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Synthesis of Novel α-Substituted and α,α-Disubstituted Amino Acids by Rearrangement of Ammonium Ylides Generated from Metal Carbenoids

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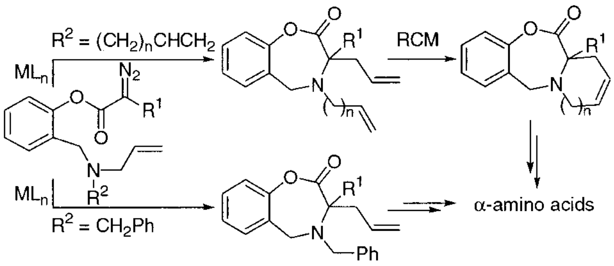
ABSTRACT



A new and general four-step synthesis of protected α-substituted and α,α-disubstituted amino acids has been developed. The key step involves intramolecular ammonium ylide generation from a copper carbenoid with concomitant [2,3] rearrangement. The aromatic template serves as a tether, protecting group, and activating group for peptide coupling. The ylide rearrangement products can be converted into protected cyclic amino acids by ring-closing metathesis.

Rare and non-natural α-substituted and α,α-disubstituted amino acids are of increasing importance for the preparation of conformationally restricted peptide analogues and peptide libraries. The lack of availability of these compounds from natural sources necessitates the development of efficient methods for their synthesis.[1]

The [2,3]-sigmatropic or [1,2]-Stevens rearrangement of ammonium ylides generated by reaction of amines with metal carbenoids produced by transition metal catalyzed decomposition of diazo ketones and esters has been shown to be a powerful strategy for the synthesis of nitrogen heterocycles.[2–4] West and Naidu have used the [1,2]-Stevens rearrangement of carbenoid-derived ammonium ylides to prepare α-amino acid derivatives and morpholinones.[5] However, the resulting amino acid derivatives are not readily amenable to the attachment of additional amino acids.

We now describe a general method for the rapid synthesis of highly functionalized amino acids in a form that allows them to be readily incorporated into polypeptides. The method involves the generation of an ammonium ylide by intramolecular trapping of a metal carbenoid by an allylic amine and subsequent rearrangement to give an azalactone (Scheme 1). In principle, this tandem reaction offers a highly flexible route to amino acids bearing a variety of unusual

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[1] (a) Williams, R. M.; Hendrix, J. A. *Chem. Rev.* **1992**, *92*, 889. (b) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517. (c) Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789.

[2] (a) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley: New York, 1998.

[3] (a) For examples of [2,3]-sigmatropic rearrangement of ammonium ylides derived from metal carbenoids, see: (a) Clark, J. S.; Hodgson, P. B. *Chem. Commun.* **1994**, 2701. (b) Clark, J. S.; Hodgson, P. B. *Tetrahedron Lett.* **1995**, *36*, 2519. (c) Wright, D. L.; Weekly, R. M.; Groff, R.; McMills, M. C. *Tetrahedron Lett.* **1996**, *36*, 2165.

[4] (a) For examples of [1,2]-Stevens rearrangement of ammonium ylides derived from metal carbenoids, see: (a) West, F. G.; Naidu, B. N. *J. Am. Chem. Soc.* **1993**, *115*, 1177. (b) West, F. G.; Naidu, B. N. *J. Am. Chem. Soc.* **1994**, *116*, 8420.

[5] (a) West, F. G.; Glaeske, K. W.; Naidu, B. N. *Synthesis* **1993**, 977. (b) West, F. G.; Naidu, B. N. *J. Org. Chem.* **1994**, *59*, 6051.

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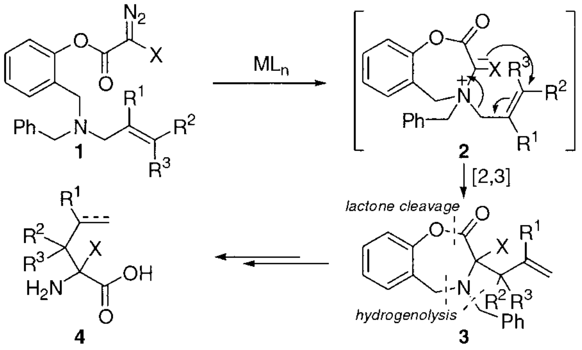
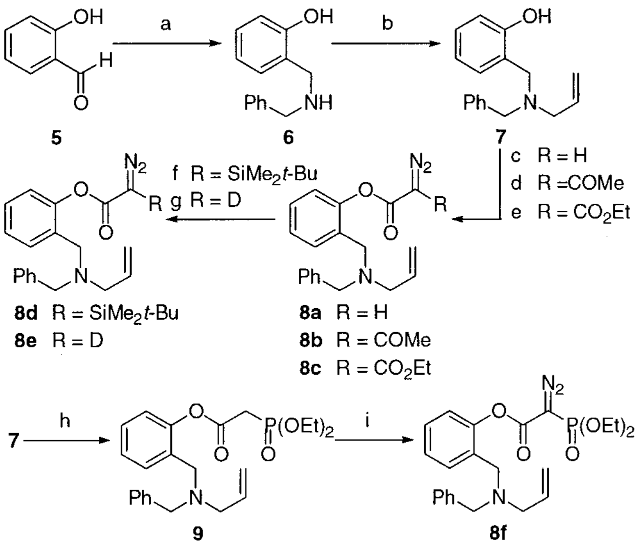
Scheme 1. General Strategy for Amino Acid Synthesis



