

Functionalizing Glycine Derivatives by Direct C–C Bond Formation**

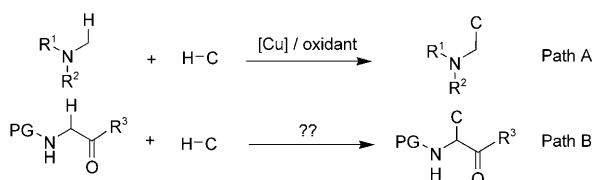
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With the recent advances in proteomics, there has been a great interest in the study of properties and functions of natural and non-natural (synthetic) amino acids.^[1] By using non-natural (synthetic) α -amino acids, the conformation and/or stability of biologically active peptides can be modified.^[2] For example, by incorporating α -aminoisobutyric acid into oligopeptides, the peptide backbone can be rigidified through the formation of β -turns or α -helices.^[3] In addition, the demand for peptide-based structures is increasing rapidly for drug discoveries.^[4] Thus, general methods to synthesize non-natural α -amino acids and/or to modify natural amino acids rapidly are highly desirable. The direct α -functionalization of natural peptides takes advantage of existing structure and provides rapid access to diverse new peptides. The best-known methods of α -functionalization of amino acid derivatives or amides include: functionalization of α -carbanions (performed by deprotonation with a strong base),^[5] radical (α -bromination by *N*-bromosuccinimide^[6a,b] or UV photolysis in the presence of di-*tert*-butyl peroxide^[6c]), Claisen rearrangements,^[7] and a ruthenium-catalyzed α -oxygenation.^[8] However, direct C–C bond formation by C–H bond functionalization of amino acid derivatives is unprecedented. We and other groups have developed C–C bond forming reactions based on oxidative activation of the C–H bond adjacent to a tertiary nitrogen atom.^[9] Although these results provide new or alternative ways to construct different C–C bonds by the activation of C–H bonds (Scheme 1, Path A), they are not applicable to amino acid derivatives. Thus selective oxidative functionalization of α -amino acid derivatives is still rare.^[10] Herein, we wish to report a novel method

for functionalizing peptido-amides through the direct reaction at α -peptido C–H bonds, to give new C–C bonds in a cross-dehydrogenative coupling (CDC) process (Scheme 1, Path B).

To begin our study, with a view to peptide functionalization, we decided to use the amino acid derivative *N*-acetylglycine ethyl ester (**1**) to react with diethyl malonate (**2**; see Table 1). However, we could not obtain any desired C–C bond formation product under the previously optimized conditions for amines, that is, CuBr as catalyst and TBHP (*t*BuOOH) as oxidant. When 2 equivalents of Cu(OAc)₂ were used, however, we obtained a small amount of the C–C coupling product between *N*-acetylglycine ethyl ester (**1**) and diethyl malonate (**2**; Table 1, entry 1). After extensive optimizations, we identified di(2-pyridyl) ketone as the best ligand for this reaction (Table 1, entry 5) affording considerably higher yields than either 4,4'-dimethyl-2,2'-bipyridine or 1,10-phenanthroline (Table 1, entries 2 and 3). This high reactivity is probably due to the fact that, in coordinating with copper, di(2-pyridyl) ketone forms a six-membered ring complex, which is more reactive than the five-membered ring complexes formed with the other nitrogen ligands. In addition, the presence of a catalytic amount of base is beneficial to the reaction (Table 1, entries 6, 7, 8). After further screening, 20 mol % of Cs₂CO₃ gave the best results (Table 1, entry 8). A catalytic amount of Cu(OAc)₂ under 1 atm O₂ with or without Pd(OAc)₂ gave only low yields of the desired products (Table 1, entries 9 and 10). The use of 1.2 equivalents of Cu(OAc)₂ furnished a lower yield; however, it demonstrated that Cu(OAc)₂ served as a stoichiometric oxidant in the reaction (Table 1, entry 11).

