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Synthesis of (2*S*)-isopropyl-5-alkynylpyrimidin-2-ones: precursors of β-aminoacids

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ABSTRACT

The efficient palladium-catalyzed Suzuki-Miyaura cross-coupling reaction of (2*S*)-isopropyl-5-iodo-2,3-dihydro-4(*H*)-pyrimidin-4-one with, arylethynyl-, heteroarylethynyl-, and alkylethynyltrifluoroborate salts is reported. The standard protocol was evaluated and optimized in order to gain access to suitable precursors of enantiopure 2-substituted β-amino acids. The scope and limitations of this methodology are discussed.

1. Introduction

The cross-coupling reaction between organic halides, or related electrophiles, with organometallic reagents constitutes one of the most direct methods for the formation of C–C bonds.[1] In particular, the Suzuki-Miyaura and the Sonogashira palladium-catalyzed cross-coupling reactions of organoboron compounds with organic halides are remarkably useful tools in organic synthesis. These reactions have been extensively employed in academic laboratories as well as in pharmaceutical and other fine-chemical industries to synthesize a large variety of organic molecules.[2]

In this context, organoboron compounds are among the most widely used organometallic reagents for carbon–carbon bond formation.[3] Among the most commonly used organoboron compounds are boronic acids and boronate esters; nevertheless, these compounds present some drawbacks, including their low stability, the rather high price of some derivatives, as well as their high sensitivity to air and moisture. To solve these limitations, alternative organoboron reagents have recently been developed in the form of potassium organotrifluoroborate salts.[4] These reagents have turned out to be quite stable in the presence of air and moisture, they usually exist as crystalline solids, are easily prepared from inexpensive starting materials, and actually exhibit greater nucleophilicity.[4]

As part of their efforts to synthesize enantiomerically pure 2-substituted β-amino acids, Juaristi et al. recently reported the convenient preparation of a suitable precursor, (2*S*)-isopropyl-5-iodo-2,3-dihydro-(4*H*)-pyrimidin-4-one, (*S*)-**1**, by decarboxylation of perhydropyrimidinone-6-carboxylic acid with diacetoxyiodobenzene (DIB) and iodine in the presence of $BF_3{\cdot}Et_2O$ (Scheme 1).[5,6]

Iodopyrimidinone (*S*)-**1** was successfully employed in Sonogashira cross-coupling reactions that afforded the corresponding acetylenic intermediates, which were hydrogenated and hydrolyzed to afford highly enantioenriched α-substituted β-amino acids (Scheme 2).[6]

We report herein an alternative procedure for the synthesis of (2*S*)-isopropyl-5-alkynylpyrimidin-2-ones by means of the Suzuki-Miyaura palladium-catalyzed cross-coupling reaction between (2*S*)-isopropyl-5-iodo-2,3-dihydro-(4*H*)-pyrimidin-2-one and potassium alkynyltrifluoroborates,[7,8] using palladium acetate as the catalyst.

2. Results and discussion

The starting material (2*S*)-isopropyl-5-iodo-2,3-dihydro-(4*H*)-pyrimidinone, (*S*)-1, and alkynyltrifluoroborate salts **2a**–**r** were prepared using procedures described in the literature.[5,8] With the required reagents in hand, we proceeded to examine the cross-coupling reaction of iodoenone (*S*)-1 with phenylethynyltrifluoroborate (**2a**) as model substrates (Table 1).

Of the various palladium catalysts tested, $Pd(OAc)_2$ and $PdCl_2$ proved most satisfactory in terms of the product yield and reaction

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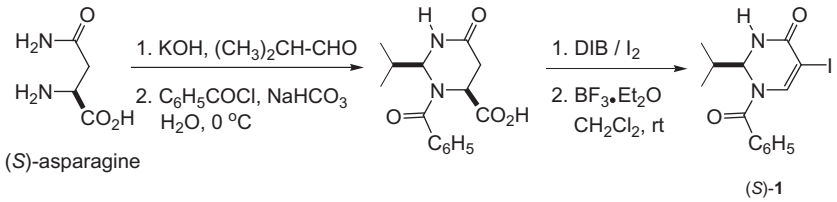
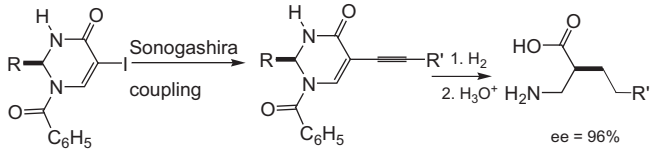
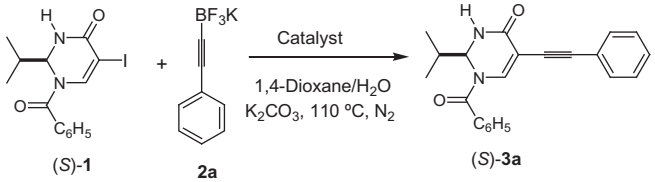


Scheme 1. Preparation of enantiopure 1-benzoyl-(2*S*)-isopropyl-5-iodo-2,3-dihydro-4(*H*)-pyrimidin-4-one (*S*)-**1**.