groups (X) at the α position. Stereoselective substitution at the *β* position is also possible when an appropriately substituted (R^2 and/or $R^3 \neq H$) allylic amine precursor is used. An aromatic template was chosen to tether the diazocarbonyl group to the amine in order to deliver a high yielding intramolecular reaction. It was anticipated that the aromatic group would also function as a protecting group for the carboxyl and amino groups and would activate the carboxyl group to permit direct coupling to other amino acids. Thus, it was anticipated that exposure of the diazoketone **1** to a suitable catalyst (ML_n) would result in sequential carbenoid and ylide (**2**) generation (Scheme 1). Subsequent rearrangement would deliver the azalactone **3**, which would be converted into the amino acid **4** by lactone hydrolysis and cleavage of the benzylic groups.

The synthesis of the diazoketones required for initial studies commenced with reductive amination of salicylaldehyde (**5**) with benzylamine (Scheme 2). Alkylation of the amine **6** with allyl bromide delivered the amine **7** in excellent yield. The diazoacetate **8a** was prepared in reasonable yield by treatment of the phenol **7** with succinimidyl diazoacetate.[6] Diketene addition and in situ diazo transfer following Doyle's procedure gave poor yields of the diazoacetoacetate **8b**.[7] However, when *p*-acetamido-benzenesulfonyl azide (*p*-ABSA) and triethylamine were used instead of methanesulfonyl azide and sodium acetate, the diazoacetoacetate **8b** was obtained in good yield.[8] Acylation of the phenol **7** using ethyl 2-diazomalonyl chloride provided the substrate **8c** in good yield.[9] The diazoacetate **8d** was prepared using Regitz's procedure: reaction of the diazoacetate **8a** with *tert*-butyldimethylsilyl triflate and Hünig's base.[10] The synthesis of the deuterated diazoacetate **8e** (96% D-incorporation) was accomplished by treatment of **8a** with potassium carbonate in D_2O and THF. Finally, coupling of the phenol **7** to diethylphosphonoacetic acid gave **9** and subsequent diazo transfer with *p*-ABSA afforded the α-phosphonyl diazoacetate **8f** (Scheme 2).

Scheme 2[a]



[a] Reagents and conditions: (a) (i) H_2NCH_2Ph, 4 Å sieves, EtOH, (ii) $NaBH_4$, EtOH, 96%; (b) $BrCH_2CH{=}CH_2$, K_2CO_3, MeCN 91%; (c) (i) KH, THF, (ii) succinimidyl diazoacetate, THF, 45% (73% based on recovered **7**); (d) diketene, *p*-ABSA, Et_3N, MeCN, 65%; (e) $ClCOCN_2CO_2Et$, 2,6-lutidine, CH_2Cl_2, 74%; (f) *t*-$BuMe_2SiOTf$, *i*-Pr_2NEt, Et_2O, −78 °C, 75%; (g) K_2CO_3, D_2O, THF, rt, 84% (96% D-incorporation); (h) $HO_2CCH_2PO(OEt)_2$, DCC, DMAP, CH_2Cl_2, 85%; (i) *p*-ABSA, DBU, MeCN, 62%.

The copper- and rhodium-catalyzed generation of ammonium ylides was investigated. In previous studies we had shown that copper(II) acetylacetonate [$Cu(acac)_2$] was the best catalyst for carbenoid generation from unsubstituted diazoketones. However, we and West and co-workers had found that carbenoids generated using copper(II) hexafluoroacetylacetonate [$Cu(hfacac)_2$] react with ethers to produce oxonium ylides, which rearrange to give cyclic ethers in excellent yield,[11] and rhodium(II) acetate has been used to generate ammonium ylides in an intermolecular fashion.[12] To identify the best catalyst for ylide generation, we explored the effectiveness of all three complexes (Table 1).