The CDC method could be applied to a variety of malonates as well as other glycine derivatives (Table 2). For most functionalized products, decomposition occurred after extended heating. To compare the relative reactivity, all the reactions were also performed and stopped at 4 h. Diisopropyl or diethyl malonates furnished better yields (Table 2, entries 1, 3, 5, and 7) than the corresponding dimethyl malonate (Table 2, entries 2 and 8), indicating that a more electron-rich malonate is beneficial to the reaction. Increased steric hindrance in the carbon center decreased the reactivity (Table 2, entries 4, 6, and 9). For the amino acid moiety, the electronic effect was shown to be more significant than the steric effect. The *i*Pr- and Et-substituted esters furnished higher yields (Table 2, entries 1 and 5) than the Me-substituted substrate (Table 2, entry 10). The effect of the substituent on the amide moiety was also studied. As shown in Table 2, when R¹ was changed from Me (Table 2, entries 6 and 9) and Et (Table 2, entries 11 and 14) to an *i*Pr group (Table 2, entries 12 and 15), the yield decreased dramatically. Furthermore, when R¹ was changed to a *t*Bu group (Table 2, entries 13 and 16), the reaction was completely shut down.



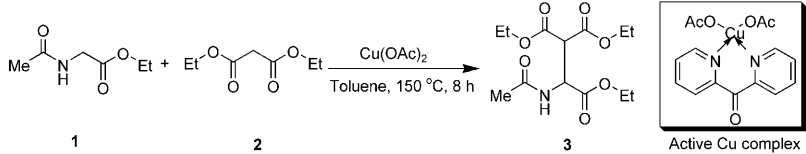
Scheme 1. Direct C–C bond formation by C–H bond functionalization adjacent to a tertiary nitrogen atom (Path A) and in amino acid derivatives (Path B). PG = Protecting group.

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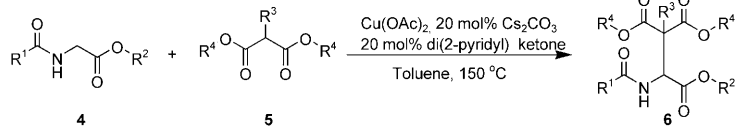
Table 1: Optimization of reaction conditions.^[a]



Entry	Ligand	Base	Cu(OAc) ₂ [equiv]	Yield [%] ^[b]
1	none	none	2.0	5
2	4,4'-dimethyl-2,2''-bipyridine	none	2.0	30
3	1,10-phenanthroline	none	2.0	12
4	TMEDA	none	2.0	23
5	di(2-pyridyl) ketone	none	2.0	56
6	di(2-pyridyl) ketone	NaOAc	2.0	70
7	di(2-pyridyl) ketone	KHCO ₃	2.0	71
8	di(2-pyridyl) ketone	Cs ₂ CO ₃	2.0	84
9 ^[c]	di(2-pyridyl) ketone	Cs ₂ CO ₃	0.2	15
10 ^[d]	di(2-pyridyl) ketone	Cs ₂ CO ₃	0.2	15
11	di(2-pyridyl) ketone	Cs ₂ CO ₃	1.2	68

[a] Reaction conditions: **1** (0.125 mmol), **2** (0.25 mmol), 20 mol % ligand, 20 mol % base in toluene (1 mL), 150 °C, 8 h. [b] Yields were based on compound **1** and determined by NMR spectroscopy using an internal standard. TMEDA = *N,N,N',N'*-tetramethylethylenediamine. [c] 5 mol % Pd(OAc)₂ was added and run under 1 atm O₂. [d] 5 mol % Pd(OAc)₂ was added.

Table 2: Functionalization of **4** by CDC reactions with malonate **5**.^[a]



Entry	Reaction <i>t</i> [h]	R ¹	R ²	R ³	R ⁴	6 ^[b]	Yield [%] ^[c]
1	6	Me	<i>i</i> Pr	H	Et	6a	82(73)
2	10	Me	<i>i</i> Pr	H	Me	6b	85(40)
3	6	Me	<i>i</i> Pr	H	<i>i</i> Pr	6c	80(62)
4	10	Me	<i>i</i> Pr	Me	Et	6d	94(48)
5	8	Me	Et	H	Et	6e	84(72)
6	10	Me	Et	Me	Me	6f	75(48)
7	6	Me	Et	H	<i>i</i> Pr	6g	73(63)
8	6	Me	Et	H	Me	6h	63(46)
9	10	Me	Et	Me	Et	6i	75(32)
10	6	Me	Me	H	Et	6j	65(55)
11	10	Et	Et	Me	Et	6k	75
12	10	<i>i</i> Pr	Et	Me	Et	6l	53
13	10	<i>t</i> Bu	Et	Me	Et	6m	NR
14	10	Et	Et	Me	Me	6n	78
15	10	<i>i</i> Pr	Et	Me	Me	6o	60
16	10	<i>t</i> Bu	Et	Me	Me	6p	NR

[a] Reaction conditions: **4** (0.125 mmol), **5** (0.25 mmol), Cu(OAc)₂ (0.25 mmol), Cs₂CO₃ (0.025 mmol), di(2-pyridyl) ketone (0.025 mmol), toluene (1 mL). [b] For full experimental data, see the Supporting Information. [c] Yields of isolated product are based on **4**, and the yields after 4 h reaction are given in parentheses. NR = No reaction.

