH_2=$CHCH_2$	**38**	77	94
7	**15A**	Bn	Bn	**39**	83	92

[a] Reactions conducted on a 0.3 mmol scale (mol ratio of imidazolone/enone/catalyst 1:2:0.1) using **C4** unless otherwise stated. Desilylation conducted in CH_3CN (1 mL), H_2O (0.5 mL), AcOH (0.3 mL). [b] Yield of isolated product after chromatography. [c] Determined by HPLC analysis using a chiral stationary phase. [d] Using catalyst **C1**, −84% *ee*; using catalyst **C2**, 91% *ee*; using catalyst **C3**, 94% *ee*.



Scheme 2. Elaboration of the 2-thio-1*H*-imidazol-4(5*H*)-one moiety. CAN = ceric ammonium nitrate.



Scheme 3. New entries to functionalized polycyclic hydantoins. NMO = *N*-methyl-morpholine *N*-oxide.

The fidelity with which chirality is transferred in the above conjugate addition reactions may be explained by assuming the catalyst tightly bound to both the reactants in the TS, as shown in models A and B (Figure 2). It should be noted that

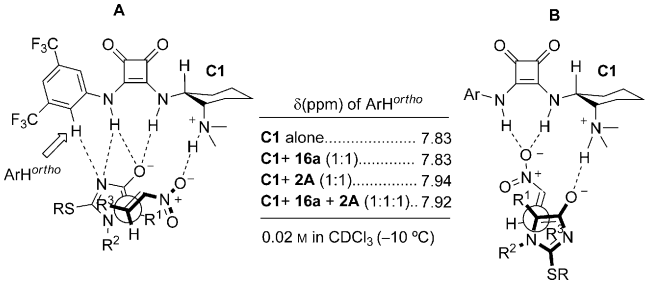


Figure 2. Plausible TS models and selected ^{1}H NMR data.

models similar to A and B, which define two major patterns for catalyst–substrate hydrogen bonding, have been previously proposed as heuristic or calculation-driven TS for related reactions involving bifunctional squaramide tertiary amine catalysis, and the prevalence of one over the other seems to be highly substrate-dependent.[15,22] As strong evidence in favor of model A, we found that the chemical shift of the *ortho*-ArH in **C1** is considerably affected ($\Delta\delta = +0.11$ ppm) by addition of 1 equivalent of **2A**, whereas it remains unaffected by addition of nitrostyrene (Figure 2 and see the Supporting Information). This observation also suggests that the polarized aromatic *ortho* protons in this type of catalysts contribute to TS stabilization.[23]

In summary, we have demonstrated for the first time that 2-thio-1*H*-imidazol-4(5*H*)-ones may serve as effective equivalents of N-substituted (alkyl, aryl, allyl) α-amino acids. Specifically, their base-catalyzed addition reaction to nitroolefins and enones to afford the corresponding quaternary α-amino acid derivatives can be carried out with very high diastereo- and enantiocontrol. Further elaboration of the thus obtained adducts opens straightforward access to an array of different N-substituted quaternary α-amino acid derivatives, including 5,5-disubstituted hydantoins and other complex N-heterocycles, in enantiomerically pure form. The scope of these imidazolones as new pronucleophiles against other acceptors, including C=X systems (1,2-addition), may be easily anticipated.

Keywords: amino acids · asymmetric catalysis · Michael additions · organocatalysis · synthetic methods

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