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S_N2-Selective allylic substitution of chiral γ-aryl substituted allylic picolinates with alkynylcopper reagents

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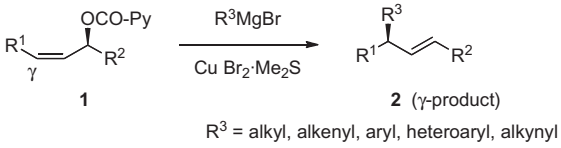
ABSTRACT

Substitution of γ-aryl secondary allylic picolinates with alkynyl copper reagents was studied. The copper reagent, prepared from TMSC≡CMgBr and CuBr·Me_2S in 2:1, was subjected to substitution of the picolinate derived from (*E*)-3-phenyl-1-methyl-2-propenyl alcohol at 0 °C for 1 h in THF to produce a mixture of α- and γ-products and the alcohol in 67:20:13, while the reagent in 3 or 4:1 ratio gave the α-product with 90–91% selectivity. On the contrary, reaction in CH_2Cl_2–THF (6–8:1) at 0 °C for 1 h furnished the α-product with 99% regioselectivity. The effect of CH_2Cl_2 was also demonstrated with eight more examples. Furthermore, 99% inversion was determined by transformation to the literature compound and by chiral HPLC.

γ-Aryl secondary allylic esters have been substrates for allylic substitution because the conjugation between the aryl and the allylic olefin moieties gives an opportunity to study the influence of the conjugation on the regio- and stereoselectivities.[1] In the substitution using alkyl and aryl copper reagents, either of the α and γ carbons has been subjected to the reaction,[2,3] and the inversion is the major stereochemical course for the reaction at the α carbon,[4] though the stereoselectivity has been varied depending on the organocopper species, steric factor, and other reaction conditions. Quite recently, the selectivity with alkyl copper reagents was improved by us to high levels.[5]

Recently, we have established substitution of secondary γ-*alkyl* allylic esters with organocopper reagents using picolinates as allylic esters to furnish anti S_N2' products with high levels of regio- and stereoselectivities (the latter being assessed by chirality transfer)[6] (Eq. (1)).[7] The method is compatible with a wide variety of alkyl, alkenyl, aryl, and heteroaryl copper reagents. Furthermore, we succeeded in picolinate-allylation with alkynyl copper reagents,[8] which are probably among the least nucleophilic reagents on the basis of the reactivity for 1,4-addition to conjugated enones. Apparently, the high potency of the picolinoxy group as the leaving group compensates the low nucleophilicity of the alkynyl reagents. With these findings in mind, we focused our attention to substitution of γ-*aryl* allylic picolinates with alkynyl copper reagents (Eq. (2)). Although α regioselection and inversion of the stereochemistry at the α carbon were expected on the basis of the results by us[5] and other groups,[4] the regio- and product-selectivities we have examined were somewhat lower than those for the γ-*alkyl* allylic picolinates. Fortunately, we found that several solvents increase the regioselectivity and stereoselectivity to high levels. Herein, we report these findings.

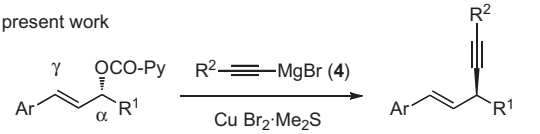
previous work



1 **2** (γ-product) (1)

R^3 = alkyl, alkenyl, aryl, heteroaryl, alkynyl

present work



3 **5** (α-product) (2)

In relation to the present investigation, Chen and Deng disclosed a nickel-catalyzed substitution of a γ-*aryl* secondary allylic carbonate with alkynyl borates to produce the α-products.[9] Despite the high regioselectivity, chiral induction of the reaction with a chiral nickel catalyst was 13% ee, whereas stereoselectivity using any optically active carbonate was not investigated.

