ORGANIC LETTERS

2011
Vol. 13, No. 23
6252–6255

Allylic Substitution on Cyclopentene and -hexene Rings with Alkynylcopper Reagents

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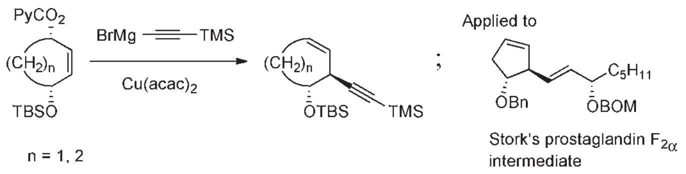
Received October 10, 2011

ABSTRACT



Substitution of cyclic allylic picolinates with a reagent derived from TMS-C$\equiv$CMgBr and a copper salt was investigated. Although the previous type of reagent (TMSC$\equiv$CMgBr and CuBr·Me$_2$S) developed for linear allylic picolinates was less product selective and regioselective, the Cu(acac)$_2$-derived reagent was highly selective (94–95%) to afford the S$_N$2′ product in good yields. As an application, several C–C bond formations at the acetylenic carbon and the synthesis of the PG intermediate were studied with success.

Recently, we reported the substitution of linear allylic picolinates **1** (Figure 1) with alkynyl copper reagents derived from RC$\equiv$CMgBr and CuBr·Me$_2$S to afford anti S$_N$2′ products with high regio- and stereoselectivity.[1] The chelation-induced reactivity of the picolinoxy group (2-PyCO$_2$) as a leaving group compensates for the low nucleophilicity of the alkynyl copper.[2] Subsequently, the substitution was applied to γ-aryl allylic picolinates **2** to find an acceleration effect of CH$_2$Cl$_2$ on the substitution, affording the S$_N$2-type products regioselectively due to the conjugation of the allylic olefin to the aryl group.[3] We then extended our investigations to cyclic allylic picolinates such as **3** and **4** to further explore the potential of the method in organic synthesis. We anticipated that the ring conformation may restrict the necessary overlap of the C–OCOPy σ-bond and π-orbital in the transition state, resulting in lower reactivity and/or regioselectivity. In the substitution of **3a** (R = TBS) under the conditions established for **1** and **2**, this was indeed found to be the case. Fortunately, further study led us to find a powerful reagent derived from Cu(acac)$_2$. Herein, we present the results of these investigations and the synthetic utility of the reaction products.

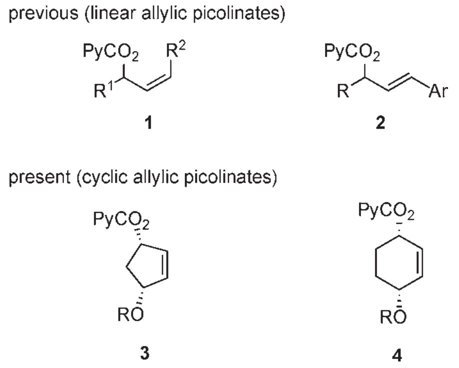


Figure 1. Allylic picolinates used previously and presently (Py = 2-pyridyl).

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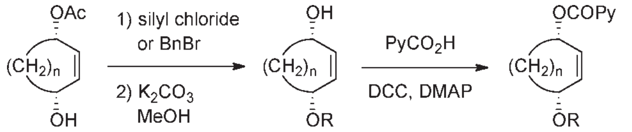
Racemic allylic picolinates **3a**–**e** and **4a** were prepared according to the standard method[4] (Scheme 1), while (1*S*,4*R*)-**3a** of >99% ee was synthesized from (1*R*,4*S*)-**5**[5] according to the literature method[6] and used for the synthesis of the prostaglandin intermediate (Scheme 3). In addition, TES, TBDPS, Bn, and Ac congeners **3b**–**e** were synthesized similarly.

