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Synthesis of *trans*-2,6-Disubstituted Cyclohexanones through Allylic Substitution

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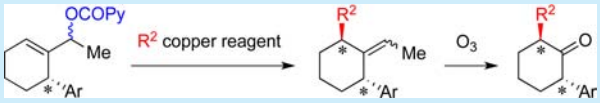
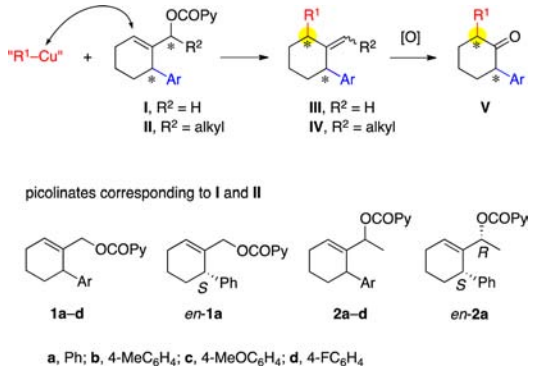
Supporting Information

ABSTRACT: *trans*-2,6-Disubstituted cyclohexanones were synthesized with high regio- and stereoselectivity by allylic substitution followed by ozonolysis. Both alkyl and aryl groups were successfully installed to the cyclohexane ring. The stereochemistry of the S_N2' products was determined to be controlled by the pre-existing chirality on the ring. The present method is highlighted by the synthesis of enantiomerically enriched cyclohexanones.



2,6-Disubstituted cyclohexanones are potentially valuable intermediates for the synthesis of biologically active compounds,[1] and several methods for the synthesis of this class of compounds have been developed.[2,3] Among them, only a few methods are stereoselective in relation to the stereochemistry of the substituents.[2] However, the methods experience racemic synthesis or symmetrical substrates. To establish a stereoselective access to 2,6-disubstituted cyclohexanones in enantiomerically enriched forms, we envisioned the strategy illustrated in Scheme 1, which consists of allylic substitution of

Scheme 1. Synthesis of 2,6-Disubstituted Cyclohexanones



I or **II** with copper reagents followed by the oxidation of the S_N2' product **III** or **IV**. The use of the allylic picolinates is based on the high S_N2' selectivity and sufficient reactivity of the picolinates even with aryl copper reagents, which are, in general, less reactive than alkyl copper reagents.[4] In the past, allylic substitution of simple cycloalkenylmethyl substrates has been reported,[5] although the stereochemical issue in question was rarely studied.[6]

In practice, reaction of **1a–d** chosen as the representative picolinates of **I** with alkyl and aryl copper reagents afforded S_N2' products **III**; however, they suffered from low regio- and product selectivities. Conversely, allylic substitution of picolinates **II** as exemplified by **2a–d** afforded **IV** selectively, and subsequent oxidation furnished the *trans* isomers **V** without isomerization to the thermodynamically more stable *cis* isomers. In addition, the transformation was applied to the enantiomerically enriched (*en*) picolinate *en*-**2a** successfully.

Primary picolinates **1a–d** (type **I** substrates) in racemic forms and secondary picolinates **2a–d** (type **II**) with approximately 1:1 diastereomeric ratio (dr) were synthesized by methods delineated in Scheme 2. In brief, allylic substitution[7] of **4** with $Ar_2CuMgBr{\cdot}MgBr_2$ afforded the key intermediates **5a**[8]**–d**, which were converted to **1a–d** and **2a–d**. In contrast, the substitution of (*R*)-**4** with $Ph_2CuMgBr{\cdot}MgBr_2$ proceeded with almost complete racemization, whereas the use of $PhCu{\cdot}MgBr_2$ afforded *en*-**5a**, which was converted to *en*-**1a** with a 94:6 enantiomeric ratio (er). The CBS reduction[9] of ketone **8** afforded (1*R*,1*S*)-**7a** with a 91:9 dr, and subsequent esterification with $PyCO_2H$ afforded *en*-**2a** with a high dr of 97:3 as a consequence of the separation of the minor diastereomer by chromatography.

For allylic substitution of the primary picolinate **1a**, both RLi- and RMgBr-based copper reagents (R = **A**, Me; **B**, Bu; **C**, Ph) were examined. In the case of the RLi-based reagents, $MgBr_2$ was added to activate the $PyCO_2$ leaving group. First, MeCu species derived from MeLi and MeMgBr afforded the desired S_N2' product **9aA** (R = Me) with 93 and 94% regioselectivity over the regioisomer **10aA** (Table 1, entries 1 and 2). The *trans* configuration of the two substituents on the cyclohexane ring was determined by analogy with that determined for the substitution product of the picolinates **II**. In contrast, a cuprate $Me_2CuMgBr{\cdot}MgBr_2$ produced the regioisomer **10aA** as a major product (entry 3).[10] Butyl copper (BuCu·LiBr) also produced **9aB** with 97% regioselectivity (entry 4; cf. entry 5). Reaction of **1b–d** (Ar = 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4) with MeCu·LiBr and BuCu·LiBr resulted in the S_N2' products with similar regioselectivities in 89–97% yields.