Scheme 2. Hydrogenation of the unsaturated C–C moieties in the Sonogashira products followed by acid hydrolysis to afford highly enantioenriched α-substituted β-amino acids.[6]

Table 1
Cross-coupling reaction of 1-benzoyl-(2*S*)-isopropyl-5-iodo-2,3-dihydro-4(*H*)-pyrimidin-4-one, (*S*)-**1**, with potassium phenyltrifluoroborate, **2a**, to afford the acetylenic derivative (*S*)-**3a**. Screening of the catalyst



Entry	Catalyst[a]	Yield[b] (%)
1	$PdCl_2$	30
2	$Pd_2(dba)_3$	22
3	$PdCl_2(dppf)\cdot CH_2Cl_2$	20
4	$Pd(OAc)_2$	45
5	No catalyst	nr
6	NiBr(dppe)	nr
7	$PdCl_2$(3-pyridyl)	20
8	$Pd(PPh_3)_4$	25

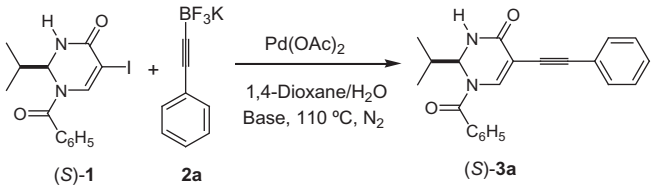
[a] 9 mol % catalyst.
[b] Isolated yield.

rate. $Pd_2(dba)_3$, $PdCl_2(dppf)\cdot CH_2Cl_2$, and $PdCl_2$(3-pyridyl) were found to be less efficient. No reaction took place in the absence of a catalyst or in the presence of NiBr(dppe).

Once $Pd(OAc)_2$ and $PdCl_2$ were identified as the best catalysts, the influence of the base employed on the cross-coupling reaction was examined. Inorganic bases, such as potassium carbonate, cesium carbonate, and sodium hydroxide (Table 2, entries 2, 4, and 6, respectively), led to a decrease in the yield of the desired product and to an increased formation of the homocoupled (diacetylenic) product in 5–10% yield. The unsatisfactory reaction yield observed with the use of NaOH as the base was a consequence of dehalogenation of (2*S*)-isopropyl-5-iodo-2,3-dihydro-4(*H*)-pyrimidin-4-one, leading to the corresponding dehalogenated pyrimidinone. Although the reaction yield remained low in the presence of tertiary amines such as triethylamine (TEA) or diisopropylethylamine (DIPEA) (Table 2, entries 1 and 3, respectively), with the secondary amine diisopropylamine as base, the desired product was formed in 53% yield (Table 2, entry 5).

The influence of the reaction solvent was also investigated. No reaction occurred in methanol, water, α,α,α-trifluorotoluene, or a mixture of H_2O–tetrabutylammonium hydroxide, using $Pd(OAc)_2$ as the catalyst and diisopropylamine as the base. The use of an

Table 2
Cross-coupling reaction of 1-benzoyl-(2*S*)-isopropyl-5-iodo-2,3-dihydro-4(*H*)-pyrimidin-4-one, (*S*)-**1**, with potassium phenyltrifluoroborate, **2a**, to afford the acetylenic derivative (*S*)-**3a**. Screening of the base



Entry	Base[a]	Yield[b] (%)
1	Et_3N	44
2	K_2CO_3	45
3	DIPEA	39
4	Cs_2CO_3	32
5	$(iPr)_2NH$	53
6	NaOH	22

[a] Two equivalents of base were employed.
[b] Isolated yield.

aqueous mixture of THF/H_2O (5:1) led to 12% yield. The highest yield was achieved in acetonitrile and 1,4-dioxane/H_2O (3:1) as the solvent, affording the cross-coupled product in 53% yield.