Interestingly, it should be noted that α -amino acid derivatives bearing a substituent on the α -position did not react under the present conditions, possibly because of steric effects.

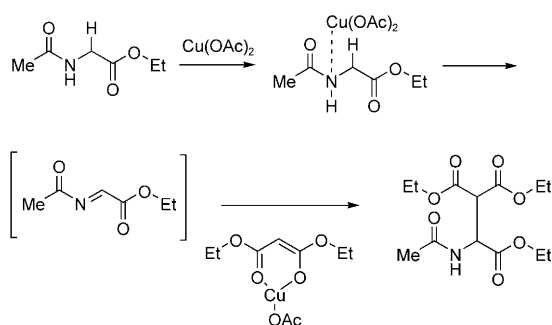
The mechanism of this novel transformation was explored briefly. Adding a radical inhibitor BHT (2,6-di-*tert*-butyl-4-methylphenol) did not have a significant influence on the reaction, suggesting that the involvement of a free radical intermediate is unlikely. We tentatively propose that coordination of nitrogen to Cu^{II}, followed by oxidation to generate

an imino intermediate (Scheme 2), precedes a copper(II)-catalyzed Mannich-type reaction between the imino ester and malonate to afford the final coupling product. The di(2-pyridyl) ketone serves as a better ligand in this reaction probably owing to its electron-withdrawing nature, which renders the Cu^{II} center in the transition state more electronegative. As a result, abstraction of the NH proton occurs more easily. Cs₂CO₃ neutralizes the generated acetic acid and helps the enolization of the malonate.

To extend the scope of the direct functionalization of α -peptide C–H bonds, we found that, by switching the protected amino acid derivative from amide **1** to compound **7** (see Table 3), a CDC reaction with phenylacetylene could proceed readily at room temperature using the CuBr/TBHP system.^[9p–v] This enhanced reactivity could be attributed to the *para*-methoxyphenyl (PMP) protecting group (the oxidation potential of an amine is much lower than that of an amide). The success of this transformation is also dependent on R¹ being a substituted amine moiety. If R¹ was an OEt group (Table 3, entry 10), the coupling reaction did not occur at all at room temperature. By switching R¹ to a phenyl group (Table 3, entry 11), the reaction afforded a complex unidentified mixture of products, indicating that the presence of a substituted amine moiety reduces the oxidation potential of the substrate and stabilizes the imine intermediate. Under the optimized conditions, various substituted glycine derivatives could be coupled with aromatic alkynes (Table 3). Secondary (Table 3, entries 1–4) and tertiary (Table 3, entry 5) amides all reacted well.

The aromatic alkyne counterparts, 4-ethynylbiphenyl (Table 3, entry 6), 1-bromo-4-ethynylbenzene (Table 3, entry 7), and 4-ethynyltoluene (Table 3, entry 8) all afforded the corresponding products in decent yields. However, 2-methoxyphenylacetylene (Table 3, entry 9) proved less reactive than the other substrates, indicating that the steric hindrance on the alkyne retarded its reactivity.

Encouraged by this promising result, we tested this method on a simple peptide **10** (Scheme 3). To our delight,

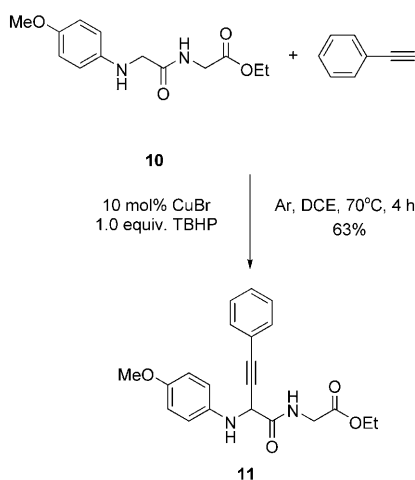


Scheme 2. Proposed mechanism for the oxidative functionalization of glycine derivatives with diethyl malonate.

