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Amino Acid-Based Synthesis of Trifluoromethylalkene Dipeptide Isosteres by Alcohol-Assisted Nucleophilic Trifluoromethylation and Organozinc−Copper-Mediated S_N2' Alkylation

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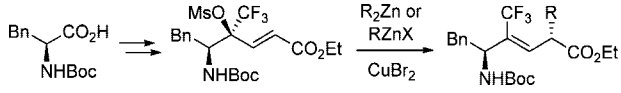

A novel synthetic approach to Xaa-Yaa-type (*Z*)-trifluoromethylalkene dipeptide isostere (CF_3-ADI) has been developed. Starting from readily available L-phenylalanine and L-alanine, several CF_3-ADIs were obtained through nucleophilic trifluoromethylation of γ-keto esters and S_N2' alkylation of trifluoromethylated mesylates. The influence of a trifluoromethyl group on the diastereoselectivity of the S_N2' reaction is also discussed.

Replacement of native hydrolyzable peptide bonds with nonhydrolyzable mimetics is one of the most promising approaches toward overcoming the major drawbacks of peptides, including poor bioavailability and short physiological half-lives due to rapid proteolysis.[1] Among the known isosteric units, the (*E*)-alkene-type dipeptide isostere (EADI), designed on the basis of the planar structure of the parent peptide bond in its resonance structure, is well-known as a potential *trans*-peptide bond-equivalent.[2] We have been engaged in the stereoselective synthesis and functional evaluation of EADIs.[3] We found that the simple alkene unit is not always sufficient as a peptide mimetic partially because of a smaller dipole moment than that of the native peptide bond (EADI: 0.1 D; native peptide bond: 3.6 D; Figure 1).[4]

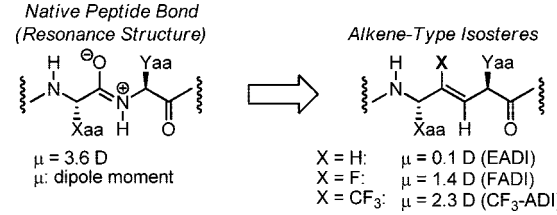

FIGURE 1. Structures of native peptide bond and corresponding alkene-type isosteres. Xaa, Yaa = amino acid side chains.

We turned our attention to fluoroalkene and trifluoromethylalkene dipeptide isosteres (FADI and CF_3-ADI, respectively). These isosteres can be considered to be more ideal peptide bond mimetics because a carbonyl oxygen of the peptide bond is replaced by a highly electronegative fluorine atom or trifluoromethyl group: induced polarization of the C−X bond by these substituents contributes to have a closer dipole moment to a native peptide bond (FADI: 1.4 D; CF_3-ADI: 2.3 D).[4] The potential character of these substituents as hydrogen bond acceptors can also be expected.[5] Whereas we and others have reported diastereoselective synthetic methodologies for FADIs as well as their applications to biologically active peptides,[6] only a few examples of a diastereoselective synthesis and functional evaluation of CF_3-ADI have been reported to date.[4,7] We recently developed an efficient stereoselective methodology for the preparation of optically pure Xaa-Gly-type CF_3-ADI utilizing palladium-catalyzed carbonylation.[8] Our next subject is the synthesis of Xaa-Yaa CF_3-ADIs, which requires the stereoselective introduction of the α-alkyl group.

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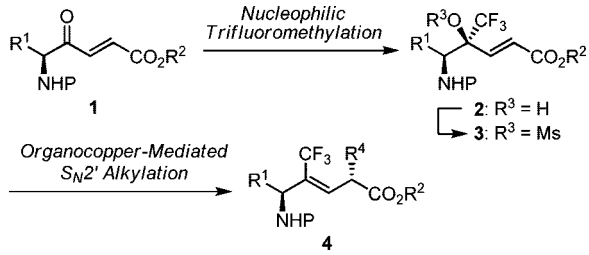
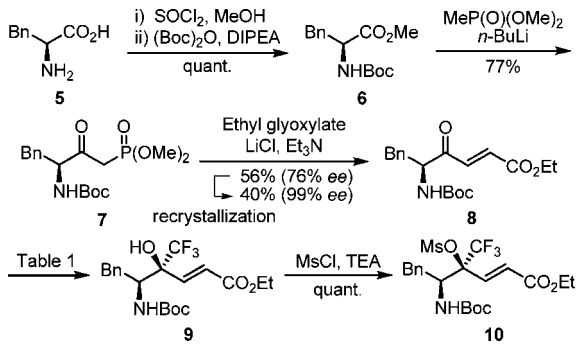
SCHEME 1. Synthesis of Xaa-Yaa-Type CF_3-ADI with S_N2' Alkylation



