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Synthesis of α-Amino Acid Derivatives and Peptides via Enantioselective Addition of Masked Acyl Cyanides to Imines

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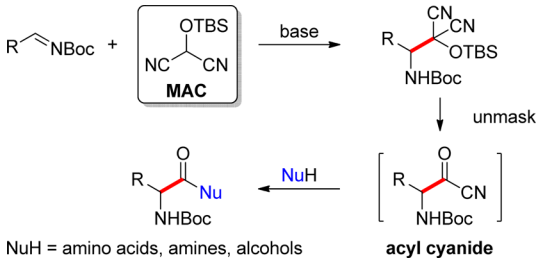
Supporting Information

ABSTRACT: A general, asymmetric synthesis of amino acid derivatives is reported. Masked acyl cyanide (MAC) reagents are shown to be effective umpolung synthons for enantioselective additions to *N*-Boc-aldimines. The reactions are catalyzed by a modified cinchona alkaloid, which can function as a bifunctional, hydrogen bonding catalyst, and afford adducts in excellent yields (90−98%) and high enantioselectivities (up to 97.5:2.5 er). Unmasking the addition products gives acyl cyanide intermediates that are intercepted by a variety of nucleophiles to afford α-amino acid derivatives. Notably, the methodology provides an alternative method for peptide bond formation.

Constituting the structural basis of peptides and proteins, α-amino acids continue to be at the forefront of chemical synthesis research.[1] The prevalence of natural and unnatural forms of amino acid fragments in medicinal agents, natural products, catalysts, and materials has motivated immense effort directed toward the synthesis of these foundational building blocks.[2] Among the many routes for the de novo asymmetric synthesis of amino acids, the Strecker reaction—the hydrocyanation of imines followed by hydrolysis—has garnered considerable attention.[3] Much of the effort in recent years has focused on the enantioselective version of this reaction, and this has resulted in the development of an assortment of effective catalysts, metal-based and metal-free.[4] Central to the Strecker reaction are the practical challenges of handling hydrogen cyanide (or its derivative) and the inherent robustness of the resulting nitrile. Indeed, hydrolysis of the nitrile group requires prolonged heating in harsh acidic conditions (HCl or H_2SO_4), which can erode enantioselectivity and diminish the yield of the amino acid product.[5] Additionally, this method necessarily gives the free amino acids, rather than their *N*- or *C*-protected derivatives, required for further elaboration. We recently reported the use of protected hydroxyl malononitriles, known as masked acyl cyanide (MAC) reagents,[6] for the enantioselective conjugate addition to α, β-unsaturated aryl ketones, demonstrating the capacity of these umpolung synthons to function as carbon monoxide equivalents, with both nucleophilic and electrophilic reactivity.[7] Given the fundamental importance of amino acids and our continued interest in hydrogen bonding promoted reactions, we explored the enantioselective addition of MAC reagents to *N*-Boc-aldimines (Scheme 1) and have found the reactions to be effectively catalyzed by a modified cinchona alkaloid, affording the adducts

Scheme 1. Synthesis of α-Amino Acid Derivatives via Addition of Masked Acyl Cyanides (MAC)



in excellent yields (90−98%) and high enantioselectivities (up to 97.5:2.5 er).[8] Unmasking the addition products gives acyl cyanide intermediates that can be intercepted by a variety of nucleophiles to afford α-amino acid derivatives. Significantly, the methodology provides a direct path to peptide bond formation.

