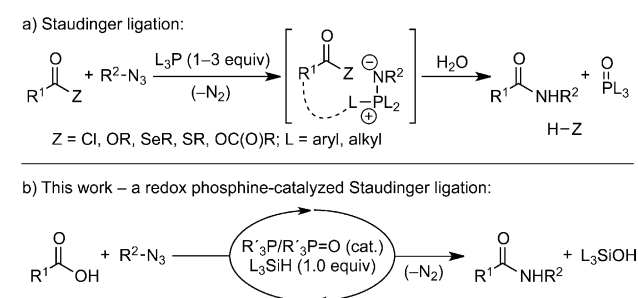


Phosphine-Based Redox Catalysis in the Direct Traceless Staudinger Ligation of Carboxylic Acids and Azides**

Andrew D. Kosal, Erin E. Wilson, and Brandon L. Ashfeld*

The synthesis of amide C–N bonds through nucleophilic acyl substitutions constitutes one of the most fundamental transformations in chemical synthesis.^[1] Recently, the Staudinger-type ligation^[2] of carboxylic acid derivatives (e.g., acid chlorides, anhydrides, acyl selenides, and thioesters) and azides has become a preeminent strategy for amide C–N bond construction (Scheme 1a).^[3] However, the generation of

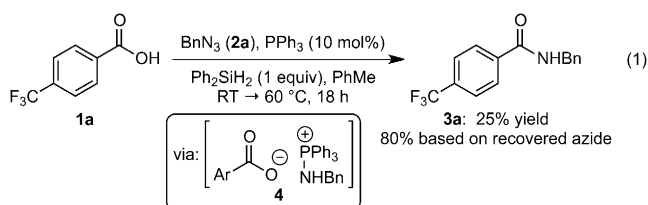
turnover without interfering with C–N bond formation. Given the reactivity of silanes^[6] toward the chemoselective reduction of phosphine oxides, our initial efforts focused on this class of hydride donors.^[7] However, the aqueous conditions required for amidophosphonium hydrolysis in the conventional Staudinger ligation are incompatible with silanes.^[8] A catalytic design is further complicated by the tendency of silanes to reduce aza-ylides to their corresponding silyl amines. Competitive aza-ylide reduction would hinder formation of an activated phosphonium carboxylate and thus the subsequent acyl substitution.^[7a] Therefore, we speculated that oxygen transfer directly from the carboxylic acid to phosphorus under anhydrous conditions would be compatible with a silane reductant. However, recent reports by van Delft and co-workers showed that while phospholane oxides and dibenzophospholes are effective redox catalysts, their corresponding aza-ylides are readily reduced by silanes.^[7a,b] In contrast, Ph₃P-derived aza-ylides were found to reduce at a slower rate in the presence of Ph₂SiH₂, which prompted us to begin our study toward the first phosphine-catalyzed Staudinger ligation using this reagent combination. By treating benzoic acid **1a** and benzyl azide (**2a**) with PPh₃ (10 mol %) and Ph₂SiH₂ (1 equiv), the ostensible phosphonium carboxylate **4** led to benzyl amide **3a** in 25 % yield [Eq. (1)]. In spite of the modest yield, we were encouraged by the catalytic behavior of PPh₃ in the Staudinger ligation.



Scheme 1. Staudinger ligation approach to amide synthesis.

stoichiometric by-products (e.g., R₃P=O) often complicates efforts to isolate products, leads to waste disposal issues, and limits the overall synthetic efficiency of this method.^[4] Thus, a phosphine-catalyzed Staudinger ligation involving the direct coupling of carboxylic acids and azides would concomitantly minimize the formation of undesired by-products while avoiding the need for an additional acid derivatization (Scheme 1b). We envisioned a P^{III}/P^V-redox-driven cycle wherein an acid/base reaction of the carboxylic acid and intermediate aza-ylide would form an activated phosphonium carboxylate in situ and thus enable catalytic C–N bond formation.^[5] Herein, we report a conceptually new approach toward the phosphine-catalyzed Staudinger ligation for the chemoselective, direct conversion of carboxylic acids to amides.