SCHEME 2. Synthesis of Mesylate 10 Bearing a CF_3 Group

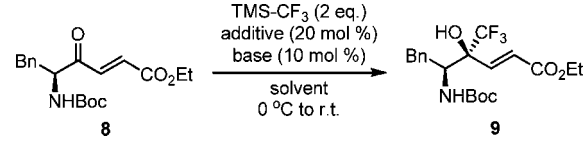


We envisioned that the Xaa-Yaa-type CF_3-ADI can be diastereoselectively synthesized by organocopper-mediated S_N2' alkylation of trifluoromethylated mesylates **3**, which will be obtained by nucleophilic introduction of the trifluoromethyl group to α,β-unsaturated γ-keto ester **1** (Scheme 1) followed by mesylation. Wipf and co-workers did pioneering work on the efficient synthesis of Ala-Ala-type CF_3-ADI using organocopper-mediated S_N2' methylation of a chiral diol-derived mesylate.[4] This isolated example shows the potential utility of the S_N2' reaction for synthesis of CF_3-ADIs, but the introduction of other various substituents is necessary. For a convenient synthesis of CF_3-ADIs with various patterns of amino acid side chains, it is desirable to obtain requisite substrates starting from readily available amino acids. In this contribution, we report a novel synthetic route to Xaa-Yaa-type CF_3-ADIs starting from amino acids. The notable effect of alcoholic additives in the nucleophilic trifluoromethylation and the stereoselectivity of the S_N2' reaction are also presented.

Our synthesis started from commercially available L-phenylalanine **5** (Scheme 2). After esterification with $SOCl_2$/MeOH and Boc protection of the amino group, treatment with dimethyl methylphosphonate in the presence of *n*-BuLi afforded the phosphonate **7**. The α,β-unsaturated γ-keto ester **8** was obtained by the Horner−Wadsworth−Emmons reaction of ethyl glyoxylate with **7**. Although a partial racemization of the ester **8** was observed during this reaction, enantiopure **8** was obtained by simple recrystallization (99% ee, chiral HPLC).

Next, we investigated the nucleophilic trifluoromethylation of the ester **8** using TMS-CF_3 (Table 1).[9] The reaction with TMS-CF_3 (2 equiv)[10] in the presence of K_2CO_3 (10 mol %) gave the allyl alcohol **9** in 59% yield with 77% de within 12 h (entry 1). Prakash proposed hexa- or pentacoordinated silicates

TABLE 1. Synthesis of Allyl Alcohol 9 via Nucleophilic Trifluoromethylation of Ester 8



entry	additive	base	solvent	time	yield[a] (%)	de[b] (%)
1	none	K_2CO_3	DMA	12 h	59	77
2	(*R*)-BINOL[c]	K_2CO_3	DMA	2.5 h	61	77
3	(*S*)-BINOL[c]	K_2CO_3	DMA	2 h	68	83
4	2,2′-biphenol[c]	K_2CO_3	DMA	4.5 h	58	63
5	ethylene glycol[c]	K_2CO_3	DMA	2.5 h	66	79
6	phenol	K_2CO_3	DMA	2 h	64	78
7	MeOH	K_2CO_3	DMA	1.5 h	60	79
8	MeOH	Na_2CO_3	DMA	19 h	60[d]	61
9	MeOH	Cs_2CO_3	DMA	50 min	67	77
10	MeOH	Cs_2CO_3	THF	5 h	27	22
11	MeOH	Cs_2CO_3	DMSO	30 min	dec	
12	(MeOH)	Cs_2CO_3	MeOH	30 min	dec	

[a] Combined isolated yields of both isomers of **9** (**a** and **b**). [b] Determined by HPLC. [c] 10 mol % of the diol was added. [d] TMS ether was also observed.