Our investigations began with the reaction of *N*-Boc-benzaldimine **1a** with TBS-MAC reagent **2**, the two blocking groups chosen for the mild yet orthogonal conditions required for their selective removal. Several different hydrogen-bonding, bifunctional catalysts were examined for the Mannich-type addition reaction, including thioureas, squaramides, and cinchona alkaloids.[9] Of these, derivatives of cinchona alkaloids provided the most promising results with regard to yield and enantioselectivity (Table 1). Quinidine **Ia** in toluene was effective in catalyzing the reaction, but induced unexceptional enantioselection (Entry 1). The corresponding TBS-protected quinidine **Ib** offered even lower selectivity. Remarkably, demethylated catalyst **IIa**, endowed with an additional hydrogen bond donor functionality, was far superior, affording the MAC adduct in an 86.5:13.5 er (entry 3). The enantioselectivity improved noticeably when the reaction was carried out in chloroform, and even further at lower temperature (−40 °C; entries 4 and 5). Further increase in selectivity was found with the related alkaloid **IIc**, possessing the phenanthryl (PHN) group rather than the TBS or TIPS groups (entries 5−7). The corresponding dihydroquinidine catalyst (**III**) improved the enantioselectivity to 97:3 er in chloroform at −40 °C (entry 8). Catalyst **III** enjoys the advantage that it is readily available, prepared in only two steps from dihydroquinidine.[10] Importantly, comparable enantioselection (96:4 er) was obtained in toluene at ambient

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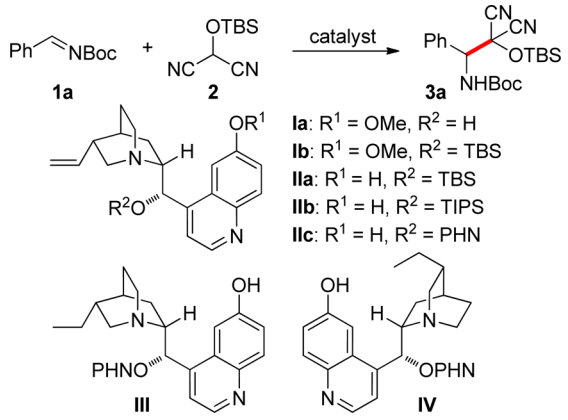
Table 1. Optimization of MAC Addition to *N*-Boc-aldimines



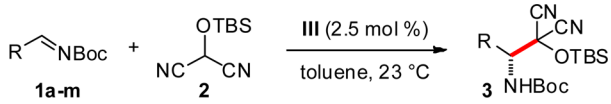
entry[a]	catalyst	solvent (M)	temp (°C)	time (h)	conv. (%)[b]	e.r.[c]
1	**Ia**	toluene (0.3)	23	1.5	>95	41.5:58.5
2	**Ib**	toluene (0.3)	23	1.5	80	47:53
3	**IIa**	toluene (0.3)	23	1.5	>95	86.5:13.5
4	**IIa**	$CHCl_3$ (0.3)	23	1.5	>95	90:10
5	**IIa**	$CHCl_3$ (0.3)	−40	17	>95	94:6
6	**IIb**	$CHCl_3$(0.1)	−40	17	70	94.5:5.5
7	**IIc**	$CHCl_3$ (0.3)	−40	23	69	95.5:4.5
8	**III**	$CHCl_3$ (0.2)	−40	20	92	97:3
9	**III**	$CHCl_3$ (0.05)	23	1	50	95:5
10	**III**	toluene (0.05)	23	1	55	96:4
11	**III**	toluene (0.1)	−20	21	81	95:5
12	**III**	toluene (0.3)	23	1	>95	95:5
13[d]	**III**	toluene (0.07)	23	1	53	96:4
14[d]	**IV**	toluene (0.07)	23	1	40	6.5:93.5

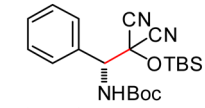
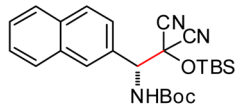
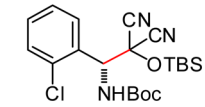
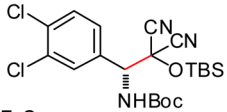
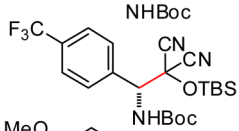
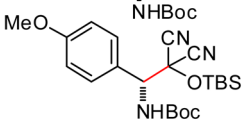
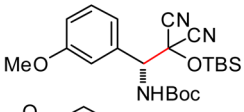
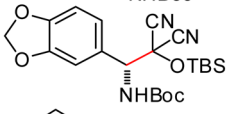
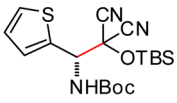
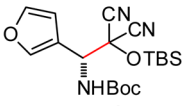
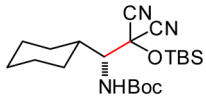
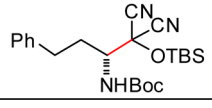
[a]Conditions: **1a** (0.05 mmol), **2** (0.05 mmol), catalyst (5 mol %). [b]Percent conversion determined by ^{1}H NMR. [c]E.r. determined by chiral stationary phase HPLC. [d]Catalyst (2.5 mol %).

