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Total synthesis of *rac*-longamide B

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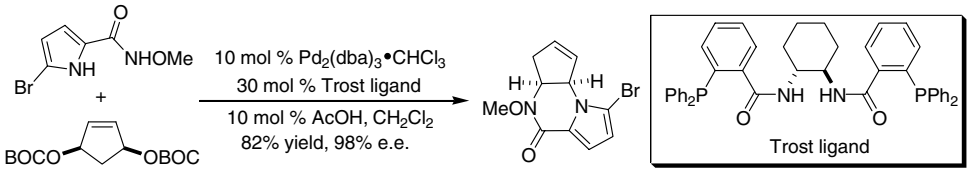
Abstract—*rac*-Longamide B has been synthesized in six-steps from known starting materials. The synthesis is highlighted by a novel palladium-catalyzed double allylic alkylation of amidopyrroles with 2-butene-1,4-di-*tert*-butyl dicarbonate.

Longamide B **1**, a brominated pyrrole alkaloid isolated from the Caribbean sponge *Angelas dispar* in 1988 by Fattorusso et al., was found to possess moderate activity against Gram-positive bacteria *Bacillus subtilis* and *Bacillus aureus* (MIC of 45 and 55 $\mu g\,mL^{-1}$, respectively).[1] Since its isolation, both racemic[2] and nonracemic[3] syntheses of **1** have been reported.

Trost et al. have recently disclosed that both pyrrole and *N*-methoxyamide are competent nucleophiles in palladium-catalyzed asymmetric allylic alkylation of BOC-activated cyclopentene-1,4-diol (Scheme 1).[4] If such a transformation can also be carried out on a similarly activated acyclic 2-butene-1,4-diol system with high regio- and stereo-chemical control, a succinct synthesis of **1** could then be realized following minimal oxidative re-adjustments (Scheme 2).

We were pleased to observe that olefin **3** did in fact undergo the desired cyclization with amidopyrrole **2** to afford **4** under Trost's reported conditions, albeit with only modest conversion (Table 1, entry 1). Unreacted **2** (42%) and N-alkylated amidopyrrole **5** (47%, isolated as mixture of *E*- and *Z*-isomers) constituted the majority of the mass balance. Unfortunately, no improvement in conversion was observed with either longer reaction times or at elevated reaction temperatures. The solvent, however, was found to have a significant influence on conversion and the best result was obtained in toluene (entry 2). Departure from bisphosphines (entries 2, 5) to a monophosphine (entry 6) also proved to be beneficial for the initial amide alkylation. Furthermore, the subsequent ring closing step was better facilitated (i.e. ratio of **4** to **5**) when ligands with Tolman's cone angle smaller than 130° were used (entries 7, 9 and 10).[5] In fact, quantitative consumption of **2** could be achieved with $P(O\text{-}i\text{-}Pr)_3$ to furnish **4** in 72% isolated yield (entry 10). It should also be noted that while only the desired regioisomer **4** was observed with amidopyrrole **2** as the nucleophile, cyclization with either *N*-benzyloxy amidopyrrole **6** or dibromopyrrole **7** afforded instead a mixture of regioisomers (Table 2).[6]

With racemic **4** in hand, we proceeded towards the completion of the total synthesis of longamide B (Scheme 3). Attempts to hydroborate the terminal olefin in **4** with



Scheme 1. Amidopyrroles as nucleophiles in Pd-catalyzed asymmetric allylic alkylation.

Keywords: Palladium-catalyzed allylic alkylation; Longamide B; Total synthesis.
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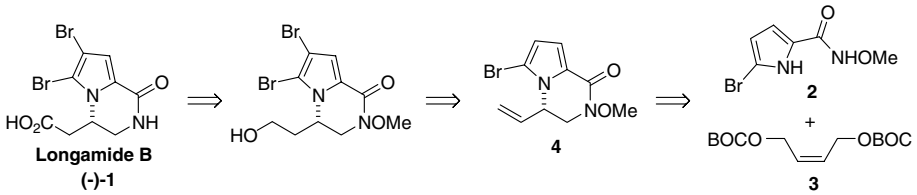
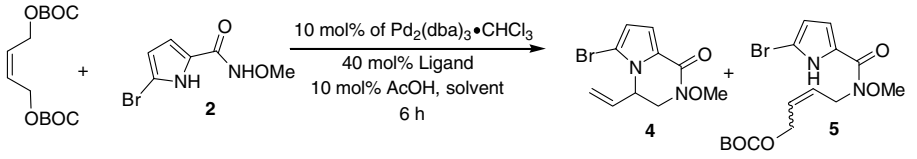
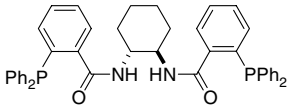
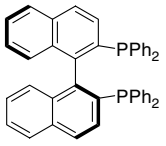


Scheme 2. Retrosynthetic analysis for longamide B.

