Intramolecular Staudinger Ligation towards Biaryl-Containing Lactams

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Abstract: Both 15- and 16-membered biaryl-type lactams were prepared in good yield using the intramolecular Staudinger ligation strategy.

Key words: biaryls, macrolactams, cyclizations, atropisomerism, ring contractions

Various natural and synthetic compounds based on a cyclic peptide scaffold with an endocyclic biaryl moiety have been shown to possess important bioactivities (e.g. biphenomycins A,B and RP-66453, Figure 1).[1] In these compounds rotation around the aryl–aryl bond is hindered due to ring strain, even in the absence of *ortho* substituents, causing atropisomerism. Consequently, these fascinating molecular architectures are attractive yet challenging synthetic targets.

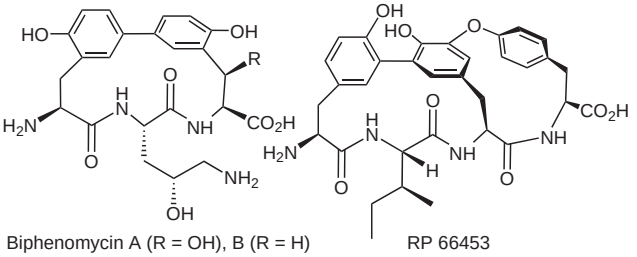
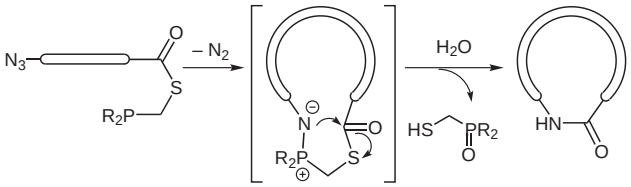


Figure 1

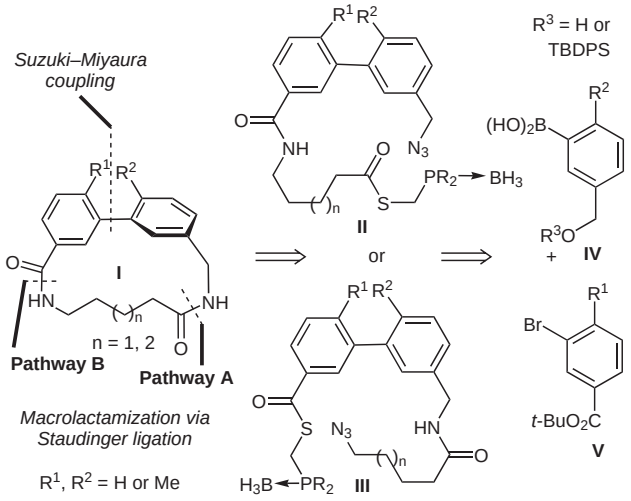
Recently, we disclosed a new strategy for the synthesis of the otherwise difficult-to-prepare medium-sized lactams based on the intramolecular Staudinger ligation.[2] This method involves a Staudinger reaction of a *C*-terminal phosphinomethylene ester with an *N*-terminal azide resulting in an intermediate iminophosphorane, which undergoes an intramolecular ring-contracting S→N acyl-transfer reaction, via a favored five-membered transition state (Scheme 1).[3]

The auxiliary residue is hydrolyzed in situ by the presence of a small amount of water in the reaction mixture providing the liberated lactam. We envisaged that this approach might be applicable to the construction of synthetically challenging biaryl-type macrolactams displaying atropisomerism as the only source of chirality. Herein, we



Scheme 1

present an efficient method for the synthesis of chiral macrocyclic lactams **I** containing a *meta–meta* connected biaryl moiety (Scheme 2). Retrosynthetic analysis of the target macrolactams shows that disconnection via the Staudinger-type macrolactamization can follow two possible pathways to give ω-azido phosphinothioesters **II** or **III** and that formation of the biaryl linkage via Suzuki coupling gives two appropriately functionalized aryls **IV** and **V** (Scheme 2).



Scheme 2

Our ultimate goal was to introduce an appropriate chiral phosphinothioester that would enable enantioselective lactamizations. In addition, we chose the highly nucleophilic bisalkylphosphine auxiliaries instead of the previously used bisarylphosphines.[4] For this, we developed a convenient synthesis of the air-stable borane-protected phosphinothiol auxiliary **2** and its optically enriched analogue **3** (Scheme 3).