Catalyst loading was also studied, indicating that the use of 5 mol % of $Pd(OAc)_2$ was most effective, affording 73% yield of the desired cross-coupled product in addition to a relatively small amount (10%) of the homocoupled product. In contrast, when the catalyst loading was increased to 9 and 15 mol %, reaction yields dropped considerably (14% and 29%, respectively).

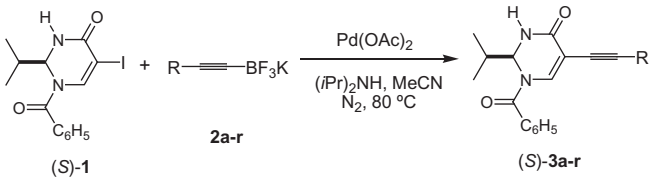
Finally, the potential effect of additives was examined. For this, several additives including AgOAc and Ag_2O were tested. However, no reaction was observed under these conditions, probably due to palladium catalyst poisoning by silver, which can oxidize Pd^0 to Pd^2. On the other hand, the phosphine additives Ph_3P, PCy_3, and S-Phos led to moderate reaction yields (59%, 63%, and 61%, respectively).

Thus, it was deemed that the optimum conditions[11] for the cross-coupling reaction of interest involve the use of (2*S*)-isopropyl-5-iodopyrimidinone [(*S*)-**1**, 1.0 equiv), potassium arylethynyl-, and heteroarylethynyltrifluoro-borate salt **2a–r** (1.2 equiv), $Pd(OAc)_2$ (5 mol %), and $(iPr)_2NH$ (3.0 equiv) in an acetonitrile solvent at reflux temperature (Table 3).

It was observed that electron-deficient alkenes give either low yields (Table 3, substrates **2b**, **2f**, **2j**, **2l,** and **2p**) or not react to form the coupled product (Table 3, entries **2d**, **2g–i,** and **2r**) probably due to the low reactivity of these salts. On the other hand, electron-rich and electron-neutral alkynes gave moderate to good yields of the corresponding coupled products.

In order to gain further insight into the reaction of interest, in situ ReactIR technology[9,10] was employed to monitor the conversion of (2*S*)-isopropyl-5-iodo-2,3-dihydro-(4*H*)-pyrimidin-2-one, (*S*)-**1**, to the corresponding 5-phenylalkynylpyrimidinone **3a**. As can been seen in Figure 1, following addition of phenyl alkynyltrifluoroborate salt to the iodopyrimidinone, a sharp peak appeared

Table 3
$Pd(OAc)_2$ catalyzed Suzuki-Miyaura cross-coupling reaction of 1-benzoyl-(2*S*) isopropyl-5-iodo-2,3-dihydro-4(*H*)-pyrimidin-4-one, (*S*)-**1**, with potassium akynyltrifluoroborates, **2a**–**r**, to afford the acetylenic derivatives (*S*)-**3a**–**r**



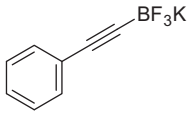
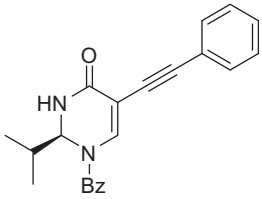
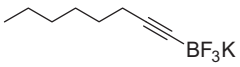
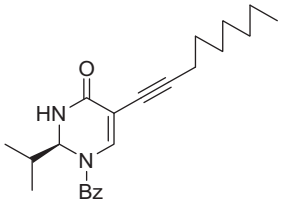
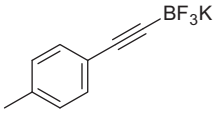
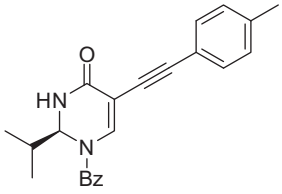
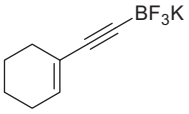
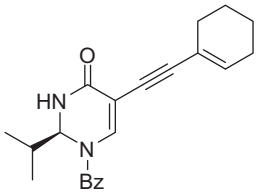
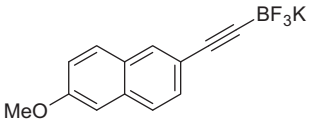
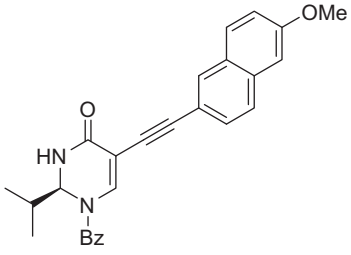
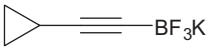
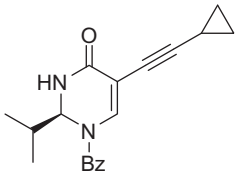
Entry	ArBF3K (**2**)[a]	Reaction time (h)	Product (**3**)	Yield (%)[b]
1	 **2a**	3	 **3a**	73
2	 **2b**	24	 **3b**	25[b]
3	 **2c**	3	 **3c**	65
4	 **2d**	24	 **3d**	nr
5	 **2e**	3	 **3e**	85
6	 **2f**	24	 **3f**	15[b]