At the outset, we sought to identify an appropriate phosphine/reductant combination that would enable catalyst



We began our reaction optimization by examining the efficacy of various silanes to facilitate catalyst turnover (Table 1). Although known to efficiently reduce phosphine oxides, alkoxy silanes (MeO)₃SiH and (EtO)₂MeSiH, and Cl₃SiH failed to provide amide **3a** (Table 1, entries 1–3).^[7d,9] However, use of PhSiH₃ improved the yield to 70 %, while a slight excess of azide **2a** provided **3a** in 98 % yield (Table 1, entries 4 and 5). Interestingly, employing either 0.5 or 1.5 equiv of PhSiH₃ led to a reduction in the yield of **3a** (Table 1, entries 6 and 7). The observation that 4 equiv of PhSiH₃ prevented amide formation indicates that minimizing competitive aza-ylide reduction is critical (Table 1, entry 9).^[10]

We next turned our attention toward examining catalyst structure and loading. Unfortunately, reducing the amount of

[*] A. D. Kosal,^[‡] E. E. Wilson,^[‡] Prof. Dr. B. L. Ashfeld
Department of Chemistry and Biochemistry
University of Notre Dame
251 Nieuwland Science Hall, Notre Dame, IN 46556 (USA)
E-mail: bashfeld@nd.edu

[‡] These authors contributed equally to this work.

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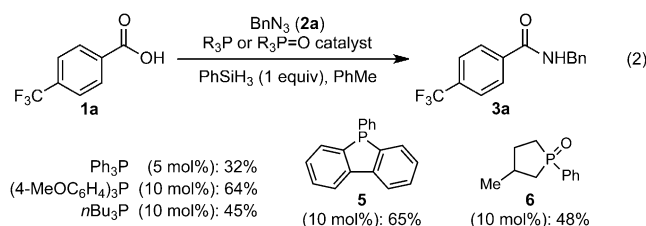
Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/ange.201206533>.

Table 1: Effect of silane reductant and azide equivalents.^[a]

Entry	Equiv. of 2a	Silane	Equiv. of silane	Yield [%] ^[b]
1	1.0	(MeO) ₃ SiH	1.0	NR
2	1.0	(EtO) ₂ MeSiH	1.0	< 5
3	1.0	Cl ₃ SiH	1.0	NR
4	1.0	PhSiH ₃	1.0	70
5	1.2	PhSiH₃	1.0	98
6	1.2	PhSiH ₃	0.5	45
7	1.2	PhSiH ₃	1.5	28
8	1.2	PhSiH ₃	2.0	50
9	1.2	PhSiH ₃	4.0	< 5

[a] Conditions: **1a** (0.30 mmol), PPh₃ (10 mol %), **2a**, and R₃SiH in PhMe (0.3 M). [b] Yields of isolated products. Entry in bold highlights optimized conditions.

PPh₃ to 5 mol % gave amide **3a** in only 32 % yield [Eq. (2)]. Lowering the amount of phosphine even further led to a similar reduction in yield. Employing the more-electron-rich aryl phosphines (4-MeOC₆H₄)₃P or *n*Bu₃P provided amide **3a** in 64 % and 45 % yield, respectively. As expected, dibenzophosphole **5** and phospholane oxide **6** gave **3a** in decreased yield. With our optimized conditions in hand, we then focused on determining substrate compatibility in the PPh₃-catalyzed Staudinger ligation.



In general, treatment of carboxylic acids **1** and azides **2** with PPh₃ (10 mol %) and PhSiH₃ provided good to excellent yields of amides **3** (Table 2). Ligation of benzoic acid **1b** and **2a** gave benzamide **3b** in 94 % yield (Table 2, entry 1). Electron-rich and electron-deficient benzoic acid derivatives also proceeded smoothly to give the corresponding benzamides (Table 2, entries 2–4). Cinnamic acid **1f** underwent amidation with exclusive 1,2 addition, and aliphatic acids **1g** and **1h** provided amides **3g** and **3h** in 88 % and 61 % yield, respectively (Table 2, entries 5–7). Notably, the conversion of pivalic acid **1h** to amide **3h** indicates that ketene formation is not likely involved in the amidation event.^[11] Aliphatic and allylic azides **2b** and **2c**, respectively, also proved effective in the ligation of acid **1a** (Table 2, entries 8 and 9). Finally, heteroaromatic compounds bearing a pendant azide were viable substrates, as demonstrated by the formation of amide **3k** from acid **1a** and furfural azide **2d** in 78 % yield (Table 2, entry 10).^[12]