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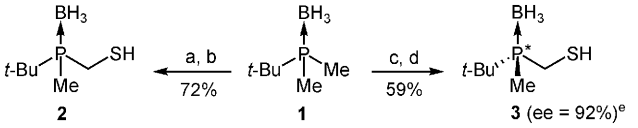
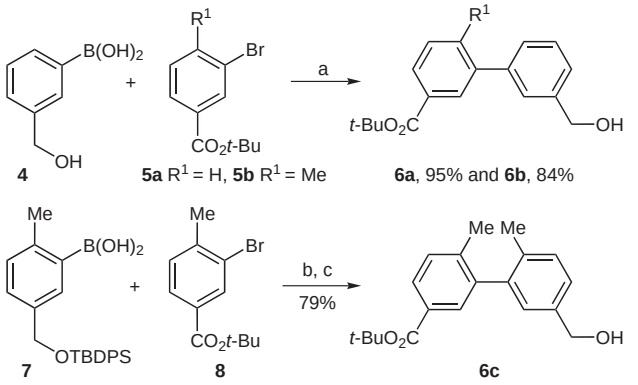


Scheme 3 *Reagents and conditions*: a) *s*-BuLi, THF,–78 °C, 3 h; b) S_8, THF,–78 °C to r.t., 2 h; c) *s*-BuLi, (–)-sparteine, Et_2O,–78 °C, 3 h; d) S_8, THF, –20 °C to r.t., 2 h. The ee was determined by HPLC analysis using a Chiralcel OJ column and heptane–*i*-PrOH (95:5) as the eluent (UV detection at 210/240 nm).

tert-Butyl(dimethyl)phosphine borane (**1**)[5] was deprotonated with *s*-BuLi (THF, –78 °C) and then trapped with S_8 (1.1 equiv, THF, –20 °C to r.t.) to provide **2** in 72% yield.[6,7] The optically enriched analogue **3** was obtained by asymmetric deprotonation by *s*-BuLi (THF, –78 °C) of **1** in the presence of (–)-sparteine providing **3** in 59% yield and 92% ee.[7–9]

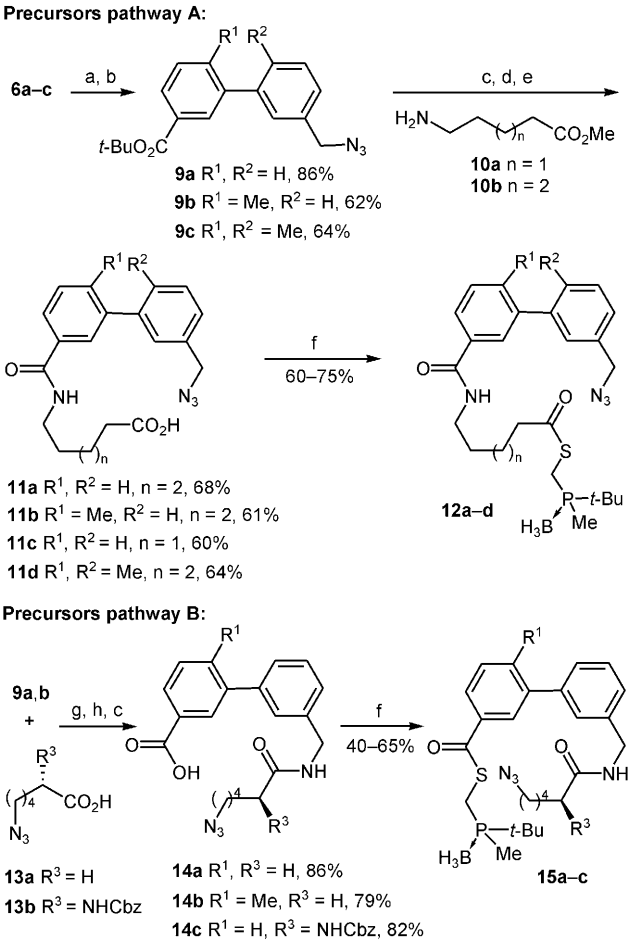
The construction of the *C*-terminal phosphinoester and an *N*-terminal azide containing lactamization precursor is depicted in Scheme 5. The required biaryl frameworks were prepared using the Suzuki–Miyaura coupling as the key step (Scheme 4).[10]



Scheme 4 *Reagents and conditions*: a) $Pd(PPh_3)_4$ (2 mol%), aq Na_2CO_3, THF, 80 °C, 18 h; b) $Pd(OAc)_2$ (2 mol%), S-Phos (5 mol%), aq K_3PO_4, toluene, 90 °C 16 h; c) TBAF, THF, 0 °C to r.t., 4 h, 95%.