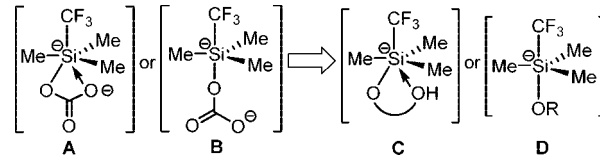


FIGURE 2. Proposed hexa- and pentacoordinated silicates in trifluoromethylation.

A or **B**, respectively, as plausible reactive species of the reaction with TMS-CF_3 and K_2CO_3 (Figure 2).[11] Expecting that alcohols would form these types of reactive intermediates (**C** or **D**), which efficiently accelerate the reaction, we used a catalytic amount of alcohols as an additive. The reaction with catalytic (*R*)-BINOL afforded **9** in 61% yield with 77% de within 2.5 h (entry 2). The reaction with (*S*)-BINOL gave a similar result (entry 3), showing little effect of the chirality of BINOL on the stereoselectivity of this reaction. Other alcohols (including mono-ols) also accelerated the reaction rate (entries 4−7). Among the alcohols examined, MeOH was the most effective additive to accelerate the reaction (entry 7). When Na_2CO_3 was used as the base, a prolonged reaction time was required (entry 8). The reaction in the presence of Cs_2CO_3 was completed within 50 min (entry 9). Optimization of the reaction solvent was then conducted by using a catalytic amount of MeOH and Cs_2CO_3. The reaction in THF gave the desired product **9** in only 27% yield (entry 10). DMSO and MeOH were less effective solvents, leading to decomposition of the starting material without producing **9** (entries 11 and 12). These results demonstrate that the combination of 20 mol % of MeOH and 10 mol % of Cs_2CO_3 in DMA was the condition of choice. With use of a standard protocol, the allyl alcohol **9** was converted to mesylate **10**. In a similar manner, mesylate **16** was prepared from L-alanine **11** by a sequence of reactions similar to the preparation of **10** (Scheme 3).

The relative configuration of both diastereomers of the allyl alcohol **9** was determined by an NOE correlation of oxazoli-

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(10) When the reaction was conducted with 1 equiv of TMS-CF_3 in the presence of K_2CO_3 (10 mol %) and MeOH (20 mol %), the allyl alcohol **9** was obtained in 32% yield with 75% de.

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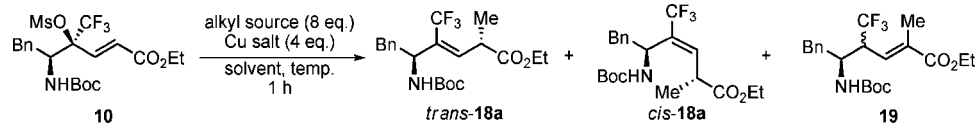
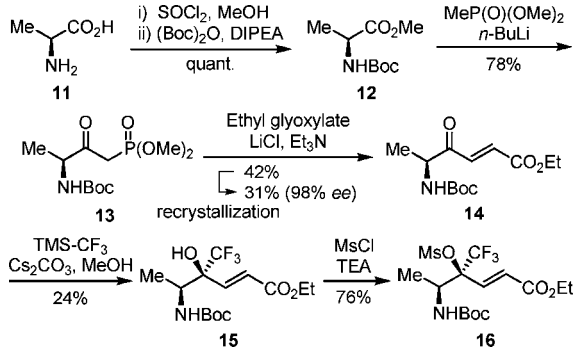
TABLE 2. Organocopper-Mediated S_N2' Methylation of CF_3-Containing Mesylate 10