Table 3: Functionalization of **7** by CDC reaction with alkyne **8**.^[a]

Entry	R ¹	R ²	9 ^[b]	Yield [%] ^[c]
1	NHMe	H	9a	68 (93)
2	NHEt	H	9b	55 (73)
3	NH(CH ₂) ₃ CH ₃	H	9c	62 (79)
4	NH(CH ₂) ₃ Ph	H	9d	76 (93)
5	1-pyrrolidinyl	H	9e	67 (90)
6	NHMe	4-Ph	9f	72 (86)
7	NHMe	4-Br	9g	78 (89)
8	NHMe	4-Me	9h	60 (81)
9	NHMe	2-OMe	9i	50 (63)
10	OEt	H	NA	NR
11	Ph	H	NA	ND

[a] Reaction conditions: **7** (0.30 mmol), **8** (0.90 mmol), TBHP (54 μ L, 5–6 M in decane), CuBr (0.03 mmol), CH₂Cl₂ (0.5 mL). [b] For full experimental data, see the Supporting Information [c] Yields of isolated product are based on **7**, and NMR yields, using an internal standard, are given in parentheses. NA = Not applicable. NR = No reaction. ND = Not determined.

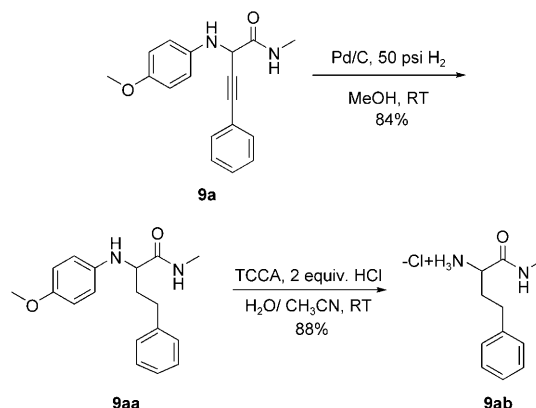


Scheme 3. Functionalization of simple peptide **10** with ethynylbenzene.

the coupling reaction proceeded at 70 °C in dichloroethane (DCE), affording the isolated coupling product **11** in 63 % yield. Compared with previous methods in functionalizing glycine derivatives,^[5,6] this method distinguished itself by specifically introducing the alkynyl group at the protected glycine terminus. In contrast, the carbanion- or radical-based methods would not have any significant selectivity between the two CH₂ groups in peptide **10**.

It should be noted that the existing methods to synthesize β,γ -alkynyl α -amino acid derivatives requires the coupling of α -halo glycines with alkynyltin reagents under refluxing conditions,^[11] alkynylmagnesium reagent at –78 °C,^[12] or transition-metal catalyzed alkylation of α -imino esters.^[13] Pre-functionalizations of amino acid derivatives at the α -position are essential in all cases. The CDC reaction described above takes advantage of the existing structures and allows the facile installation of the alkynyl group under very mild conditions. Furthermore, this method is the first reported CDC reaction on a secondary amine substrate.

This methodology also provides a versatile method to synthesize homophenylalanine derivatives (Scheme 4), which are an important synthon in many important angiotensin-converting enzyme inhibitors.^[14] Hydrogenation of the alkylation product **9a** provided compound **9aa**. Subsequent cleavage of the PMP protecting group afforded the homophenylalanine product **9ab**.



Scheme 4. Synthesis of homophenylalanine derivative **9ab**. TCCA = Trichloroisocyanuric acid

In conclusion, we have developed a new way to functionalize α -amino acid derivatives, which allows the efficient installation of a malonate or a phenylethynyl group, using an oxidative C–H/C–H coupling. Starting from commercially inexpensive starting materials, a range of α -functionalized amino acid derivatives can be readily obtained. Further studies on expanding the scope of the substrates and on enantioselective reactions are in progress.

Experimental Section

For full experimental and spectroscopic data, see the Supporting Information.