Table 3 (*continued*)

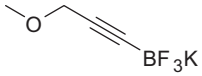
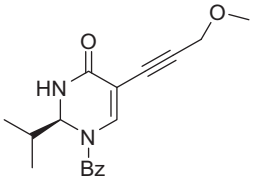
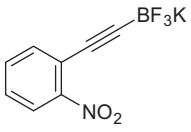
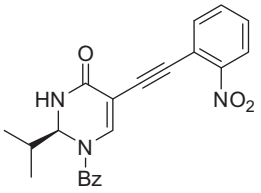
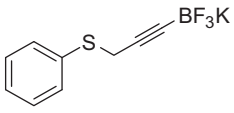
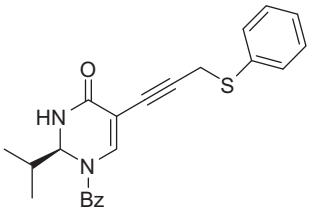
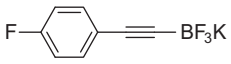
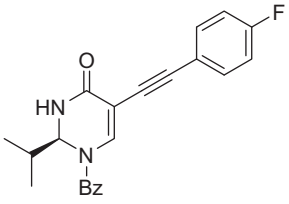
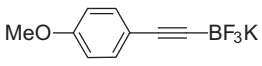
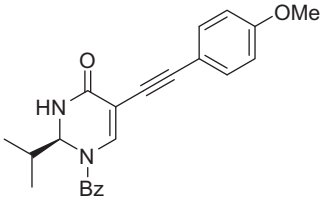
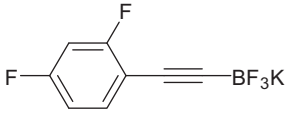
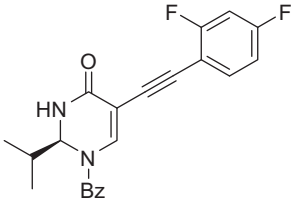
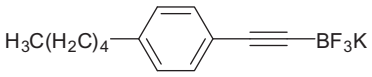
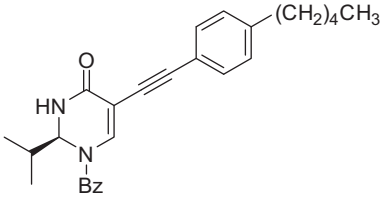
Entry	ArBF3K (**2**)[a]	Reaction time (h)	Product (**3**)	Yield (%)[b]
7	 **2g**	3	 **3g**	nr
8	 **2h**	24	 **3h**	nr
9	 **2i**	24	 **3i**	nr
10	 **2j**	3	 **3j**	35
11	 **2k**	2	 **3k**	65
12	 **2l**	3	 **3l**	30
13	 **2m**	3	 **3m**	60

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Table 3 (*continued*)

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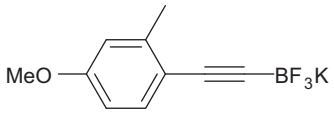
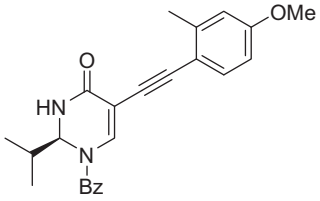
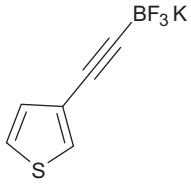
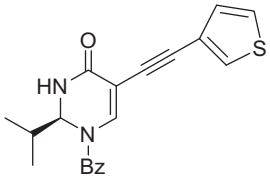
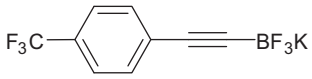
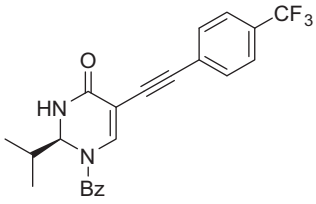
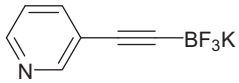
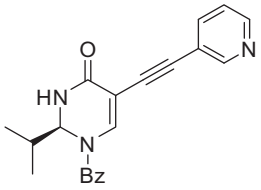
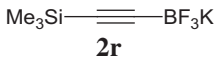
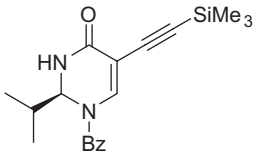
14	 **2n**	2	 **2n**	87
15	 **2o**	3	 **3o**	78
16	 **2p**	3	 **3p**	15
17	 **2q**	3	 **3q**	92
18	 **2r**	24	 **3r**	nr

[a] Isolated yields.
[b] GC-MS yield.