In addition to azides **2a–d**, aryl and acyl azides participated as coupling partners in the PPh₃-catalyzed Staudinger

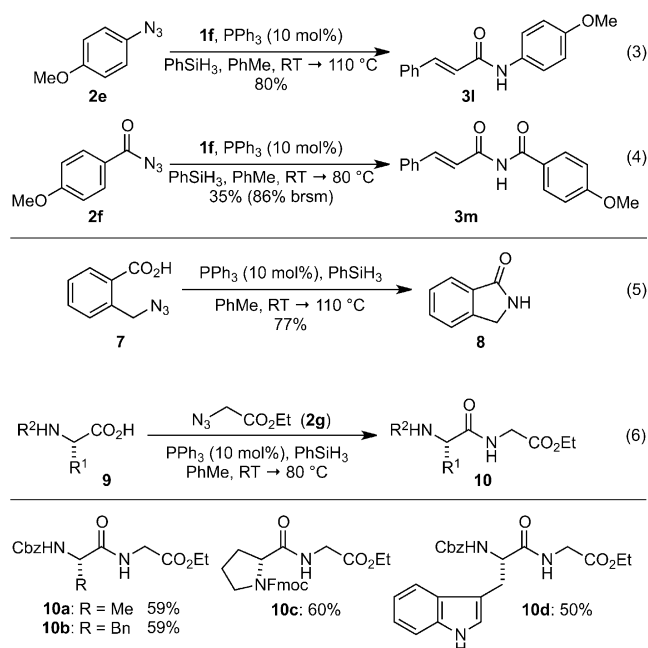
Table 2: Substrate exploration.^[a]

Entry	Acid	Azide	Product	Yield [%] ^[b]
1	1b	2a 3b		94
2	1c	2a 3c		79
3	1d	2a 3d		95
4	1e	2a 3e		97
5	1f	2a 3f		95
6	1g	2a 3g		88
7	1h	2a 3h		61
8	1a	2b 3i		76
9	1a	2c 3j		76
10	1a	2d 3k		78

[a] Conditions: **1** (0.30 mmol), **2** (0.36 mmol), PPh₃ (10 mol %), and PhSiH₃ (0.30 mmol) in PhMe (0.3 M). [b] Yields of isolated products.

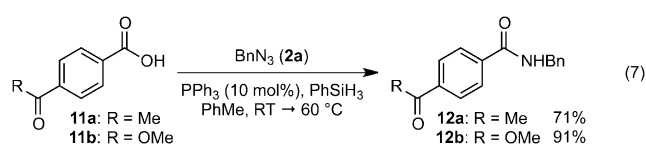
amidation. Ligation of aryl azide **2e** and acid **1f** gave amide **3l** in 80 % yield [Eq. (3)]. However, acyl azide **2f** provided imide **3m** in modest yield [Eq. (4)].^[13] Attempts to improve this result through longer reaction times led to azide decomposition. The intramolecular ligation of carboxylic acid **7** with PPh₃ (10 mol %) and PhSiH₃ gave lactam **8** in 77 % yield [Eq. (5)]. Given the pervasiveness of the lactam motif in chemotherapeutics,^[14] and the role lactamization reactions play in the construction of biologically active natural products,^[15] the phosphine-catalyzed Staudinger ligation constitutes a formidable method for the synthesis of this motif.