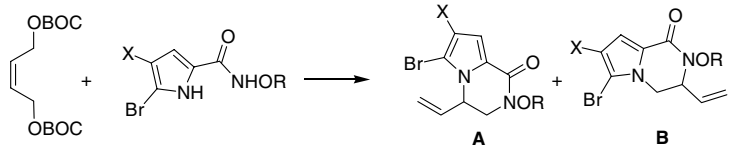
Table 1. Optimization of Pd-catalyzed allylic alkylation



Entry	Ligand	Solvent	Conversion (%)	Ratio of **4**:**5**[a,b]
1[c]		CH_2Cl_2	58	18:82
2[c]		Toluene	55	42:58
3[c]		Hexanes	<5	ND
4[c]		THF	<5	ND
5[d]		Toluene	32	16:84
6	PPh_3	Toluene	98	15:85
7	$P(OPh)_3$	Toluene	100	68:32
8	$P(O\text{-}2\text{-}MePh)_3$	Toluene	97	18:82
9	$P(O\text{-}4\text{-}MePh)_3$	Toluene	93	43:57
10	$P(O\text{-}i\text{-}Pr)_3$	Toluene	100	>95:5 (72)
11	$P(O\text{-}2,6\text{-}di\text{-}t\text{-}BuPh)_3$	Toluene	<5	ND

[a] Determined by ^1H NMR analysis of the crude reaction mixture.
[b] Isolated yield of **4** in parentheses.
[c] 30 mol % of ligand used.
[d] 20 mol % of ligand used.

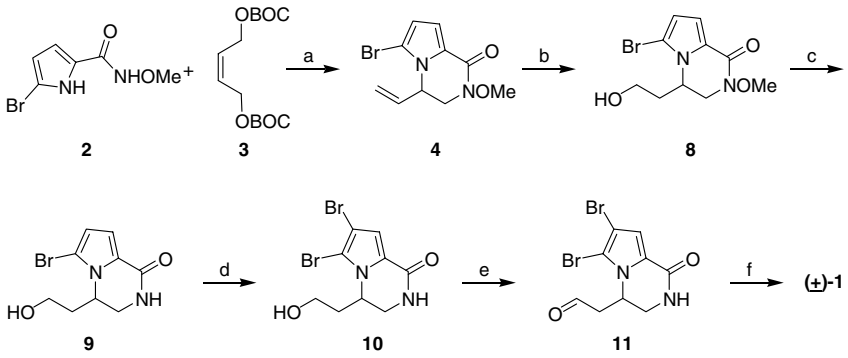
Table 2. Regioselectivity of Pd-catalyzed allylic alkylation



		Ratio of **A**:**B**[a,b]	Isolated yield of **A** (%)
R = Me, X = H	**2**	>95:5	72
R = Bn, X = H	**6**	1.44:1	46
R = Me, X = Br	**7**	1.5:1	38

[a] All reactions performed with 10 mol % of $Pd_2(dba)_3{\cdot}CHCl_3$, 40 mol % of $P(O\text{-}i\text{Pr})_3$, 10 mol % of AcOH in toluene (0.1 M) at rt for 6 h.
[b] Determined by ^1H NMR analysis of the crude reaction mixture.

classical reagents such as 9-BBN afforded exclusively the product derived from the reduction of the amide carbonyl group. This chemoselectivity issue was obviated by the use of Crudden's Ir-catalyzed hydroboration.[7] Oxidative workup with hydrogen peroxide[8] then afforded alcohol **8** in 73% isolated yield. The remaining steps to **1** proceeded uneventfully. Specifically, SmI_2-mediated reductive cleavage of the N–O bond[9] (43% yield), regioselective bromination with NBS in methanol[3,10] (83% yield) and a sequential DMP[11]-Lindgren oxidation[3,12] (87% yield over two steps) afforded longamide B as a white, crystalline solid. Spectral data of synthetic **1** thus obtained were in agreement with those in the literature.[2,3]



Scheme 3. Reagents and conditions: (a) 10 mol % $Pd_2(dba)_3{\cdot}CHCl_3$, 40 mol % P(O-*i*-Pr)$_3$, 10 mol % AcOH, toluene, rt, 6 h, 72%; (b) (i) $[Ir(COD)Cl]_2$, DPPB, pinacolborane, rt, 18 h; (ii) aq NaOH, aq H_2O_2, 0 °C–rt, 40 min, 73%; (c) SmI_2, THF, 0 °C–rt, 2 h, 43%; (d) NBS, MeOH, 0 °C, 10 h, 83%; (e) DMP, $NaHCO_3$, CH_2Cl_2, 4 h, 99%; (f) $NaClO_2$, NaH_2PO_4, 2-methylbut-2-ene, CH_2Cl_2, 12 h, 88%.

In summary, we have disclosed a six-step racemic synthesis of longamide B from known starting materials with an overall yield of 16%. The key transformation in this approach is the palladium-catalyzed double allylic alkylation of amidopyrroles with acyclic 2-butene-1,4-dicarbonates. Attempts to render this reaction enantioselective are currently being carried out in our laboratory.[13]

Acknowledgements

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References and notes

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