Initially, two types of copper reagents with the established compositions were investigated. In brief, magnesium reagent **4A** (R^2 = TMS), freshly prepared from TMSC≡CH and *i*-PrMgBr in THF (rt, 2 h), was added to an ice-cold suspension of CuBr·Me_2S in THF in a 1:1 ratio of **4A**/Cu, and the mixture was stirred at

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0 °C for 30 min to produce TMSC≡CCu·$MgBr_2$, which was subjected to reaction of **3A** at 0 °C in THF. The reaction was completed within 1 h, but afforded a mixture of α and γ products (**5a** and **6a**) and alcohol **7** (Table 1, entry 1). Next examined was $(TMSC{\equiv}C)_2CuMgBr{\cdot}MgBr_2$, which produced the mixture in a similar ratio (entry 2). The observed regioselectivity indicates that α regioselection by the Ph group is slightly predominant over the γ selection inherent in the γ-alkyl picolinates. We then studied reagents derived from **4A**/Cu in other ratios of 3:1 and 4:1, both of which showed higher α regio- and product-selectivities for **5a** (entries 3 and 4).

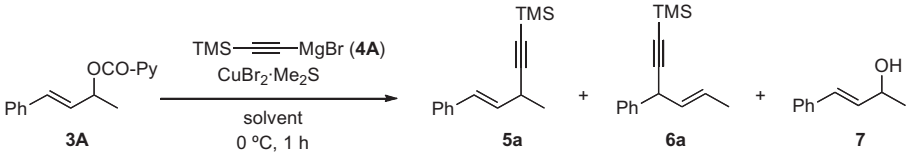
Although the improved regio- and product-selectivities are probably in good levels (entries 3 and 4), we continued investigation to attain higher selectivity, which was realized by using a mixed solvent of CH_2Cl_2 and THF.[10,11] Thus, a THF solution of **4A** (3–4 equiv) was added to a suspension of CuBr·Me_2S (1 equiv) in CH_2Cl_2 at 0 °C and, after 30 min, picolinate **3A** was added to the mixture. The reaction in CH_2Cl_2–THF (6–8:1) was completed within 1 h at 0 °C to afford α-product **5a** with high selectivity and in 85% isolated yield (entry 5). Use of $(CH_2Cl)_2$, PhCl, and hexane as solvents was also effective, giving **5a** with high selectivity (entries 6, 9, and 11), whereas the selectivity obtained from the reaction in EtBr was comparable to that recorded in THF (entry 10 vs entry 3). Reactions examined in $CHCl_3$ and in CCl_4 produced alcohol **7** (entries 7 and 8). Other copper sources such as CuBr and CuCN were also effective (entries 13 and 15 vs entries 12 and 14). In conclusion, we succeeded in the production of **5a** with >96% selectivity in entries 5, 6, 9, 11, 13, and 15. On the basis of these results and an additional result[12] as well as handling, we decided to apply the protocol using CuBr·Me_2S in CH_2Cl_2–THF to other substrates/alkynyl copper reagents and the results are described in the next paragraphs.

Picolinate **3B** (Ar = *p*-MeC_6H_4) upon reaction with **4A**-based copper reagent (**4A**/CuBr·Me_2S = 3:1) in CH_2Cl_2–THF gave **5b** with higher efficiency in yield and selectivity than that in THF (Table 2, entry 2 vs entry 1). Picolinate **3C** with the long pentyl group participated in the reaction uneventfully, producing the expected product **5c** efficiently (entry 4 vs entry 3). Similarly, picolinate **3D** (Ar = *p*-FC_6H_4) furnished **5d** regioselectively (entry 5). Alkynyl copper reagent with the *p*-MeC_6H_5 group, which was prepared from **4B** and CuBr·Me_2 as a typical example of substituted acetylenes, afforded **5e**, **5f**, and **5g** in reactions with **3A**, **3B**, and **3C**, respectively (entries 7–9). The efficiency for the reaction of **3A** in CH_2Cl_2–THF was higher than that observed in THF (entry 6). High regioselectivities were also found in entries 10 and 11. Thus, we attained high levels of regio- and product-selectivity with the copper reagents derived from $R^2C{\equiv}CMgBr$ (**4**) and CuBr·Me_2S in the 3–4:1 ratios in CH_2Cl_2–THF. Furthermore, these results indicate that the selectivity is irrespective of the electronic nature of Ar in the picolinates and of R^2 in the alkynyl reagents.