The mono *ortho*- and unsubstituted biaryl compounds **6a** and **6b** were synthesized using classical Suzuki–Miyaura [$Pd(PPh_3)_4$, aq Na_2CO_3, THF, reflux] conditions starting from arylboronic acid **4**[11] and aryl bromides **5a** and **5b** to give **6a** and **6b** in yields of 95% and 84%, respectively. To obtain the hindered *o*,*o*-disubstituted biaryl **6c** in good yield, S-Phos[12] was required as the ligand.

For the preparation of pathway A precursors **12a**–**d**, alcohols **6a**–**c** were converted into azides by mesylation followed by nucleophilic substitution with sodium azide (Scheme 5). TFA-mediated *tert*-butyl ester cleavage of **9a**–**c** resulted in acids **11a**–**d** that were coupled with the amino esters **10a** and **10b**. Ester hydrolysis was followed by introduction of the phosphinothiol auxiliary **2** to provide the precursors **12a**–**d**. To obtain pathway B precursors **15a**–**c**, the azides **9a** and **9b** were reduced to their amines using triphenylphosphine in THF–water and acylated with the azido acids **13a** and **13b**,[13] followed by liberation of the acids **14a**–**c** by *tert*-butyl ester cleavage and thioesterification with the borane-protected auxiliary **2** (Scheme 5).



Scheme 5 *Reagents and conditions*: a) MsCl, Et_3N, CH_2Cl_2, 0 °C to r.t., 1 h; b) NaN_3, DMF, overnight, r.t.; c) TFA–H_2O (7:3), r.t., 18 h; d) **10a** or **10b**, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), DMAP (cat.), $NaHCO_3$, CH_2Cl_2, r.t., 18 h; e) 4 N NaOH, EtOH, r.t., 5–10 h; f) **2**, EDC, DMAP, CH_2Cl_2, r.t., 16 h; g) PPh_3, THF–H_2O (1:9), 70 °C, 4 h; h) **13a** or **13b**, EDC, DMAP (cat.), CH_2Cl_2, r.t., 18 h.

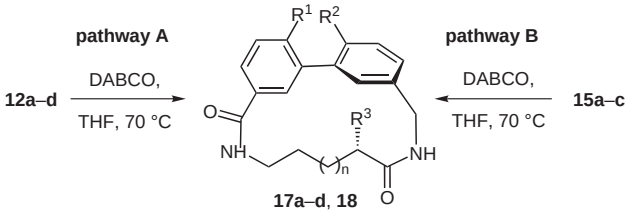
The intramolecular Staudinger reaction was initiated by liberation of the phosphane by decomplexation with DABCO (5 equiv) in THF at 70 °C (Table 1).[14,15] Based on our preliminary investigation, we employed high-dilution conditions (10^{-3} M).[2] Cyclization of **12a** gave the corresponding 16-membered lactam **17a** in an isolated yield of 67%.

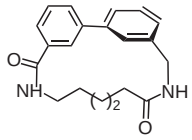
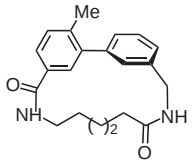
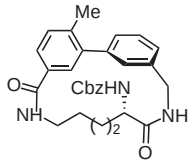
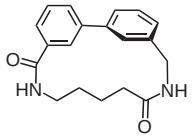
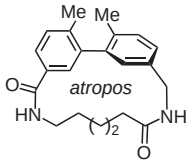
Cyclization of the substituted precursor **15c** gave lactam **18** in 57% yield. On the other hand, formation of the more strained 15-membered lactam **17c** took two days to produce the product in a reasonable 40% isolated yield (Table 1).[16] The *o*,*o*-dimethyl substituted biaryl lactam **17d** was isolated in 61% yield as a racemic mixture of stable atropenantiomers separable by chiral HPLC.[17] The observation that **17a**–**c** are all achiral suggests that the

presence of two methyl groups *ortho* to the biaryl linkage is essential to obtain stable atropisomers. The degree of stability of the axial chirality of **17d** was studied by dynamic ^{1}H NMR spectroscopy. It was found that even at 150 °C (DMSO-d_6), no signals coalesced, demonstrating the high rotational barrier of the aryl–aryl single bond.[18]