Scheme 1. Synthesis of Allylic Substrates **3a**–**e** and **4a**[a]



5, n = 1
7, n = 2

6a–e, n = 1
8a, n = 2

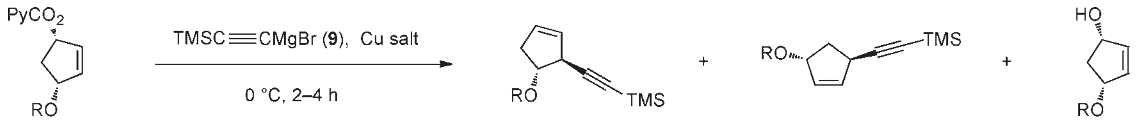
3a–e, n = 1
4a, n = 2

[a] R: **a**, TBS; **b**, TES; **c**, TBDPS; **d**, Bn; **e**, Ac.

Substitution of the TBS derivative **3a** was investigated using copper reagents derived from 3 or 6 equiv of TMSC≡CMgBr (**9**) and 1 or 2 equiv of CuX at 0 °C for 2–4 h, and the results are summarized in entries 1–11 of Table 1, while those of **3b**–**e** are presented in entries 12–15. The product ratio of **10**/**11**/**6**/**3** was calculated by ^{1}H NMR spectroscopy of the crude product and used to determine the regioselectivity (**10**/**11**). Initially, the original conditions[1] established for the picolinates **1** were applied to **3a** by using a copper reagent derived from **9** (3 equiv) and $CuBr\cdot Me_2S$ (1 equiv) in THF at 0 °C. The reaction proceeded slowly to afford the S_N2' product **10a**[7] with somewhat low regioselectivity and with competitive production of alcohol **6a** (entry 1). We surmised that the carbonyl carbon of the picolinate that remained in the solution without forming the σ-allyl copper intermediate was attacked by the reagent to produce alcohol **6** and that the slow reaction allowed time for the conversion of σ-allyl copper to π-allyl copper prior to the substitution. Such a σ- to π-transition has previously been discussed by Goering to explain the low selectivity.[8] Next, the forcing solvent system (CH_2Cl_2/THF) developed for picolinates **2**[3] was applied to improve product selectivity to a certain extent (entry 2). By using a larger quantity of the reagent, the formation of byproduct **6a** was considerably reduced, whereas the regioselectivity was moderately improved to 82% (entry 3). The level of selectivity observed was consistent with the above considerations.

Further investigation revealed that different compositions of **9**/$CuBr\cdot Me_2S$ in CH_2Cl_2/THF were marginally reactive (entries 4, 5), whereas the use of mixed solvents of THF with Et_2O, toluene, or hexane resulted in ca. 65% regioselectivity (data not shown). Use of reagents based on CuX (X = Cl, Br) in larger quantities (6 equiv of **9** and 2 equiv of CuX) showed 85% regioselectivity (entry 6 and footnote c attached to entry 3), whereas other reagents derived from CuX (X = I, CN) were less productive (entries 7, 8). Pleasingly, the $Cu(acac)_2$-based reagent even in a smaller quantity (3 equiv of **9** and 1 equiv of $Cu(acac)_2$) produced **10a** with 86% regioselectivity and with mitigation of **6a** (entry 9). This selectivity was higher than that of entry 2. We then increased the reagent quantity on the basis

Table 1. Reaction of **3** with Copper Reagents Derived from Acetylene **9** and Copper Salts of CuX and CuX_2 Types



3 (racemic)