For the determination of stereoselectivity and the stereochemical outcome of the reaction, (*R*)-**3A**, -**3B**, and -**3D** were synthesized from alcohol **7** (99% ee) as shown in Scheme 1.[13] In brief, the Sonogashira coupling of **7** with PhI under the standard conditions gave **8** in good yield. The acetylene part of **8** was reduced to *trans* olefin and the hydroxyl group was esterified with Py-CO_2H using DCC to afford (*R*)-**3A** in 68% yield from **7**. Enantiomeric excess (ee) of (*R*)-**3A** was 99% by chiral HPLC analysis (Chiralcel OD-H, hexane/*i*-PrOH = 96:4, 0.3 mL/min, rt, t_R/min = 65.7 (*R*-isomer), 72.9 (*S*-isomer)). Similarly, alcohol **7** was converted to (*R*)-**3B** (87% ee) and (*R*)-**3D** (92% ee).

Substitution of (*R*)-**3A** with the **4A**-based copper reagent in CH_2Cl_2–THF was repeated to elucidate 99% inversion (inv.) on the basis of the observed ee of (*R*)-**3A** and (*S*)-**5a** (Scheme 2), whereas the (*S*) configuration was determined unambiguously by comparing the specific rotation of the derived hydrocarbon **11** (Scheme 3)[14] with that reported,[15] thus indicating the inversion mode of reaction at the α carbon. For the other products shown in Scheme 2 the same (*S*) configuration was assigned by analogy. Reaction of (*R*)-**3A** with **4B** delivered (*S*)-**5e** with 99% inv. In contrast, reaction of (*R*)-**3B** and copper reagents **4A**–**C** furnished (*S*)-**5b**, -**5f**, and -**5h**, respectively, but with varying % inv. On the other hand, (*R*)-**3D** was a good substrate for reaction with **4A** and **4C** producing (*S*)-**5d** and -**5i,** respectively, with high % inv. These results indicate that (1) TMS acetylenic copper is an excellent reagent for attaining high regio- and stereoselectivity; (2) electron-donating Ar group tends

Table 1
Optimization of reaction conditions for the reaction shown below[a]



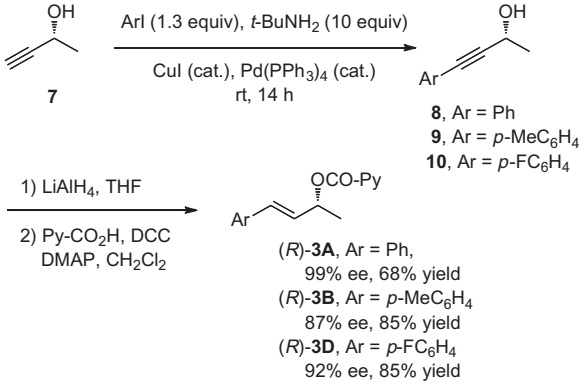
Entry	Solvent	Equiv of **2a**	Cu salt (equiv)	**5a**:**6a**:**7**:**3A**[b]	Yield of **5a** + **6a**[c]
1	THF	2	CuBr·Me_2S (2)	63:16:21:0	nd
2	THF	2	CuBr·Me_2S (1)	67:20:13:0	nd
3	THF	3	CuBr·Me_2S (1)	90:4:6:0	85
4	THF	4	CuBr·Me_2S (1)	91:4:5:0	84
5	CH_2Cl_2–THF	3	CuBr·Me_2S (1)	99:1:0:0	85
6	$(CH_2Cl)_2$–THF	3	CuBr·Me_2S (1)	99:1:0:0	84
7	$CHCl_3$–THF	3	CuBr·Me_2S (1)	0:0:100:0	—[d]
8	CCl_4–THF	3	CuBr·Me_2S (1)	0:0:100:0	—[d]
9	PhCl–THF	3	CuBr·Me_2S (1)	98:1:1:0	86
10	EtBr–THF	3	CuBr·Me_2S (1)	90:2:8:0	80
11	Hexane–THF	3	CuBr·Me_2S (1)	96:2:2:0	82
12	THF	3	CuBr (1)	69:3:23:5	nd
13	CH_2Cl_2–THF	3	CuBr (1)	99:1:0:0	84
14	THF	3	CuCN (1)	63:2:30:5	nd
15	CH_2Cl_2–THF	3	CuCN (1)	97:3:0:0	86