We next focused our attention on atropenantioselective lactamization[19] by using the enantiomerically enriched phosphine auxiliary, however, the cyclization of **12d** containing the optically enriched auxiliary **3** provided lactam **17d** with no detectable enantioselectivity. Most probably, no enantioselectivity was achieved because the chiral phosphine is too remote from the prochiral biaryl system to allow any stereocontrol during the macrolactamization.

Table 1 Lactamizations via Intramolecular Staudinger Ligation



Entry	Precursors	Product	Time (h)	Yield (%)
1	**12a**		18	67
2	**15a**		18	65
		17a		
3	**12b**		18	72
4	**15b**		18	60
		17b		
5	**15c**		18	57
		18		
6	**12c**		48	40
		17c		
7	**12d**		18	61
		17d		

In conclusion, the intramolecular Staudinger ligation strategy is a powerful method to ring-closed biaryl-type macrolactams. A 16-membered *o*,*o*-dimethyl substituted biaryl containing a medium-sized lactam has been prepared featuring axial chirality as the only asymmetric element. The same product was also prepared using an enantiomerically enriched P-chiral auxiliary but without any detectable asymmetric induction. Further studies to reach this ultimate goal are currently in progress.

Acknowledgment

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References and Notes

(1) (a) Schmidt, U.; Meyer, R.; Leitenberger, V.; Griesser, H.; Lieberknecht, A. *Synthesis* **1992**, 1025. (b) Schmidt, U.; Leitenberger, V.; Griesser, H.; Schmidt, J.; Meyer, R. *Synthesis* **1992**, 1248. (c) Bois-Choussy, M.; Cristau, P.; Zhu, J. *Angew. Chem. Int. Ed.* **2003**, *42*, 4238. (d) Krenitsky, P. J.; Boger, D. L. *Tetrahedron Lett.* **2003**, *44*, 4019.

(2) David, O.; Meester, W. J. N.; Bieräugel, H.; Schoemaker, H. E.; Hiemstra, H.; van Maarseveen, J. H. *Angew. Chem. Int. Ed.* **2003**, *42*, 4373.

(3) (a) Köhn, M.; Breinbauer, R. *Angew. Chem. Int. Ed.* **2004**, *43*, 3106. (b) Lin, F. L.; Hoyt, H. M.; van Halbeek, H.; Bergman, R. G.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2005**, *127*, 2686. (c) Soellner, M. B.; Nilsson, B. L.; Raines, R. T. *J. Org. Chem.* **2002**, *67*, 4993.

(4) He, Y.; Hinklin, R. J.; Chang, J.; Kiessling, L. L. *Org. Lett.* **2004**, *6*, 4479.

(5) Imamoto, T.; Watanabe, J.; Wada, Y.; Masuda, H.; Yamada, H.; Tsuruta, H.; Matsukawa, S.; Yamaguchi, K. *J. Am. Chem. Soc.* **1998**, *120*, 1635.

(6) For a similar approach using phenyl disulfide for the introduction of sulfur, see: Sugama, H.; Saito, H.; Danjo, H.; Imamoto, T. *Synthesis* **2001**, 2348.