It transpired that similar yields of the rearrangement products **10** were obtained using either $Cu(acac)_2$ or $Cu(hfacac)_2$, but inferior yields were obtained when $Rh_2(OAc)_4$ was used for carbenoid generation. A variety of groups could be accommodated adjacent to the diazo group, allowing the preparation of protected amino acids bearing ketone (**10b**), ester (**10c**), and phosphonate (**10f**) groups at the α position. Protected α-deuterated allyl glycine was also prepared. Unfortunately, the copper-catalyzed reaction of the trialkylsilyl-substituted compound **10d** afforded the C−H insertion product **11** instead of the expected ylide rearrangement

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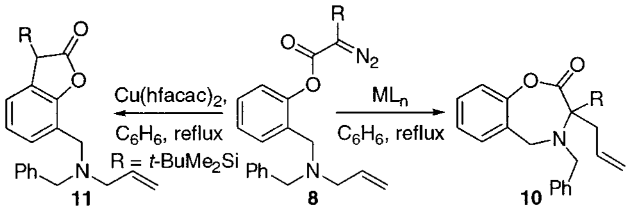
Table 1. Reaction of the Diazo Compounds **8** to Form the Azalactones **10**



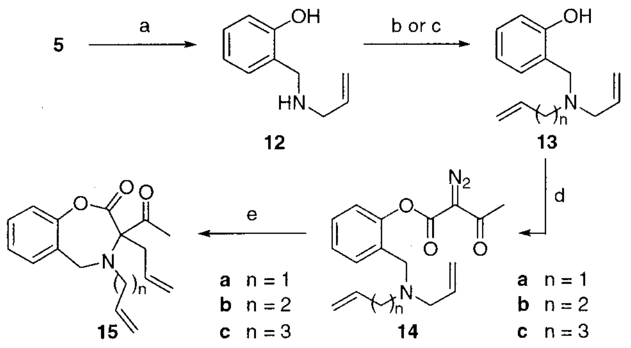
substrate	R	catalyst	product	yield (%)
8a	H	Cu(acac)$_2$	**10a**	59
8a	H	Cu(hfacac)$_2$	**10a**	48
8a	H	Rh$_2$(OAc)$_4$	**10a**	36
8b	COMe	Cu(acac)$_2$	**10b**	54
8b	COMe	Cu(hfacac)$_2$	**10b**	66
8b	COMe	Rh$_2$(OAc)$_4$	**10b**	37
8c	CO$_2$Et	Cu(acac)$_2$	**10c**	59
8c	CO$_2$Et	Cu(hfacac)$_2$	**10c**	81
8c	CO$_2$Et	Rh$_2$(OAc)$_4$	**10c**	42
8d	SiMe$_2$*t*-Bu	Cu(hfacac)$_2$	**11**	82
8e	D	Cu(acac)$_2$	**10e**	61
8f	PO(OEt)$_2$	Cu(acac)$_2$	**10f**	25
8f	PO(OEt)$_2$	Cu(hfacac)$_2$	**10f**	22
8f	PO(OEt)$_2$	Rh$_2$(OAc)$_4$	**10f**	0

product, probably as a result of the bulk of the silyl group. None of the product arising from benzylic C−H insertion was isolated from this reaction.

Cyclic amino acids are of great interest as conformationally constrained analogues of natural amino acids.[1b,c] Having established that tandem intramolecular ammonium ylide generation and rearrangement offered a viable route to protected amino acids, we explored the synthesis of cyclic amino acids by performing tandem ylide generation and rearrangement to give diene products followed by ring-closing metathesis (RCM).[13]

The precursors were prepared by the route shown in Scheme 3. Reductive amination of salicylaldehyde with allylamine gave the amine **12** in good yield. Unsaturated side chains were introduced by alkylation of the amine **12**. Thus, treatment with allyl bromide at room temperature gave the diallylamine **13a** in good yield. Higher temperatures (100 °C in DMF) and the addition of sodium iodide were required to alkylate amine **12** with butenyl and pentenyl bromide. The synthesis of diazoacetoacetates **14a**−**c** was accomplished in one pot by treatment of **13a**−**c** with diketene and in situ diazo transfer using *p*-ABSA.

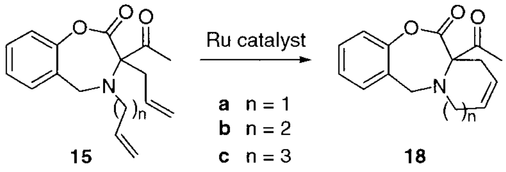
Scheme 3[a]



[a] Reagents and conditions: (a) (i) H$_2$NCH$_2$CH=CH$_2$, 4 Å sieves, EtOH, (ii) NaBH$_4$, EtOH 85%; (b) BrCH$_2$CH=CH$_2$, K$_2$CO$_3$, MeCN, 82% **13a**; (c) Br(CH$_2$)$_n$CH=CH$_2$, NaI, K$_2$CO$_3$, DMF, 100 °C, 68% **13b**, 72% **13c**; (d) diketene, *p*-ABSA, Et$_3$N, MeCN, reflux, 61% **14a**, 59% **14b**, 64% **14c**; (e) Cu(hfacac)$_2$, benzene, reflux, 66% **15a**, 76% **15b**, 72% **15c**.