[a] Reactions were carried out at 0 °C for 1 h in THF or in a mixed solvent with THF.
[b] Determined by ^1H NMR spectroscopy.
[c] nd: not determined.
[d] Unidentified products were coproduced.

Table 2
Generality of the reaction[a]

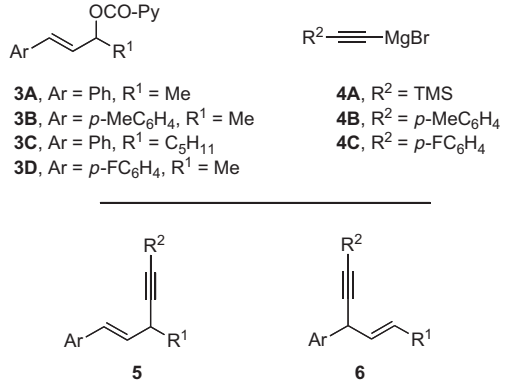
Entry	Picolinate	Alkynyl-MgBr	Solvent	Major product	**5**:**6**:alcohol[b]	Yield of **5** + **6**
1	**3B**	**4A**	THF	**5b**	91:9:0	82
2	**3B**	**4A**	CH_2Cl_2–THF	**5b**	97:3:0	87
3	**3C**	**4A**	THF	**5c**	90:4:6	85
4	**3C**	**4A**	CH_2Cl_2–THF	**5c**	99:1:0	94
5	**3D**	**4A**	CH_2Cl_2–THF	**5d**	96:4:0	94
6	**3A**	**4B**	THF	**5e**	94:2:4	80
7	**3A**	**4B**	CH_2Cl_2–THF	**5e**	97:3:0	84
8	**3B**	**4B**	CH_2Cl_2–THF	**5f**	92:8:0	86
9	**3C**	**4B**	CH_2Cl_2–THF	**5g**	94:4:2	91
10	**3B**	**4C**	CH_2Cl_2–THF	**5h**	90:4:6	82
11	**3D**	**4C**	CH_2Cl_2–THF	**5i**	91:4:5	82

[a] Reactions were carried out with copper reagents derived from **4A**, **4B**, or **4C** (3–4 equiv) and CuBr·Me_2S (1 equiv) at 0 °C for 1 h in CH_2Cl_2–THF or in THF.
[b] Determined by ^1H NMR spectroscopy.



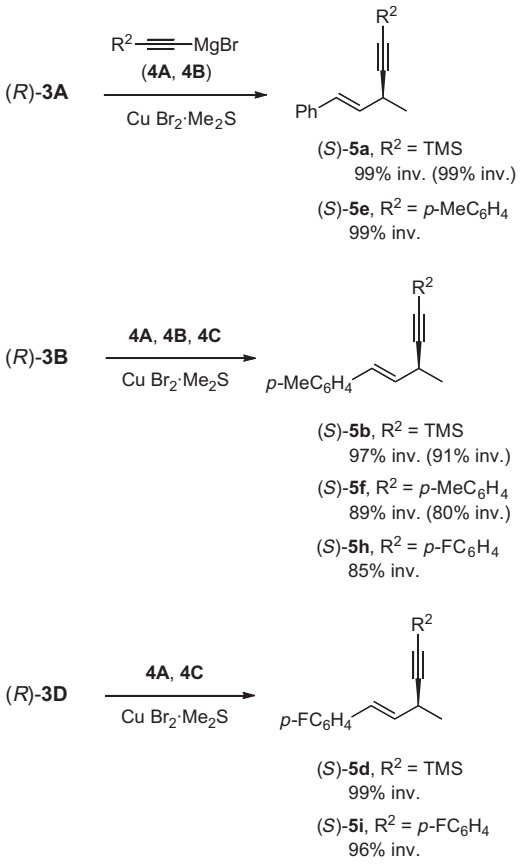
Scheme 1. Synthesis of optically active picolinates.

to lower the stereoselectivity;[16] (3) electron-withdrawing Ar group does not affect the inversion.