Recently, the Staudinger ligation has arisen as a powerful alternative to the “native chemical ligation” approach toward peptide fragments,^[16] addressing the inherent limitations associated with the need for a cysteine residue at the site of elaboration.^[17] To determine, whether the PPh₃-catalyzed Staudinger ligation would lead to racemization of chiral α-amino acids, we examined the coupling of acids **9** with azido glycinate **2g** [Eq. (6)]. Gratifyingly, peptide coupling of N-



Cbz-protected amino acids alanine and phenylalanine with **2g** provided dipeptides **10a** and **10b**, respectively, without loss of optical purity.^[18] N-Fmoc-protected proline also underwent conversion to dipeptide **10c** in 60% yield. Interestingly, a free indole N-H in N-Cbz-protected tryptophan did not hinder the formation of peptide **10d**.^[19] These results highlight the utility of this phosphine-catalyzed Staudinger ligation to facilitate the construction of optically enriched dipeptide fragments.

Speculating that formation of a putative phosphonium carboxylate would provide high chemoselectivity for the coupling of carboxylic acid and azide, we next examined the PPh₃-catalyzed Staudinger ligation in the presence of other carbonyl electrophiles. Treatment of acid **11a** bearing a 4-acetyl group to our optimized conditions provided amide **12a** in 71% yield [Eq. (7)]. It is noteworthy that neither imine

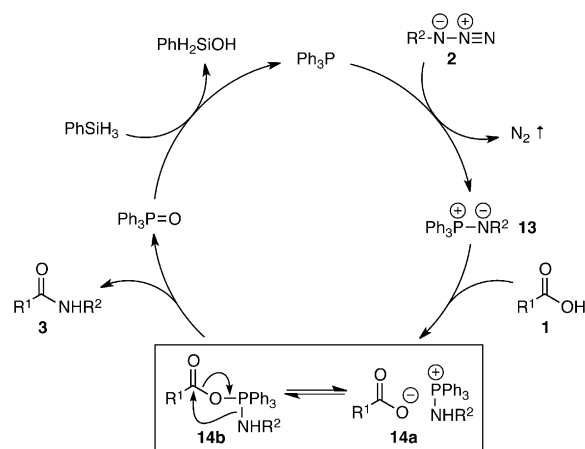


products, resulting from an aza-Wittig reaction,^[20] nor Schmidt rearrangement products^[21] were observed. Aryl acid **11b**, which bears an ester at the *para* position, also underwent chemoselective ligation of the carboxylic acid motif in 91% yield. Although esters are readily converted to the corresponding amides by employing Bertozzi's conditions, treatment of methyl benzoate and **2a** with 10 mol % PPh₃ and PhSiH₃ provided benzamide **3b** in less than 10% yield. These results suggest that the amidophosphonium salt proposed by Bertozzi and Raines is not a viable intermediate in the catalytic variant.^[3d,e]

To gain insight into the reaction mechanism, and the importance of a presumptive phosphonium carboxylate

intermediate (e.g., **4**), we examined the effect of carboxylic acid structure on the rate of amidation (Figure 1).^[22] In general, our results indicate that while steric and electronic factors influence C–N bond formation, the Brønsted acidity of the carboxylic acid also played a prominent role in the rate of conversion. Electron-deficient acid **1a** exhibited a faster rate of benzamidation than electron-rich acid **1c**, whereas hindered acids **1i** (*o*-tolyl) and **1j** (mesityl) proceeded slower than the less sterically encumbered acids **1b** and **1g** (Graph 1). However, if the degree of covalent character in the phosphonium carboxylate salt affects the rate of acyl substitution, then lower *pK_b* values of carboxylates should lead to faster rates of amidation. This hypothesis is consistent with the observed rate of ligation of acid **1g**, indicating a direct correlation between the rate of amidation and ionic character of the resulting phosphonium carboxylate. These results seem to suggest that promotion of a tight phosphonium carboxylate ion pair is a crucial factor in the rate of amidation. Additionally, the faster rate of consumption of acid **1** (Graph 2) in comparison to formation of amide **3** further implies that acyl substitution leading to C–N bond formation, and not phosphonium carboxylate generation, is rate determining.