6e (Table 2, entry 5): Cu(OAc)₂ (45 mg, 0.25 mmol), di(2-pyridyl) ketone (4.6 mg, 0.025 mmol), Cs₂CO₃ (8.2 mg, 0.025 mmol), *N*-

acetylglycine ethyl ester (18 mg, 0.125 mmol), and diethyl malonate (40 mg, 0.25 mmol) were added to a 5 mL reaction tube. Toluene (1 mL) was then added. The tube was sealed and heated at 150 °C for 8 h and the resulting mixture was filtered through a small pad of silica gel and concentrated in vacuo. Flash chromatography on silica gel using ethyl acetate/hexane (gradient elution from 1:4 to 1:1) furnished the final product.

9a (Table 3, entry 1): 2-(4-methoxyphenylamino)-*N*-methylacetamide (59 mg, 0.30 mmol), CuBr (4.2 mg, 0.03 mmol), phenylacetylene (90 mg, 0.90 mmol), and TBHP (54 μ L, 5–6 M in decane) were successively added to CH₂Cl₂ (0.5 mL) in a test tube. The test tube was purged with argon and the mixture stirred for 15 h. The mixture was filtered through a small pad of silica gel, and concentrated in vacuo. Flash chromatography on silica gel using ethyl acetate/hexane (gradient elution from 1:4 to 1:2) furnished the final product.