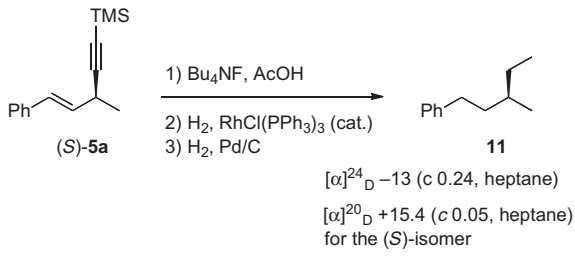


for **5** and **6**: **b**, Ar = p-MeC_6H_4, R^1 = Me, R^2 = TMS
c, Ar = Ph, R^1 = C_5H_{11}, R^2 = TMS
d, Ar = p-FC_6H_4, R^1 = Me, R^2 = TMS
e, Ar = Ph, R^1 = Me, R^2 = p-MeC_6H_4
f, Ar = p-MeC_6H_4, R^1 = Me, R^2 = p-MeC_6H_4
g, Ar = Ph, R^1 = C_5H_{11}, R^2 = p-MeC_6H_4
h, Ar = p-MeC_6H_4, R^1 = Me, R^2 = p-FC_6H_4
i, Ar = p-FC_6H_4, R^1 = Me, R^2 = p-FC_6H_4

In conclusion, we have described the unusual effect of CH_2Cl_2 on the regio- and stereoselectivities for substitution of γ-aryl allylic picolinates with alkynyl copper reagents. The reaction proceeded



Scheme 2. Chirality transfer of the reaction and the supposed absolute configuration. % Inv. = % inversion. Inv. shown in parenthesis was determined in THF.



Scheme 3. Transformation of (*S*)-**5a** to the enantiomer of the known compound.

at the α carbon exclusively with high inversion, except in a few cases, thus expanding a scope of allylic substrates for installing the alkynyl group.[17]