10

11

6

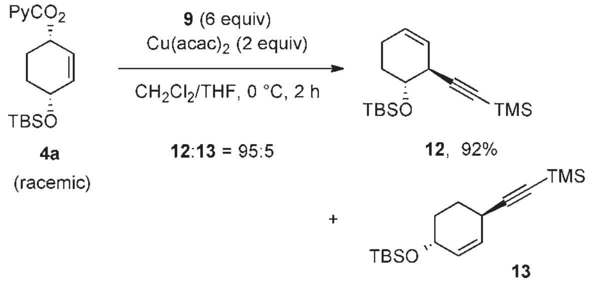
entry	R[a]	series[a]	**9** (equiv)	Cu salt (equiv)	**9**/Cu	solvent (ratio)	**10**:**11**:**6**:**3**[b]	**10**:**11**[b]	isolated yield[c]
1	TBS	**a**	3	$CuBr\cdot Me_2S$ (1)	3:1	THF	49:13:24:14	79:21	nd
2	TBS	**a**	3	$CuBr\cdot Me_2S$ (1)	3:1	CH_2Cl_2/THF (4:1)	63:18:15:4	78:22	nd
3[d]	TBS	**a**	6	$CuBr\cdot Me_2S$ (2)	3:1	CH_2Cl_2/THF (2:1)	81:18:1:0	82:18	nd
4	TBS	**a**	2	$CuBr\cdot Me_2S$ (1)	2:1	CH_2Cl_2/THF (6:1)	15:0:46:39	nd	nd
5	TBS	**a**	3	$CuBr\cdot Me_2S$ (3)	1:1	CH_2Cl_2/THF (4:1)	0:0:0:100	–	–
6[e]	TBS	**a**	6	CuCl (2)	3:1	CH_2Cl_2/THF (2:1)	80:14:6:0	85:15	nd
7	TBS	**a**	3	CuI (1)	3:1	CH_2Cl_2/THF (4:1)	0:0:78:22	–	–
8	TBS	**a**	3	CuCN (1)	3:1	CH_2Cl_2/THF (4:1)	34:3:29:34	92:8	nd
9	TBS	**a**	3	$Cu(acac)_2$ (1)	3:1	CH_2Cl_2/THF (4:1)	81:13:5:1	86:14	nd
10	**TBS**	**a**	**6**	**$Cu(acac)_2$ (2)**	**3:1**	**CH_2Cl_2/THF (2:1)**	**92:6:2:0**	**94:6**	**91**
11	TBS	**a**	4	$Cu(acac)_2$ (2)	2:1	CH_2Cl_2/THF (6:1)	70:20:10:0	78:22	nd
12	**TES**	**b**	**6**	**$Cu(acac)_2$ (2)**	**3:1**	**CH_2Cl_2/THF (2:1)**	**90:6:4:0**	**94:6**	**83**
13	TBDPS	**c**	6	$Cu(acac)_2$ (2)	3:1	CH_2Cl_2/THF (2:1)	69:21:10:0	77:23	nd
14	Bn	**d**	6	$Cu(acac)_2$ (2)	3:1	CH_2Cl_2/THF (2:1)	76:24:0:0	76:24	nd
15	Ac	**e**	6	$Cu(acac)_2$ (2)	3:1	CH_2Cl_2/THF (2:1)	nd[f]	–	–

[a] For compounds **3**, **10**, **11**, and **6**. [b] Determined by ^{1}H NMR spectroscopy. [c] Of **10** and **11**. nd: Not determined. [d] The reagent derived from **9** (6 equiv) and CuBr (2 equiv) gave a product ratio of 80:14:6:0. [e] Use of a half quantity of the reagent gave a product ratio of 30:13:28:29. [f] Complex mixture.

of the improved results of entry 3 to attain 94% regioselectivity, and **10a** was isolated in 91% yield (entry 10). Later, entry 10 was scaled up (40 mg to 1.5 g) in the synthetic application to find similar efficiency. The copper reagent with a different ratio (**9**/Cu(acac)$_2$ = 2:1) was less selective (entry 11). Reagents prepared from Cu(OAc) and Cu(OAc)$_2$ showed no reactivity toward the substitution (data not shown).

To clarify the influence of the protective group in **3**, picolinates **10b**−**e** were subjected to the substitution under the optimized conditions (entry 10). The TES ether **3b** showed similar selectivity and reactivity (entry 12), whereas TBDPS and Bn derivatives **3c**,**d** produced **10c**,**d** less efficiently than **3a**,**b** (entries 13,14). Acetate **3e** gave a mixture of unidentified products (entry 15).

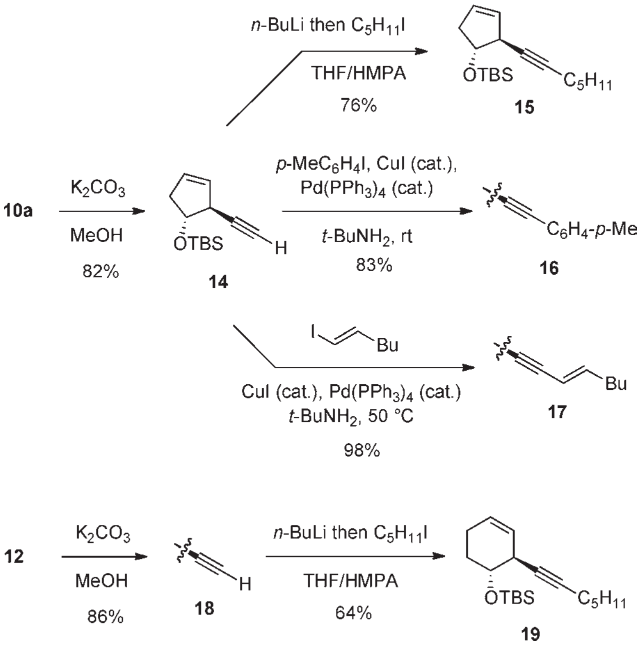
We then applied the method to the cyclohexene derivative **4a**, which upon reaction with **9**/Cu(acac)$_2$ in CH_2Cl_2/THF at 0 °C for 2 h afforded the S_N2' product **12** with high product selectivity and regioselectivity and in good yield (eq 1).