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- [1] R. M. Twyman, *Principles of Proteomics*; BIOS Scientific Publishers: New York, **2004**.
- [2] For selected examples of peptide modifications, see: a) D. Seebach, A. K. Beck, A. Studer in *Modern Synthetic Methods*, Vol. 7 (Eds.: B. Ernst, C. Leumann), VCH, Weinheim, **1995**, pp. 1–178; b) S. Kotha, K. Lahiri, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2887–2890.
- [3] a) W. D. Kohn, R. S. Hodges, *Trends Biotechnol.* **1998**, *16*, 379–389; b) P. Balaram, *Curr. Opin. Struct. Biol.* **1992**, *2*, 845–851; c) C. L. Wysong, T. S. Yokum, M. L. McLaughlin, R. P. Hammer, *CHEMTECH* **1997**, *27*, 26–33; d) V. J. Hruby, *Acc. Chem. Res.* **2001**, *34*, 389–397.
- [4] a) O. Pillai, R. Panchagnula, *Drug Discovery Today* **2001**, *6*, 1056–1061; b) R. W. Carrell, D. A. Lomas, *Lancet* **1997**, *350*, 134–138; c) A. G. Cochran, *Chem. Biol.* **2000**, *7*, R85–R94; d) J. C. M. van Hest, D. A. Tirrell, *Chem. Commun.* **2001**, 1897–1904.
- [5] For reviews, see: a) A. I. Meyers, *Aldrichimica Acta* **1985**, *18*, 59–68; b) P. Beak, W. J. Zajdel, D. B. Reitz, *Chem. Rev.* **1984**, *84*, 471–523.
- [6] a) C. J. Easton, I. M. Scharfbillig, E. W. Tan, *Tetrahedron Lett.* **1988**, *29*, 1565–1568; b) C. J. Easton, C. A. Hutton, G. Rositano, E. W. Tan, *J. Org. Chem.* **1991**, *56*, 5614–5618; c) H. S. Knowles, K. Hunt, A. F. Parsons, *Tetrahedron Lett.* **2000**, *41*, 7121–7124.
- [7] a) B. Kübel, G. Hofle, W. Steglich, *Angew. Chem.* **1975**, *87*, 64–66; *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 58–59; b) K. Burger, K. Geith, K. Gaa, *Angew. Chem.* **1988**, *100*, 860–861; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 848–849; c) R. E. Ireland, R. H. Mueller, A. K. Willard, *J. Am. Chem. Soc.* **1976**, *98*, 2868–2877; d) P. A. Bartlett, J. F. Barstow, *J. Org. Chem.* **1982**, *47*, 3933–3941; e) U. Kazmaier, H. Mues, A. Krebs, *Chem. Eur. J.* **2002**, *8*, 1850–1855.
- [8] a) S.-I. Murahashi, T. Naota, T. Kuwabara, T. Saito, H. Kumobayashi, S. Akutagawa, *J. Am. Chem. Soc.* **1990**, *112*, 7820–7822; b) T. Naota, T. Nakato, S.-I. Murahashi, *Tetrahedron Lett.* **1990**, *31*, 7475–7478; c) S.-I. Murahashi, A. Mitani, K. Kitao, *Tetrahedron Lett.* **2000**, *41*, 10245–10249; d) G. Cainelli, M. DaCol, P. Galletti, D. Giacomini, *Synlett* **1997**, 923–924.
- [9] a) S.-I. Murahashi, N. Komiya, H. Terai, T. Nakae, *J. Am. Chem. Soc.* **2003**, *125*, 15312–15313; b) S. Doye, *Angew. Chem.* **2001**, *113*, 3455–3457; *Angew. Chem. Int. Ed.* **2001**, *40*, 3351–3353; c) N. Chatani, T. Asaumi, S. Yorimitsu, T. Ikeda, F. Kakiuchi, S. Murai, *J. Am. Chem. Soc.* **2001**, *123*, 10935–10941; d) N. Chatani, T. Asaumi, T. Ikeda, S. Yorimitsu, Y. Ishii, F. Kakiuchi, S. Murai, *J. Am. Chem. Soc.* **2000**, *122*, 12882–12883; e) C.-H. Jun, D.-C. Hwang, S.-J. Na, *Chem. Commun.* **1998**, 1405–1406; f) S. Sakaguchi, T. Kubo, Y. Ishii, *Angew. Chem.* **2001**, *113*, 2602–2604; *Angew. Chem. Int. Ed.* **2001**, *40*, 2534–2536; g) B. DeBoef, S. J. Pastine, D. Sames, *J. Am. Chem. Soc.* **2004**, *126*, 6556–6557; h) H. M. L. Davies, Q. Jin, *Org. Lett.* **2004**, *6*, 1769–1772; i) H. M. L. Davies, C. Venkataramani, T. Hansen, D. W. Hopper, *J. Am. Chem. Soc.* **2003**, *125*, 6462–6468; j) T. Yoshimitsu, Y. Arano, H. Nagaoka, *J. Am. Chem. Soc.* **2005**, *127*, 11610–11611; k) T. Maruyama, S. Suga, J.-I. Yoshida, *J. Am. Chem. Soc.* **2005**, *127*, 7324–7325; l) S. Suga, T. Nishida, D. Yamada, A. Nagaki, J.-I. Yoshida, *J. Am. Chem. Soc.* **2004**, *126*, 14338–14339; m) S. Suga, S. Suzuki, J.-I. Yoshida, *J. Am. Chem. Soc.* **2002**, *124*, 30–31; n) J.-I. Yoshida, S. Suga, S. Suzuki, N. Kinomura, A. Yamamoto, K. Fujiwara, *J. Am. Chem. Soc.* **1999**, *121*, 9546–9549; o) C. S. Yi, S. Y. Yun, I. A. Guzei, *Organometallics* **2004**, *23*, 5392–5395; p) Z. Li, C.-J. Li, *J. Am. Chem. Soc.* **2006**, *128*, 56–57; q) Z. Li, C.-J. Li, *Eur. J. Org. Chem.* **2005**, 3173–3176; r) Z. Li, C.-J. Li, *J. Am. Chem. Soc.* **2005**, *127*, 6968–6969; s) Z. Li, C.-J. Li, *J. Am. Chem. Soc.* **2005**, *127*, 3672–3673; t) Z. Li, C.-J. Li, *Org. Lett.* **2004**, *6*, 4997–4999; u) Z. Li, C.-J. Li, *J. Am. Chem. Soc.* **2004**, *126*, 11810–11811; v) Z. Li, D. S. Bohle, C.-J. Li, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 8928–8933.
- [10] S.-I. Murahashi, N. Komiya in *Modern Oxidation Methods* (Ed.: J.-E. Backvall), Wiley-VCH, Weinheim, **2004**, pp. 165–191.
- [11] R. M. Williams, D. J. Aldous, S. C. Aldous, *J. Org. Chem.* **1990**, *55*, 4657–4663.
- [12] A. L. Castelhana, S. Horne, G. J. Taylor, R. Billedeau, A. Krantz, *Tetrahedron* **1988**, *44*, 5451–5466.
- [13] a) J. X. Ji, T. L. Au-Yeung, J. Wu, C. W. Yip, A. S. C. Chan, *Adv. Synth. Catal.* **2004**, *346*, 42–44; b) J. X. Ji, J. Wu, A. S. C. Chan, *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 11196–11200.
- [14] a) M. J. Wyvratt, *Clin. Physiol. Biochem.* **1988**, *6*, 217–229; b) H. R. Brunner, J. Nussberger, B. Waeber, *J. Cardiovasc. Pharmacol.* **1985**, *7*, S2–S11.