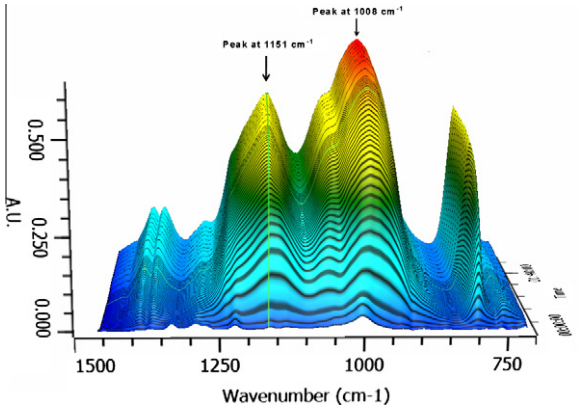


Figure 1. Reaction course observed by in situ IR spectroscopy (3D plots).

at 1151 cm^{-1}. The intensity of this peak gradually decreased and a new peak appeared at 1008 cm^{-1}. It was deduced that the reaction presented an induction period of approximately 15 min, associated with the formation of palladium(0) (1151 cm^{-1} peak). After this time, cross-coupling took place quickly, leading to the formation of the product (1008 cm^{-1} peak), with up to 95% conversion in 50 min. The rest of the reaction time was consumed in the conversion of the remaining 5% (Fig. 1).

3. Conclusion

In summary, we have developed an efficient methodology for the introduction of arylacetylenes at the C(5) position of pyrimidin-4-ones using Suzuki-Miyaura cross-coupling protocols. This reaction system tolerates various functional groups at the aromatic rings of aryl alkynyltrifluoroborate salts. Conversion of the acetylenic

products to enantiomerically pure or enantioenriched α-alkyl β-amino acids is possible via a hydrogenation-hydrolysis protocol.[6]

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures, spectral data and copies of spectra for all compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.12.087.

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11. *Representative procedure for the Suzuki-Miyaura cross-coupling reaction of iodenone with alkynyltrifluoroborate salts*: To a solution of potassium alkynyltrifluoroborate (1.2 mmol), iodopyrimidinone (1.0 mmol), $Pd(OAc)_2$ (5 mmol %, 11.2 mg), $(iPr)_2NH$ (2.0 mmol, 202.4 mg, 0.3 mL) and 10 mL of degassed acetonitrile were added. The reaction was heated to 80 °C and monitored by TLC and/or GC. Upon completion, the reaction mixture was cooled to room temperature and was then transferred to an extraction funnel and extracted with three (3 × 20 mL) portions of ethyl acetate, and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude 5-alkynylpyrimidinone was purified by flash chromatography (hexanes/EtOAc, 1:1) to afford the desired product as a brown solid (see Table 3).
(S)-1-Benzoyl-2-isopropyl-5-(phenylethynyl)-2,3-dihydropyrimidin-4-(1H)-one (**3a**). Isolated yield 78%, brown solid, mp = 248.2–249.5 °C (dec); literature[6] mp = 249–251 °C (dec). $[\alpha]_D^{25}$ +659.0 (*c* 1, $CHCl_3$); literature[6] $[\alpha]_D^{20}$ +652.8 (*c* 1, $CHCl_3$). ^1H RMN (300 MHz, $CDCl_3$) δ (ppm) 7.45–7.59 (m, 7H); 7.27–7.29 (m, 4H); 6.74 (d, *J* = 3.96 Hz, 1H); 5.66 (t, *J* = 6.2 Hz, 1H); 2.36–2.43 (m, 1H); 1.08 (d, *J* = 6.7 Hz, 3H); 0.99 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 168.2; 162.1; 140.7; 132.4; 131.9; 131.6 (2C); 129.0 (2C); 128.6; 128.4 (2C); 128.2 (2C); 122.7; 101.3; 92.4; 82.1; 69.4; 33.0; 18.3; 17.5. MS: *m*/*z* (%): 344 (4, M+); 239 (5); 274 (5); 207 (5); 105 (100); 77 (50); 71 (37); 43 (61).