In addition to these stereoelectronic factors, we discovered that the reaction efficiency was highly solvent dependent. Performing the phosphine-catalyzed ligation of acid **1a** and azide **2a** in polar aprotic solvents, such as *N,N*-dimethylformamide, acetonitrile, or 1,2-dimethoxyethane, failed to provide amide **3a** in greater than 57% yield. Additionally, halogenated solvents (e.g., 1,2-dichloroethane) and MeOH also proved inferior to PhMe. Based on these results, our working mechanistic hypothesis for the redox phosphine-catalyzed Staudinger ligation involves initial reduction of azide **2** by PPh₃ to give aza-ylide **13** (Scheme 2). Deprotonation of carboxylic acid **1** provides phosphonium carboxylate **14a**, and the partially covalent P–O bond in **14b** activates the carboxylate for nucleophilic acyl substitution. Amide C–N bond formation leads to formation of **3** and Ph₃P=O. Reduction of the phosphine oxide regenerates PPh₃ and completes the catalytic cycle. The likelihood of PhMe promoting the formation of a tight ion pair supports our



Scheme 2. Proposed catalytic cycle.

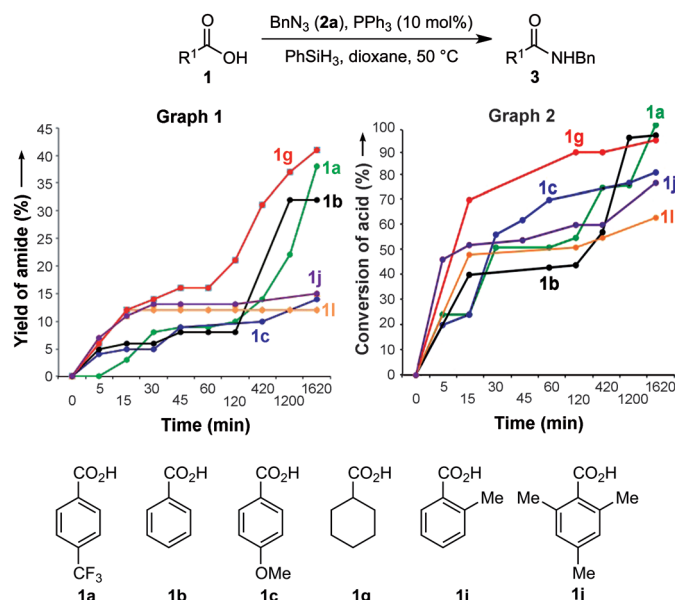


Figure 1. Absolute rate of amide formation. Aliquots taken at indicated times were quenched with CH_2N_2 , and conversion was determined by 1H NMR analysis (600 MHz) using 1,3,5-trimethoxybenzene as an internal standard.

hypothesis that intermediate **14b** is crucial for carboxylic acid activation, thus enabling nucleophilic acyl substitution.

Given the propensity for silanes to reduce aza-ylides, an alternative mechanism involving addition of the silyl amine derived from P=N bond reduction of ylide **13** to an in situ generated silyl ester was considered. However, preformation of the silyl ester derived from acid **1a** and Ph_2HSiCl followed by addition of azide **2a** and PPh_3 (10 mol %) failed to provide more than trace quantities of amide **3a**. Therefore, our results suggest that P=O bond reduction is required for catalytic turnover, and that P=N bond reduction effectively hinders the phosphine-catalyzed Staudinger ligation of carboxylic acids.

In summary, we have developed a redox phosphine-catalyzed Staudinger ligation that enables the direct conversion of carboxylic acids to amides while avoiding issues of product isolation and the disposal of stoichiometric phosphine oxide by-products. This procedure constitutes a new approach toward amide C–N bond formation, and is directly applicable to the assembly of biologically active natural products and synthetic targets that contain amides, lactams, and peptide linkages. Further mechanistic studies and use of this reaction in total synthesis is currently being pursued, and will be reported in due course.