temperature (entries 9 and 10). Higher concentration increased the reaction rate, but marginally diminished selectivity (entries 11−13). Reduction of catalyst loading to 2.5 mol % gave no deterioration in selectivity (entry 13). As expected, the pseudoenantiomeric catalyst **IV** afforded the product enriched in the opposite enantiomer, in slightly lower selectivity (entry 14).

A screening to assess the substrate scope of the reaction followed (2). For ease of reaction setup and broader substrate tolerance, the reactions were performed in toluene at room temperature, rather than at −40 °C. Generally, excellent isolated yields and high enantioselectivities were observed. It is noteworthy that the reaction with imine **1a** can be scaled up successfully to yield 1 g of product while using only 1 mol % of catalyst **III** (entry 2). Hindered 2-chlorophenyl substituted imine **1c** required prolonged reaction time and provided the product in slightly reduced enantiomeric ratio (entry 4). Electron deficient imines **1d−e** reacted smoothly to give adducts in 94:6 ratio of enantiomers (entries 5−6) Electron-rich substrate **1f** was also suitable for the addition (entry 7) and the related 3-methoxy benzaldimine **1g** and piperonal-derived imine **1h** offered similarly high enantioselectivities (entries 8−9). Furthermore, a variety of heteroaromatic imines **1i−k** furnished the corresponding products with very good selectivities. (entries 10−12) Notably, 2-thiophene carboxaldehyde derived imine **3j** gave an excellent enantioselection of 97.5:2.5 (entry 11). Aliphatic imines **1l−m** required longer

Table 2. Substrate Scope for MAC Addition to *N*-Boc-aldimines



entry	product		time (h)	yield (%)	e.r.[b]
1		**3a**	16	96	96:4
2[c]			36	98	96:4
3		**3b**	16	93	95.5:4.5
4[d]		**3c**	72	95	92.5:7.5
5		**3d**	14	97	94:6
6		**3e**	14	98	94:6
7		**3f**	24	96	95:5
8		**3g**	14	97	97:3
9		**3h**	16	96	96:4
10		**3i**	14	98	93:7
11		**3j**	12	99	97.5:2.5
12		**3k**	36	96	93.5:6.5
13[e]		**3l**	72	90	92:8[f]
14[g]		**3m**	30	91	92:8

[a]Conditions: **1** (0.33 mmol), **2** (0.3 mmol), **III** (2.5 mol %) in toluene (4.5 mL), 23 °C. [b]E.r. determined by chiral stationary phase HPLC. [c]Reaction performed with **2** (2.5 mmol), **III** (1 mol %). [d]**III** (5 mol %). [e]**III** (5 mol %) and toluene (3 mL). [f]E.r. determined by derivatization to amide **8**. [g]**III** (5 mol %), $CHCl_3$ (1 mL), −40 °C.

reaction times, but furnished the products in high yields, albeit with slightly lower selectivities. (entries 13−14). The reaction