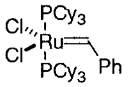
Treatment of **14a**−**c** with Cu(hfacac)$_2$ resulted in efficient ylide formation and rearrangement to deliver the azalactones **15a**−**c** in good yield (66−76%). Subsequent ring-closing metathesis reactions of the rearrangement products **15a**−**c** proved to be high yielding (Table 2). The catalyst **16** facilitated ring closure of the diene **15a** to give the tricyclic product **18a** in excellent yield.[14] However, cyclization of the dienes **15b** and **15c** proved to be less successful using the catalyst **16,** and so the more reactive ruthenium catalyst **17** was employed.[15] This catalyst delivered excellent yields of the cyclic amino acid derivatives **18b** and **18c**. These results are remarkable because dienes containing free amino groups are not usually good substrates for ruthenium-catalyzed RCM reactions. The success of our reactions is probably a

Table 2. Ring-Closing Metathesis Using Ruthenium Catalysts **16** and **17**[a]



substrate	*n*	catalyst	product	yield (%)
15a	1	**16**	**18a**	92
15b	2	**16**	**18b**	74
15b	2	**17**	**18b**	87
15c	3	**16**	**18c**	57
15c	3	**17**	**18c**	83

[a] Catalyst **16**: CH$_2$Cl$_2$, rt, 24 h. Catalyst **17**: PhMe, 80 °C, 45 min.



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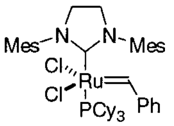

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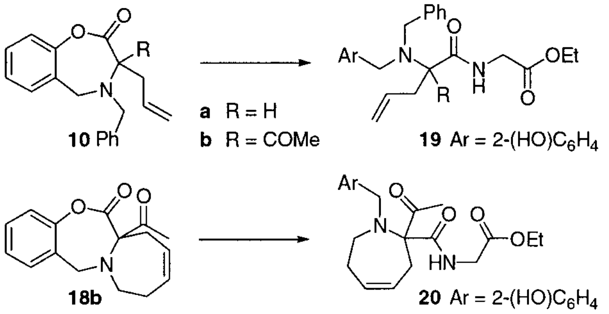
(15) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

Scheme 4[a]



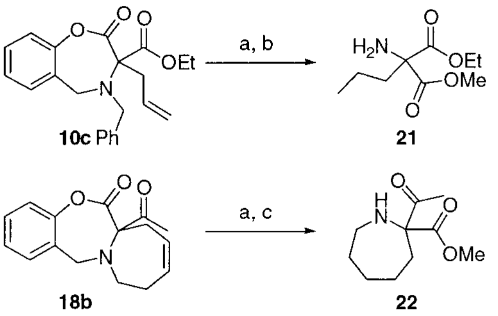
[a] Reagents and conditions: $EtO_2CCH_2NH_2$.HCl, DMAP, Et_3N, DMF, 84% (8 h) **19a**, 91% (120 h) **19b**, 85% (120 h) **20**.

reflection of the steric hindrance in the dienes **15a**−**c**, which prevents coordination of the amine to ruthenium.[16]

The reactive nature of the phenolic ester allows it to function as an activating group for direct dipeptide synthesis. To demonstrate the viability of this procedure, three of the azalactones **10** were treated with glycine ethyl ester (Scheme 4). Gratifyingly, the monosubstituted compound **10a** coupled to give the dipeptide **19** in good yield after 8 h. The azalactones **10b** and **18b** proved to be less reactive, presumably as a result of hindrance due to the adjacent quaternary center. However, good yields of the coupled products **19b** and **20** were obtained using extended reaction times.

Amino group deprotection has also been explored (Scheme 5). Attempts to deprotect the amino group by direct hydrogenolysis of the azalactone failed. However, a two-step sequence involving cleavage of the azalactone with sodium methoxide and subsequent catalytic hydrogenation resulted in debenzylation and delivered amino acid esters **21** and **22**.

Scheme 5[a]



[a] Reagents and conditions: (a) NaOMe, MeOH; (b) $Pd(OH)_2$−C, H_2 (300 psi), EtOH, rt; (c) HCO_2H, Pd−C, rt, 66**% 21** (2 steps), 73% **22** (2 steps).

In summary, we have developed a concise and general metal-catalyzed route for the synthesis of both α-substituted and α,α-disubstituted amino acids. The development of an asymmetric variant of the reaction is currently under investigation, and the results of these studies will be reported in due course.

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Supporting Information Available: Experimental procedures and data for compounds **10a**−**c**, **10e**, **10f**, **11**, **18a**−**c**, **19a**, **19b**, and **20**−**22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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