(1)

To investigate the synthetic potential of this substitution, the transformation of **10a** shown in Scheme 2 was investigated.[9] Desilylation with K_2CO_3 in MeOH afforded **14** in 82% yield. Alkylation of **14** with $C_5H_{11}I$ proceeded cleanly to furnish **15** in 76% yield, while Sonogashira coupling with *p*-MeC_6H_4I and (*E*)-I-CH=CH-Bu delivered **16** and **17** in good yields. During the transformations neither allene nor diene byproducts were formed. Previously, compounds similar to **15**−**17** have been synthesized by the reaction of cyclopentadiene monoepoxide with acetylides.[10] However, the yields and selectivity are quite low and, in addition, the monoepoxide is chemically highly unstable. Thus, the present method is advantageous with respect to selectivity and yield.

Scheme 2. Conversion of the TMS Acetylenes



Similarly, the TMS group was removed from **12** and the resulting acetylene **18** was converted to alkylacetylene **19** in 55% yield over two steps (Scheme 2). A compound similar to **19** was once synthesized by the epoxide opening of cyclohexadiene monoepoxide and lithium acetylides.[11]

We then studied the synthesis of the $PGF_{2\alpha}$ intermediate **26**, which was previously synthesized by Stork as a diastereomeric mixture via the epoxide ring opening of racemic cyclopentadiene monoepoxide with the lithium acetylide generated from the propargylic alcohol derivative.[10a] Probably due to the reasons mentioned above and/or lack of an efficient method for obtaining the optically active epoxide with a reasonable yield and high % ee,[12] the intermediate has been left obscurely in the community of

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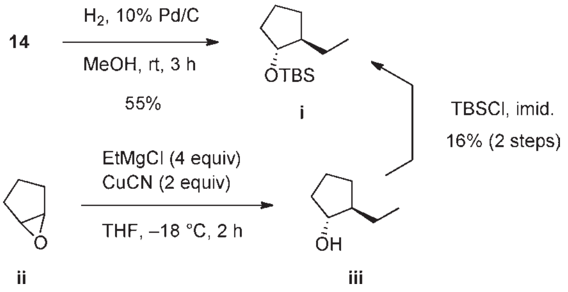
(7) The trans stereochemsitry of **10a** was determined by converting to **14** (Scheme 2) and then to **i**, which was identical by ^1H NMR spectroscopy with that derived from known alcohol **iii**.[7a,b] The low yields were probably due to high volatility. (a) Ito, M.; Matsuumi, M.; Murugesh, M. G.; Kobayashi, Y. *J. Org. Chem.* **2001**, *66*, 5881–5889. (b) Schneider, C.; Brauner, J. *Eur. J. Org. Chem.* **2001**, 4445–4450.



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(9) Allylic substitution of **3a** with RC≡CMgBr (R = C_5H_{11}, Ph) and Cu(acac)$_2$ was unsuccessful.