Acknowledgment

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References and notes

1. (a) Falciola, C. A.; Alexakis, A. *Eur. J. Org. Chem.* **2008**, 3765–3780; (b) Kar, A.; Argade, N. P. *Synthesis* **2005**, 2995–3022; (c) Negishi, E.; Liu, F. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998. Chapter 1.
2. (a) Goering, H. L.; Kantner, S. S. *J. Org. Chem.* **1981**, *46*, 2144–2148; (b) Goering, H. L.; Seitz, E. P., Jr.; Tseng, C. C. *J. Org. Chem.* **1981**, *46*, 5304–5308; and references cited therein.
3. Cf. substitution of γ-aryl *primary* allylic esters and halides: (a) Okamoto, S.; Tominaga, S.; Saino, N.; Kase, K.; Shimoda, K. *J. Organomet. Chem.* **2005**, *690*, 6001–6007; (b) Falciola, C. A.; Tissot-Croset, K.; Alexakis, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 5995–5998; (c) Falciola, C. A.; Tissot-Croset, K.; Reyneri, H.; Alexakis, A. *Adv. Synth. Catal.* **2008**, *350*, 1090–1100; and references cited therein.
4. (a) Goering, H. L.; Tseng, C. C. *J. Org. Chem.* **1983**, *48*, 3986–3990; (b) Tseng, C. C.; Yen, S.-J.; Goering, H. L. *J. Org. Chem.* **1986**, *51*, 2892–2895; (c) Norinder, J.; Bogár, K.; Kanupp, L.; Bäckvall, J.-E. *Org. Lett.* **2007**, *9*, 5095–5098.
5. Takashima, Y.; Kobayashi, Y. *J. Org. Chem.* **2009**, *74*, 5920–5926.
6. Defined as '(% ee of product/% ee of substrate) × 100'.
7. (a) Kiyotsuka, Y.; Acharya, H. P.; Katayama, Y.; Hyodo, T.; Kobayashi, Y. *Org. Lett.* **2008**, *10*, 1719–1722; (b) Kiyotsuka, Y.; Kobayashi, Y. *Tetrahedron Lett.* **2008**, *49*, 7256–7259; (c) Kiyotsuka, Y.; Katayama, Y.; Acharya, H. P.; Hyodo, T.; Kobayashi, Y. *J. Org. Chem.* **2009**, *74*, 1939–1951; (d) Hyodo, T.; Kiyotsuka, Y.; Kobayashi, Y. *Org. Lett.* **2009**, *11*, 1103–1106; (e) Kiyotsuka, Y.; Kobayashi, Y. *Tetrahedron* **2010**, *66*, 676–684.
8. Kiyotsuka, Y.; Kobayashi, Y. *J. Org. Chem.* **2009**, *74*, 7489–7495.
9. Chen, H.; Deng, M.-Z. *J. Organomet. Chem.* **2000**, *603*, 189–193.
10. The mixed solvent with low concentration of THF might be responsible for stronger coordination of the picolinoxy group to $MgBr_2$ than that in THF, thus promoting the reaction at the α carbon.
11. In contrast to the present study, γ selectivity has been increased in CH_2Cl_2 and toluene: (a) Persson, E. S. M.; Van Klaveren, M.; Grove, D. M.; Bäckvall, J. E.; Van Koten, G. *Chem. Eur. J.* **1995**, *1*, 351–359; (b) Alexakis, A.; Malan, C.; Lea, L.; Benhaim, C.; Fournioux, X. *Synlett* **2001**, 927–930; (c) Belelie, J. L.; Chong, J. M. *J. Org. Chem.* **2002**, *67*, 3000–3006.
12. CuX-based reagents (X = Br, CN) gave low selectivity in reactions of other combination of substrate/reagents.
13. Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738–8739.
14. Hydrogenation by using 10%Pd/C in solvents such as EtOAc suffered from a partial racemization.
15. Davis, D. D.; Ansari, G. G. *J. Org. Chem.* **1970**, *35*, 4285–4287.
16. The electron-donating methyl substituent in *p*-MeC_6H_4 probably assists partial racemization during the substitution reaction.
17. *Representative procedure*: To an ice-cold suspension of $CuBr{\cdot}Me_2S$ (38.6 mg, 0.188 mmol) in THF (1 mL) was added TMSC≡CMgBr (1.32 mL, 0.57 M in THF, 0.752 mmol) dropwise. The resulting mixture was stirred at 0 °C for 30 min and picolinate **3A** (99% ee by chiral HPLC, 47.6 mg, 0.188 mmol) in THF (1 mL) was added dropwise. After 1 h at 0 °C, saturated NH_4Cl was added to the solution and the resulting mixture was extracted with EtOAc three times. The combined extracts were dried over $MgSO_4$ and concentrated to afford an oil, which was purified by chromatography on silica gel with hexane/EtOAc to afford α-product **5a** (35.4 mg, 83%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.19 (s, 9H), 1.35 (d, J = 7 Hz, 3H), 3.28–3.41 (m, 1H), 6.15 (dd, J = 15, 6 Hz, 1H), 6.60 (d, J = 15 Hz, 1H), 7.19–7.42 (m, 5H); ^{13}C NMR (75 Hz, $CDCl_3$, APT in parenthesis) δ 0.3 (+), 21.8 (+), 30.0 (+), 86.6 (−), 108.7 (−), 126.4 (+), 127.4 (+), 128.6 (+), 129.6 (+), 131.0 (+), 137.2 (−). The stereochemical outcome (98% ee, 99% inversion) was determined by chiral HPLC analysis: Chiralcel OJ-H, 25 °C, hexane/*i*-PrOH = 99.1:0.1, 0.3 mL/min, t_R/min = 20.4 (*S*-isomer, major), 24.2 (*R*-isomer, minor).