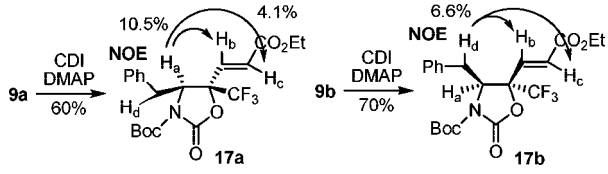
					% yield[a] (de)[b]		
entry	alkyl source	Cu salt	solvent	temp (°C)	*trans*-**18a**	*cis*-**18a**	**19**
1	MeMgCl	CuCN·2LiCl	THF	−78	51 (−7)	14 (94)	10 (ND)
2	Me_2Zn	CuCN·2LiCl	THF/NMP (2:1)	−30 to −10	53 (82)	14 (98)	trace (ND)
3	Me_2Zn	CuI	THF/NMP (2:1)	−30 to −10	64 (69)	15 (99)	− (ND)
4	Me_2Zn	CuBr·SMe_2	THF/NMP (2:1)	−30 to −10	76 (77)	14 (97)	− (ND)
5	Me_2Zn	$CuBr_2$	THF/NMP (2:1)	−30 to −10	83 (76)	13 (97)	− (ND)
6	Me_2Zn	CuCl	THF/NMP (2:1)	−30 to −10	67 (80)	21 (99)	− (ND)
7	Me_2Zn	CuF_2	THF/NMP (2:1)	−30 to −10	67 (26)	11 (88)[c]	− (ND)
8	Me_2Zn	$Cu(acac)_2$	THF/NMP (2:1)	−30 to −10	77 (20)	7 (90)	− (ND)
9	Me_2Zn	$CuBr_2$	Et_2O/NMP (2:1)	−30 to −10	73 (85)	9 (99)	− (ND)
10	Me_2Zn	$CuBr_2$	CH_2Cl_2/NMP (2:1)	−30 to −10	67 (86)	17 (99)	− (ND)
11	Me_2Zn	$CuBr_2$	MeCN/NMP (2:1)	−30 to −10	70 (86)	13 (96)	− (ND)
12	Me_2Zn	$CuBr_2$	PhMe/NMP (2:1)	−30 to −10	75 (84)	17 (99)	− (ND)

[a] Isolated yields. [b] Determined by HPLC. ND = not determined. [c] Unidentified products were detected by HPLC.

SCHEME 3. Preparation of Mesylate 16 from L-Alanine 11



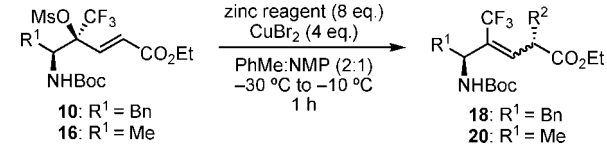
SCHEME 4. Determination of the Relative Configuration of Allyl Alcohols 9a and 9b



dinones **17a** and **17b**, obtained by the reaction of separated diastereomers **9a** and **9b** with CDI and DMAP (Scheme 4). Whereas no NOE enhancement of the signals of the olefin protons H_b and/or H_c of **17a** was observed by irradiation of the benzylic proton H_d, 10.5% and 4.1% NOE enhancements were observed by irradiation of H_a. In the oxazolidinone **17b**, a 6.6% NOE was observed between H_d and H_b/H_c (overlapped).

We then investigated the organocopper-mediated S_N2' alkylation reaction of the diastereomerically pure mesylate **10** (Table 2). Treatment of **10** with MeMgCl and CuCN·2LiCl in THF at −78 °C afforded the desired Phe-Ala-type CF_3-ADI *trans*-**18a** in 51% yield with a low diastereoselectivity (−7% de), along with *cis*-**18a** and α,β-unsaturated ester **19** in 14% and 10% yields, respectively (entry 1). When Me_2Zn was used as the alkyl source in a mixed solvent of THF/NMP,[12] *trans*-**18a** was obtained with 82% de and only a small amount of **19** was isolated (entry 2). Other copper salts such as CuI, CuBr·SMe_2, $CuBr_2$, and CuCl increased the yield of *trans*-**18a**, but with parallel diastereoselectivities (69−80% de, entries 3−6), whereas

TABLE 3. Organocopper-Mediated S_N2' Alkylation of CF_3-Containing Mesylates 10 and 16



					% yield[a] (de)[b]	
entry	substrate	zinc reagent	R^2	product	trans	cis
1	**10**	Me_2Zn	Me	**18a**	75 (84)	17 (99)
2	**10**	*i*-BuZnBr	*i*-Bu	**18b**	53 (20)	33 (99)
3	**10**	$(i\text{-Pr})_2Zn$	*i*-Pr	**18c**	62 (5)	27 (88)[c]
4	**16**	Me_2Zn	Me	**20a**	81 (79)	17 (>98)[c]
5	**16**	*i*-BuZnBr	*i*-Bu	**20b**	51 (68)	20 (>98)[c]
6	**16**	$(i\text{-Pr})_2Zn$	*i*-Pr	**20c**	51 (44)	20 (92)[d]

[a] Isolated yields. The diastereomixtures were not separable except for *cis*-**20c**. [b] Determined by HPLC. [c] Determined by ^1H NMR spectroscopy. [d] Based on isolated yields.