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- [1] a) *Comprehensive Organic Synthesis*, Vol. 6 (Eds.: B. M. Trost, I. Fleming), Pergamon, New York, **1991**, pp. 301–460; b) C. L. Allen, J. M. J. Williams, *Chem. Soc. Rev.* **2011**, *40*, 3405–3405; c) C. Gunanathan, Y. Ben-David, D. Milstein, *Science* **2007**, *317*, 790–792; d) H. Lundberg, F. Tinnis, H. Adolfsson, *Chem. Eur. J.* **2012**, *18*, 3822–3826.
- [2] L. Horner, A. Gross, *Justus Liebigs Ann. Chem.* **1955**, *591*, 117–134.
- [3] a) A. D. Kosal, E. E. Wilson, B. L. Ashfeld, *Chem. Eur. J.* **2012**, *18*, 14444–14453; b) J. Kalia, R. T. Raines, *Curr. Org. Chem.* **2010**, *14*, 138–147; c) J. Burés, M. Martín, F. L. Urpí, J. Vilarrasa, *J. Org. Chem.* **2009**, *74*, 2203–2206; d) M. B. Soellner, B. L. Nilsson, R. T. Raines, *J. Am. Chem. Soc.* **2006**, *128*, 8820–8828; e) F. L. Lin, H. M. Hoyt, H. van Halbeek, R. G. Bergman, C. R. Bertozzi, *J. Am. Chem. Soc.* **2005**, *127*, 2686–2695; f) M. Köhn, R. Breinbauer, *Angew. Chem.* **2004**, *116*, 3168–3178; *Angew. Chem. Int. Ed.* **2004**, *43*, 3106–3116; g) E. Saxon, C. R. Bertozzi, *Science* **2000**, *287*, 2007–2010.
- [4] a) S. T. Heller, T. Fu, R. Sarpong, *Org. Lett.* **2012**, *14*, 1970–1973; b) A. M. Dumas, G. A. Molander, J. W. Bode, *Angew. Chem.* **2012**, *124*, 5781–5784; *Angew. Chem. Int. Ed.* **2012**, *51*, 5683–5686; c) V. R. Pattabiraman, J. W. Bode, *Nature* **2011**, *480*, 471–479; d) D. J. Hardee, L. Kovalchuk, T. H. Lambert, *J. Am. Chem. Soc.* **2010**, *132*, 5002–5003; e) K. Ishihara, S. Ohara, H. Yamamoto, *J. Org. Chem.* **1996**, *61*, 4196–4197.
- [5] a) J. Garcia, F. Urpí, J. Vilarrasa, *Tetrahedron Lett.* **1984**, *25*, 4841–4844; b) S.-i. Yamada, Y. Takeuchi, *Tetrahedron Lett.* **1971**, *12*, 3595–3598.
- [6] a) K. L. Marsi, *J. Org. Chem.* **1974**, *39*, 265–267; b) C. Petit, A. Favre-Reguillon, B. L. Albela, L. Bonneviot, G. Mignani, M. Lemaire, *Organometallics* **2009**, *28*, 6379–6382.
- [7] a) H. A. van Kalker, J. J. Bruins, F. P. J. T. Rutjes, F. L. van Delft, *Adv. Synth. Catal.* **2012**, *354*, 1417–1421; b) H. A. van Kalker, S. H. A. M. Leenders, C. R. A. Hommersom, F. P. J. T. Rutjes, F. L. van Delft, *Chem. Eur. J.* **2011**, *17*, 11290–11295; c) R. M. Denton, J. An, B. Adeniran, A. J. Blake, W. Lewis, A. M. Poulton, *J. Org. Chem.* **2011**, *76*, 6749–6767; d) C. J. O'Brien, J. L. Tellez, Z. S. Nixon, L. J. Kang, A. L. Carter, S. R. Kunkel, K. C. Przeworski, G. A. Chass, *Angew. Chem.* **2009**, *121*, 6968–6971; *Angew. Chem. Int. Ed.* **2009**, *48*, 6836–6839.
- [8] a) B. L. Nilsson, L. L. Kiessling, R. T. Raines, *Org. Lett.* **2001**, *3*, 9–12; b) E. Saxon, J. I. Armstrong, C. R. Bertozzi, *Org. Lett.* **2000**, *2*, 2141–2143; c) H. Staudinger, J. Meyer, *Helv. Chim. Acta* **1919**, *2*, 635–646.
- [9] K. Naumann, G. Zon, K. Mislow, *J. Am. Chem. Soc.* **1969**, *91*, 7012–7023.
- [10] Z. Ruan, R. M. Lawrence, C. B. Cooper, *Tetrahedron Lett.* **2006**, *47*, 7649–7651.
- [11] A. O.-Y. Chan, C.-M. Ho, H.-C. Chong, Y.-C. Leung, J.-S. Huang, M.-K. Wong, C.-M. Che, *J. Am. Chem. Soc.* **2012**, *134*, 2589–2598.
- [12] A. V. Butin, T. A. Nevolina, V. A. Shcherbinin, I. V. Trushkov, D. A. Cheshkov, G. D. Krapivin, *Org. Biomol. Chem.* **2010**, *8*, 3316–3327.
- [13] J. Suh, B. H. Lee, *J. Org. Chem.* **1980**, *45*, 3103–3107.
- [14] a) W. Dürckheimer, J. Blumbach, R. Lattrell, K. H. Scheunemann, *Angew. Chem.* **1985**, *97*, 183–205; *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 180–202; b) R. B. Morin, M. Gorman, *Chemistry and Biology of β -Lactam Antibiotics*, Vol. 1–3, Academic Press, New York, **1982**; c) M. I. Page, *The Chemistry of β -lactams*, Chapman and Hall, London, **1992**; d) J. R. Struble, J. W. Bode, *Tetrahedron* **2009**, *65*, 4957–4967; e) X. K. Wee, W. K. Yeo, B. Zhang, V. B. C. Tan, K. M. Lim, T. E. Tay, M.-L. Go, *Biorg. Med. Chem.* **2007**, *17*, 7562–7571.