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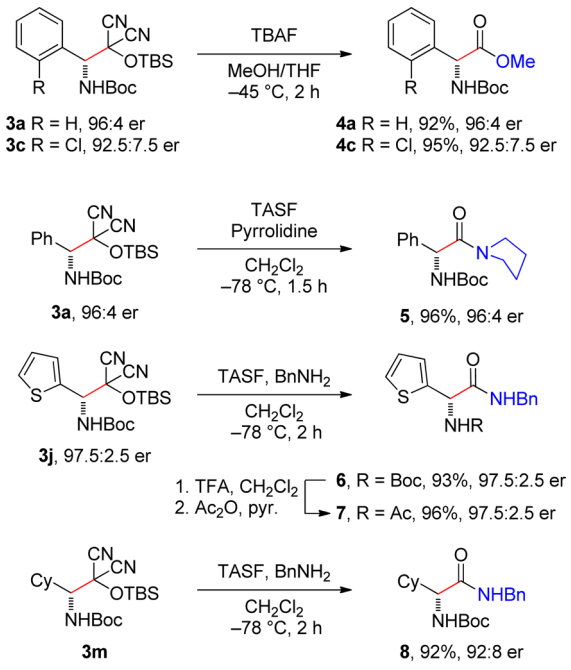
conditions were modified ($CHCl_3$, −40 °C) for imine **1m**, as the standard conditions gave significant amount of the enamide tautomer.

We next directed our efforts to the task of unmasking the MAC adducts and transforming the intermediate acyl cyanides into synthetically useful amino acid derivatives and peptides. Conditions commonly used for TBS group removal proved unsatisfactory, as the resultant amino acid derivatives displayed considerable erosion in enantiomer ratio (Scheme 2).[11] On the other hand, treatment of adduct **3a** with TBAF in THF and methanol at −45 °C led to clean transformation to known ester **4a**, isolated in a 96:4 ratio, enriched in the *R* enantiomer. Adduct **3c** was unmasked analogously to methyl ester **4c**, whose enantiomer is a known precursor to the drug clopidogel (Plavix).[12] The direct coupling of amines with MAC adducts proceeded smoothly if TASF, a mild source of anhydrous fluoride, was used for the desilylation. Thus, treatment of MAC adduct **3a** with TASF at −78 °C followed by addition of pyrrolidine intercepted the acyl cyanide intermediate to furnish amide **5** in near quantitative yield, with no loss in er. Similarly, the unmasking of thiophene adduct **3j** with benzyl amine furnished amide **6**, which was treated with TFA, followed by Ac_2O in pyridine to give **7**, a potent anticonvulsant,[13] in 97.5:2.5 er. Aliphatic adduct **3m** upon treatment with TASF and benzyl amine, revealed benzyl amide **8** in high yield and 92:8 er.[14] The successful trapping of the acyl cyanide intermediate by an amine suggested that this methodology would enable the melding of amino acid synthesis with peptide bond formation.