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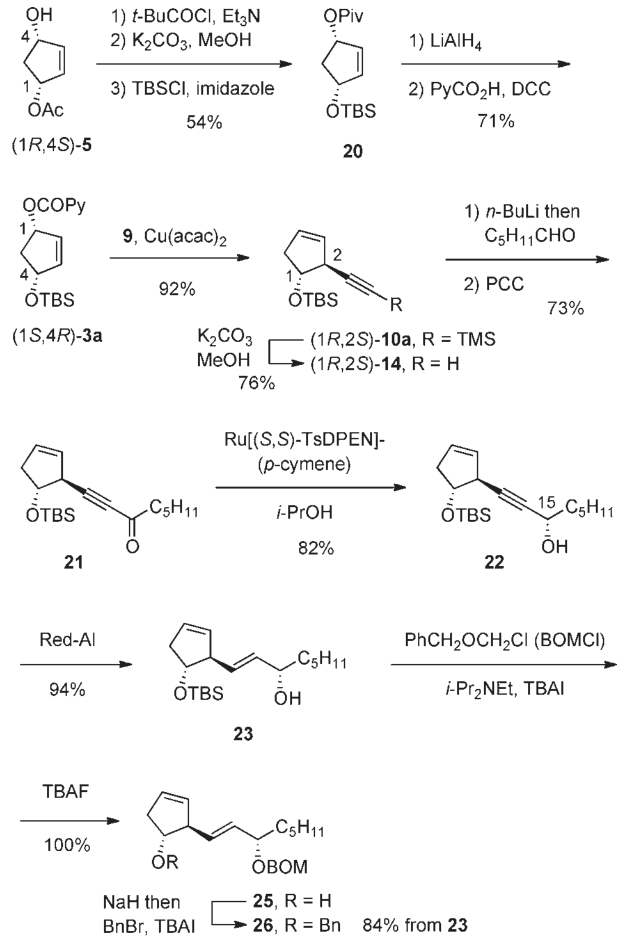
Scheme 3. Synthesis of the $PGF_{2\alpha}$ Intermediate



the prostaglandin synthesis. As shown in Scheme 3, optically active picolinate (1*S*,4*R*)-**3a** was synthesized from (1*R*,4*S*)-**5** through **20**[4d,6] and subjected to the allylic substitution with the copper reagent (**9**/$Cu(acac)_2$) under the conditions given in entry 10, Table 1. Although the reaction scale (1.5 g of (1*S*,4*R*)-**3a**) was 40 times greater than that of entry 10, the same efficiency as in the production of (1*R*,2*S*)-**10a** was attained, and subsequent desilylation afforded (1*R*,2*S*)-**14** in 76% yield. Transformation of the acetylene to ketone **21** was achieved in 73% yield by addition of the acetylene to $C_5H_{11}CHO$ and subsequent oxidation with PCC.[13] Asymmetric reduction of **21** with Ru[(*S*,*S*)-TsDPEN](*p*-cymene)[14] in *i*-PrOH gave alcohol **22** in 82% yield. Unfortunately, determination of the stereoselectivity at the newly formed chiral center by ^1H and ^{13}C NMR spectroscopy was unsuccessful due to complete overlap of the resonances for **22** and the C15-diastereomer. We then transformed the alcohol to BOM ether **24** by Red-Al reduction of the acetylene to the trans olefin **23** followed by protection of C15–OH. At this stage the diastereomer-free purity of **24** was determined by ^1H and ^{13}C NMR spectroscopy. Finally, the TBS protective group was replaced by the Bn group to afford **26** in 84% yield from alcohol **23**.[15]

In summary, a new reagent system derived from TMS-C≡CMgBr (**9**) and $Cu(acac)_2$ in CH_2Cl_2/THF was developed for the substitution of cyclic allylic picolinates **3a**,**b** and **4a**, producing the S_N2' products **10a**,**b** and **12** with high regioselectivity (94–95%) and high yield (83–92%). Alkylation and coupling reactions at the acetylenic carbon were examined to investigate the synthetic potential, culminating in the synthesis of the Stork's PG intermediate in an optically active form. The role of $Cu(acac)_2$ in achieving high selectivity is under investigation.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan.

Supporting Information Available. Experimental procedures and spectral data of compounds described herein. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Our attempted conversion of the acetylenes (1*R*,2*S*)-**10** and -**14** with $C_5H_{11}COCl$ to ketone **21** was unsuccessful.

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(15) Synthesis of the structurally similar compounds: (a) References 10a and 10c. (b) Tuetlng, D. R.; Echavarren, A. M.; Stille, J. K. *Tetrahedron* **1989**, *45*, 979–992. (c) Whitesell, J. K.; Carpenter, J. F.; Yaser, H. K.; Machajewski, T. *J. Am. Chem. Soc.* **1990**, *112*, 7653–7659.