- [15] a) K. Ishihara, Y. Kuroki, N. Hanaki, S. Ohara, H. Yamamoto, *J. Am. Chem. Soc.* **1996**, *118*, 1569–1570; b) Z. Luo, K. Peplowski, G. A. Sulikowski, *Org. Lett.* **2007**, *9*, 5051–5054; c) R. G. Vaswani, J. J. Day, J. L. Wood, *Org. Lett.* **2009**, *11*, 4532–4535.
- [16] a) T. Wieland, E. Bokelmann, L. Bauer, H. U. Lang, H. Lau, *Justus Liebigs Ann. Chem.* **1953**, 583, 129–149; b) T. Wieland, H. Determann, *Angew. Chem.* **1963**, *75*, 539–551; *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 358–370.
- [17] a) D. Bang, G. I. Makhatadze, V. Tereshko, A. A. Kossiakov, S. B. Kent, *Angew. Chem.* **2005**, *117*, 3920–3924; b) P. E. Dawson, T. W. Muir, I. Clark-Lewis, S. B. Kent, *Science* **1994**, *266*, 776–779; c) S.-Y. Han, Y.-A. Kim, *Tetrahedron* **2004**, *60*, 2447–2467; d) C. A. G. N. Montalbetti, V. Falque, *Tetrahedron* **2005**, *61*, 10827–10852; e) J. P. Tam, Q. Yu, *Biopolymers* **1998**, *46*, 319–327; f) F. I. Valiyaveetil, M. Sekedat, T. W. Muir, R. MacKinnon, *Angew. Chem.* **2004**, *116*, 2558–2561; *Angew. Chem. Int. Ed.* **2004**, *43*, 2504–2507.
- [18] See the Supporting Information for details.
- [19] a) K. Akaji, N. Kuriyama, T. Kimura, Y. Fujiwara, Y. Kiso, *Tetrahedron Lett.* **1992**, *33*, 3177–3180; b) A. Saha, H. Rapoport, P. Schultz, *J. Am. Chem. Soc.* **1989**, *111*, 4856–4859.
- [20] F. Palacios, C. Alonso, D. Aparicio, G. Rubiales, J. M. de Los Santos, *Tetrahedron* **2007**, *63*, 523–575.
- [21] a) K. F. Schmidt, *Angew. Chem.* **1923**, *36*, 511; b) K. F. Schmidt, *Ber. Dtsch. Chem. Ges. B* **1924**, *57*, 704–706.
- [22] These experiments were performed in dioxane at 50 °C to ensure homogeneity and measurable rate differences between substrates.