CuF_2 and $Cu(acac)_2$ considerably reduced diastereoselectivity (entries 7 and 8). Whereas mixed solvents containing Et_2O, CH_2Cl_2, and MeCN were less effective than THF/NMP (2:1) for improvement of the yield of **18a** (entries 9−11), PhMe/NMP (2:1) was the solvent of choice in terms of both yield and diastereoselectivity (entry 12). On the basis of these observations, we determined that use of organozinc reagent and $CuBr_2$ in PhMe/NMP (2:1) at −30 to −10 °C was the best condition (entry 12). The structure of CF_3-ADI **18a** (including stereochemistry of the α-methyl group) was established by NOE experiments and CD spectra.[3a,13] These results revealed that the organocopper-mediated S_N2'-type alkylation of the mesylate **10** preferentially proceeds in an *anti* fashion.

Finally, we investigated the introduction of various alkyl groups to diastereomerically pure mesylates **10** and **16** by an S_N2' reaction (Table 3). By use of *i*-BuZnBr and $(i\text{-Pr})_2Zn$, Phe-Leu- and Phe-Val-type CF_3-ADIs (*trans*-**18b** and *trans*-**18c**, respectively) were obtained in moderate yields (entries 2 and 3). As the steric bulk of the alkyl group increased, the diastereoselectivity of **18** significantly decreased. With use of the mesylate **16** derived from L-alanine, similar results were obtained to those of **10**. In these cases, the influence of the bulkiness of the alkyl group was very much smaller. In all cases,

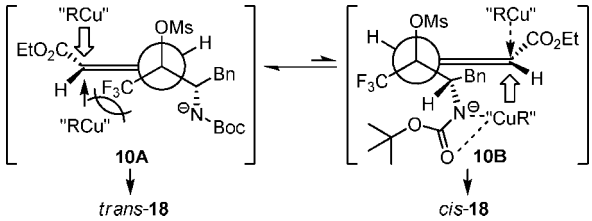


FIGURE 3. Plausible explanation for the formation of the minor products.

cis-isomers of **18** and **20** were obtained with higher diastereoselectivities than *trans*-isomers regardless of the introducing alkyl groups.

It is well accepted that the general *anti* selectivity in organocopper-mediated S_N2' reactions is due to the stereoelectronic effect.[14] The significant reduction in diastereoselectivity in the reaction of **10** with bulky reagents (entries 2 and 3, Table 3) can be explained by the relatively congested CF_3 group. The organocopper-mediated S_N2' reaction of the mesylate **10** leading to *trans*-**18** would therefore proceed via conformer **10A** (Figure 3). Because steric repulsion between the CF_3 group and a copper reagent would partly inhibit the *anti*-S_N2' reaction, the *syn*-pathway competed to afford *trans*-**18** in various de values dependent on the steric bulk of the copper reagents.[15] Compounds *cis*-**18**, produced through the conformer **10B**, were obtained with high de values, although more steric repulsion would be expected. This may be attributed to the coordination effect of a carbamate group to the organocopper reagent. This accelerates the *anti*-S_N2' reaction, thereby overcoming steric repulsion.

In summary, we developed a novel synthetic route to Xaa-Yaa-type CF_3-ADI via trifluoromethylation and organocopper-mediated alkylation. This methodology is useful because the chiral center at the δ-position of isosteres is derived from commercially available α-amino acids. The significant influence of a CF_3 group on diastereoselectivity, producing mixtures of *anti*/*syn* adducts depending on the organocopper reagents, has been demonstrated. Further studies, including the synthesis of various *trans*-CF_3-ADIs and biological evaluation of bioactive peptides containing CF_3-ADIs, are in progress.[16]