(7) To a cooled (–78 °C) solution of sparteine (0.70 mL, 3.04 mmol) in Et_2O (10 mL), *s*-BuLi (1.30 M in cyclohexane; 2.40 mL, 3.12 mmol) was added. After stirring for 15 min, dimethylphenylphosphine borane (366 mg, 2.77 mmol) was added via cannula as a solution in Et_2O (10 mL). After 3 h at –78 °C, the solution was slowly added to a suspension of sublimed sulfur (98 mg, 3.06 mmol) in THF (40 mL), and the reaction was warmed to r.t. The resulting mixture was stirred for 16 h at r.t., then 2 N HCl (20 mL) was added and the aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash chromatography (SiO_2; PE–EtOAc, 95:5 to 9:1) to afford **3** as a pasty white solid (268 mg, 59%). $[a]_D^{25}$ –8.9 (*c* 1.6, $CHCl_3$); 92% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.71 (dd, *J* = 5.2, 14.0 Hz, 1 H), 2.52–2.43 (m, 1 H), 1.97–1.92 (m, 1 H), 1.29 (d, *J* = 10.4 Hz, 3 H), 1.27 (d, *J* = 13.6 Hz, 9 H), 0.39 (qd, *J* = 96.0, 13.0 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.03 (d, *J* = 31.2 Hz), 25.4 (d, *J* = 1.8 Hz), 15.39 (d, *J* = 26.9 Hz), 4.00 (d, *J* = 35.5 Hz). ^{31}P NMR (162 MHz, $CDCl_3$): δ = 31.41 (q, *J* = 59.0 Hz).

(8) Recrystallization to increase the ee was impossible because the product is a pasty solid.

(9) The absolute configuration of **3** was determined by comparison with the known (*R*)-*tert*-butyl(hydroxymethyl)methylphosphine borane. The alcohol was converted to the thioacetate in two steps followed by acetyl group removal to give the chiral thiol, see: Nagata, K.; Matsukawa, S.; Imamoto, T. *J. Org. Chem.* **2000**, *65*, 4185.
(10) (a) Suzuki, A. *Acc. Chem. Res.* **1982**, *15*, 178. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
(11) The boronic acid component for the Suzuki coupling from **7** was prepared by lithium–halogen exchange with *n*-BuLi and treatment with triethyl borate.
(12) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 1871.
(13) ω-Azido acids were obtained from ω-amino acids by a diazo-transfer reaction: Lundquist, J. T.; Pelletier, J. C. *Org. Lett.* **2001**, *3*, 781.
(14) For an extensive review on applications of borane-protected phosphines see: Brunel, J. M.; Faure, B.; Maffei, M. *Coord. Chem. Rev.* **1998**, *180*, 665.
(15) **Intramolecular Staudinger Ligation Reaction: General Procedure**
Precursor **12d** (132.0 mg, 0.24 mmol) and DABCO (110.0 mg, 0.98 mmol) was dissolved in THF (240 mL) and then heated at reflux. Upon completion of the reaction a sat. aq solution of NH_4Cl (excess) was added. The resulting mixture was stirred for 1 h then the aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2; PE–EtOAc, 9:1 to EtOAc) to afford **17d** as a white solid (52 mg, 61%). ^{1}H NMR (400 MHz, MeOD): δ = 7.66 (dd, *J* = 2.0, 8.0 Hz, 1 H), 7.47 (d, *J* = 2.0 Hz, 1 H), 7.37 (d, *J* = 7.6 Hz, 1 H), 7.25 (s, 1 H), 7.20–7.15 (m, 2 H), 4.74 (d, *J* = 14.4 Hz, 1 H), 3.94 (d, *J* = 14.4 Hz, 1 H), 3.71–3.78 (m, 1 H), 3.07–3.01 (m, 1 H), 2.30 (s, 3 H), 2.21 (s, 3 H), 2.27–1.99 (m, 2 H), 1.80–1.58 (m, 4 H), 1.57–1.39 (m, 2 H). ^{13}C NMR (100 MHz, MeOD): δ = 175.9, 170.9, 143.1, 143.0, 140.8, 139.7, 135.7, 134.2, 133.9, 132.2, 131.6, 130.7, 128.2, 127.5, 43.8, 41.2, 37.3, 30.5, 29.1, 27.4, 30.0, 19.6.
(16) Attempts to produce **17c** via lactamization of the pentafluorophenyl ester analogue of **12c** using an aza-Wittig reaction failed.
(17) The atropenantiomers were separated by analytical HPLC analysis using a chiral Daicel OD-H column with heptane–*i*-PrOH (98:2) as the eluent.
(18) Eshdat, L.; Shabtai, E.; Saleh, S. A.; Sternfeld, T.; Saito, M.; Okamoto, Y.; Rabinovitz, M. *J. Org. Chem.* **1999**, *64*, 353.
(19) For the first example of atropenantioselective macrocyclizations see: Islas-Gonzalez, G.; Bois-Choussy, M.; Zhu, J. *Org. Biomol. Chem.* **2003**, *1*, 30.