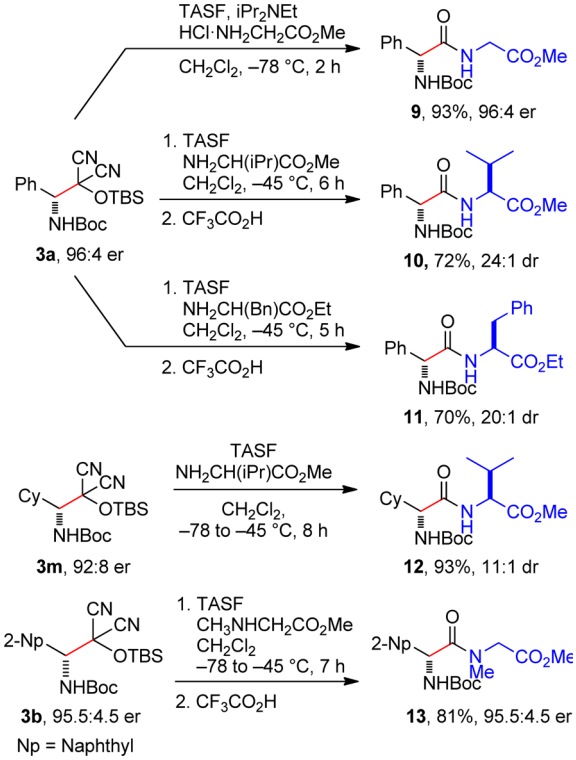
Scheme 2. Unmasking of MAC adducts



The joining of amino acids to form a peptide bond represents one of nature's most fundamental transformations. Laboratory methods for peptide bond formation typically involve activation of the carboxylic acid part followed by its reaction with the free amine of a second amino acid derivative. Complicating such coupling reactions is the susceptibility of activated carboxylic acids to epimerization, which has necessitated the development of a multitude of coupling reagents.[15] The synthesis of *N*-alkyl or aryl glycine containing peptides, which have garnered interest due to their beneficial pharmacological properties, present further difficulties and requires specialized coupling agents.[16,17] Whereas most amino acid syntheses necessitate several additional steps to proceed to a dipeptide,[18] the MAC addition chemistry offers a direct route to peptide bond formation, provided conditions can be developed to minimize epimerization.[19]

While the coupling of amino acids with acid chlorides, anhydrides, and other activated esters has been studied extensively, their coupling with acyl cyanides remains relatively unexplored.[20] We were pleased to observe that deprotection of adduct **3a** followed by addition of glycine methyl ester gave dipeptide **9** in excellent yield, with complete retention of the initial enantioselectivity (Scheme 3). The coupling with the more hindered amino acids was sluggish at −78 °C, failing to go to completion. For the coupling with valine methyl ester, carrying out the reaction at −45 °C and quenching with TFA after 6 h, gave dipeptide **10** in 72% yield and 24:1 diastereomer ratio, indicating essentially no erosion of the initial enantioselectivity.[21] The corresponding coupling with phenylalanine esters gave a comparable result. Notably, peptide formation of cyclohexyl adduct **3m** with valine methyl ester proceeded to completion providing dipeptide **12** in 93% yield, without significant epimerization. Of special interest is the direct coupling with *N*-methylated amino acids, which pose a challenge to conventional condensative peptide synthesis methods.[22] The unmasking of **3b** and its coupling with sarcosine methyl ester afforded *N*-methylated dipeptide **13** in 81% yield, with no epimerization.

Scheme 3. Unmasking of MAC Adducts to Dipeptides



In summary, we have developed the first catalytic, enantioselective Mannich-type addition of the MAC family of umpolung synthons. The addition reactions of a variety of

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structurally and electronically diverse imines are effectively catalyzed by a readily prepared cinchona alkaloid derivative (**III**), which functions as a bifunctional, hydrogen bonding catalyst, affording the products in high yields and excellent enantioselectivities. The Mannich adducts proved to be versatile intermediates that upon unmasking and trapping with suitable nucleophiles granted rapid access to α-amino acid derivatives, all in high yields and near complete retention of the original enantiomeric ratios. Significantly, the use of amino acid nucleophiles provided a direct method for peptide bond construction. Investigation of other enantioselective reactions of MAC reagents is anticipated to be of great value in organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and detailed characterization data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(9) An extensive listing of conditions examined during the screening process can be found in the Supporting Information.

(10) Wang, Y.; Li, H. M.; Wang, Y. Q.; Liu, Y.; Foxman, B. M.; Deng, L. *J. Am. Chem. Soc.* **2007**, *129*, 6364. Catalyst **III** can also be prepared in just one step, since the intermediate, dihydroquinidine 9-phenanthryl ether, is commercially available.

(11) Some epimerization was noted using conditions from ref 7a.

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(20) A review on peptide coupling methods (ref 15) discusses the use of acid chlorides, anhydrides, and other activated esters, but makes no mention of acyl cyanides. For examples of acyl cyanide use for peptide bond formation, see: (a) Davidsen, S. K.; Chumoyer, M. Y. *J. Org. Chem.* **1989**, *54*, 5558. (b) Wasserman, H. H.; Petersen, A. K. *J. Org. Chem.* **1997**, *62*, 8972.

(21) Slow epimerization, presumably of the acyl cyanide intermediate, is observed as the coupling progresses to completion.

(22) Humphrey, J. M.; Chamberlin, A. R. *Chem. Rev.* **1997**, *97*, 2243.