Experimental Section

General Procedure for Organocopper-Mediated S_N2' Reaction of Mesylates: Synthesis of Ethyl (2*S*,5*S*)-5-[*N*-(*tert*-Butoxycarbonyl)amino]-2-methyl-6-phenyl-4-(trifluoromethyl)hex-3-enoate (18a) (Table 2, Entry 12). To a mixture of $CuBr_2$ (77.7 mg, 0.348 mmol) in dry PhMe-NMP (2:1, 0.59 mL) at −30 °C was added (dropwise) Me_2Zn in *n*-hexane (1.0 M; 0.69 mL, 0.693 mmol). After the mixture was stirred at −30 °C for 30 min, a solution of mesylate **10** (42.7 mg, 0.086 mmol) in dry PhMe (0.14 mL) was added dropwise. The mixture was allowed to warm to −10 °C and stirred for an additional 1 h. The reaction was quenched by addition of saturated NH_4Cl and 28% NH_4OH at −10 °C. The whole mixture was extracted with Et_2O, and the extract washed with H_2O and brine, then dried over $MgSO_4$. Concentration under reduced pressure followed by flash chromatography over silica gel with *n*-hexane−AcOEt (5:1) gave *trans*-**18a** (26.9 mg, 75% yield, 84% de) and *cis*-**18a** (6.2 mg, 17% yield, 99% de).

***trans*-18a:** colorless oil; IR (neat) 3376 (NH), 1707 (CO); ^{1}H NMR (500 MHz, $CDCl_3$, 60 °C) major isomer δ 1.14 (d, J = 6.9 Hz, 3H), 1.24 (t, J = 6.9 Hz, 3H), 1.38 (s, 9H), 2.82 (dd, J = 13.7, 6.9 Hz, 1H), 2.98 (dd, J = 13.7, 6.9 Hz, 1H), 3.58 (dq, J = 10.9, 6.9 Hz, 1H), 4.13 (q, J = 6.9 Hz, 2H), 4.47−4.74 (m, 2H), 5.84 (d, J = 10.9 Hz, 1H), 7.12−7.17 (m, 2H), 7.18−7.23 (m, 1H), 7.24−7.30 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$, 60 °C) δ 14.0, 18.0, 28.3 (3C), 39.0, 40.8, 53.9, 60.9, 80.0, 124.0 (q, J_{C-F} = 277.1 Hz), 126.8, 128.5 (2C), 129.4 (2C), 130.7, 136.7, 137.2, 154.5, 173.1; ^{19}F NMR (471 MHz, $CFCl_3$, 60 °C) δ −58.4 (3F). HRMS (FAB) calcd for $C_{21}H_{29}F_3NO_4$ (MH^+) 416.2043, found 416.2049.

***cis*-18a:** colorless oil; IR (neat) 3380 (NH), 1705 (CO); $[\alpha]^{22}_D$ −34.1 (*c* 1.02, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 60 °C) δ 0.91 (d, J = 6.9 Hz, 3H), 1.23 (t, J = 6.9 Hz, 3H), 1.37 (s, 9H), 2.93 (dd, J = 13.6, 8.0 Hz, 1H), 2.98 (dd, J = 13.6, 8.0 Hz, 1H), 3.46 (dq, J = 10.3, 6.9 Hz, 1H), 4.13 (q, J = 6.9 Hz, 2H), 4.77 (br s, 1H), 4.90 (br s, 1H), 6.24 (d, J = 10.3 Hz, 1H), 7.17−7.23 (m, 3H), 7.25−7.31 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$, 60 °C) δ 14.0, 17.2, 28.3 (3C), 38.3, 40.6, 50.0, 61.0, 79.9, 124.4 (q, J_{C-F} = 275.9 Hz), 127.0, 128.6 (2C), 129.0, 129.2 (2C), 136.6, 137.2, 154.6, 172.8; ^{19}F NMR (471 MHz, $CFCl_3$, 60 °C) δ −61.4 (3F). HRMS (FAB) calcd for $C_{21}H_{29}F_3NO_4$ (MH^+) 416.2043, found 416.2035.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds, as well as deprotection of *trans*-**18a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) The strong electronic influence of CF_3 group may change the nature of the S_N2' process and leads to the formation of a long-lived, isomerizable π-allyl copper complex. However, the steric effect would be more important to determine the diastereoselectivity because de values of *trans*-**18** and **20** are dependent on the steric bulk of the copper reagents.
(16) At present, removal of the Boc group and ester function without epimerization is difficult. For example, treatment of *trans*-**18a** (77% de) with 6 N HCl in AcOH at 100 °C gave the corresponding deprotected isostere with 32% de in 90% yield (see the Supporting Information). Further investigation including preparation and deprotection of the *tert*-butyl ester will be necessary.