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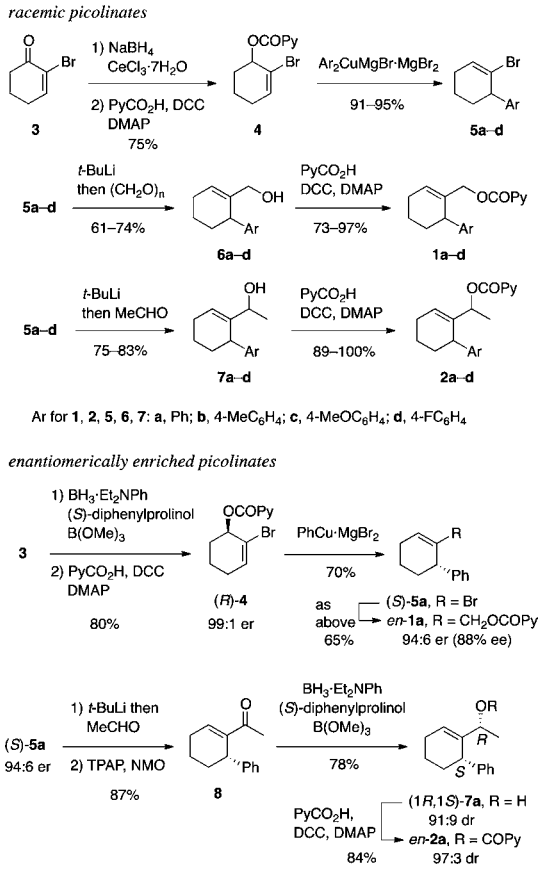
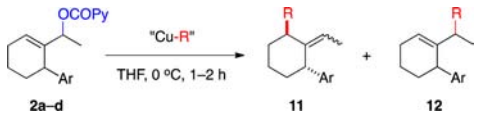
Scheme 2. Synthesis of Allylic Picolinates



In contrast to the alkyl reagents, PhCu·LiBr and PhCu·$MgBr_2$ afforded a mixture of **9aC** and regioisomer **10aC** (entries 6 and 7), whereas $Ph_2CuMgBr{\cdot}MgBr_2$ predominantly gave regioisomer **10aC** (entry 8). Recently, we have introduced ArCu·MgBr(acac) and $Ar_2CuMgBr{\cdot}MgBr$(acac) as anti-S_N2'-selective reagents.[4b,c] One of the reagents, PhCu·MgBr(acac), was applied to allylic substitution of **1a** to produce **9aC** with 82% regioselectivity (entry 9), whereas $Ph_2CuMgBr{\cdot}MgBr$(acac) in the presence of ZnI_2 furnished **9aC** with better S_N2' regioselectivity of 92% (entry 10). Next, $Ph_2CuMgBr{\cdot}MgBr$(acac) was examined with other picolinates **1b** and **1c** (Ar = 4-MeC_6H_4, 4-$MeOC_6H_4$) and resulted in slightly lower regioselectivity of 86 and 88%, respectively (data not shown). These results convinced us to switch to the investigation using the secondary picolinates (type **II**), and the results are presented in the next paragraph.[10]

Picolinate **2a** (Ar = Ph) underwent substitution with MeCu·LiBr with 96% regioselectivity to afford **11aA** as approximately 1:1 olefinic mixture (Table 2, entry 1). Alcohol **7a** and the starting picolinate **2a** were not detected by ^{1}H NMR and TLC analyses. The *trans* stereochemistry between Me and Ph was determined by NOE analysis (Figure 1) and by conversion to the known ketone **13aA** (vide infra). In contrast, $Me_2CuLi{\cdot}LiBr$

Table 2. Allylic Substitution of 2[a]

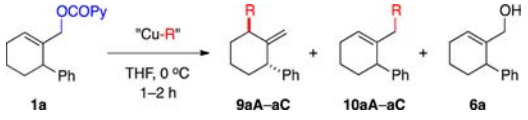


2a–d 11 12

entry	2	reagent (equiv), $MgBr_2$ (equiv)	11[b,c]	11/12[d]	yield (%)[e]
1	**2a**	MeCu·LiBr (2.7), $MgBr_2$ (3.0)	**11aA**	96:4	81
2	**2a**	$Me_2CuLi{\cdot}LiBr$ (1.5), $MgBr_2$ (3.1)		24:76	
3	**2a**	BuCu·LiBr (2.8), $MgBr_2$ (3.0)	**11aB**	98:2	85
4	**2a**	PhCu·LiBr (2.9), $MgBr_2$ (3.0)	**11aC**	95:5	83
5	**2a**	$Ph_2CuLi{\cdot}LiBr$ (1.5), $MgBr_2$ (3.0)		24:76	
6	**2a**	PhCu·$MgBr_2$ (1.5)	**11aC**	96:4	83
7	**2b**	PhCu·LiBr (2.7), $MgBr_2$ (3.0)	**11bC**	95:5	80
8	**2b**	4-MeC_6H_4Cu·$MgBr_2$ (1.5)	**11bD**	95:5	92
9	**2b**	4-MeC_6H_4Cu·MgBr(acac) (1.5)	**11bD**	95:5	82
10	**2b**	2-MeC_6H_4Cu·$MgBr_2$ (1.5)	**11bE**	83:17	67
11	**2c**	PhCu·LiBr (2.7), $MgBr_2$ (3.0)	**11cC**	94:6	84
12	**2d**	PhCu·LiBr (2.7), $MgBr_2$ (3.0)	**11dC**	94:6	81

[a]Reactions were performed at 0 °C for 1−2 h. [b]Each was obtained as approximately 1:1 olefin mixture except for **11bE** (4:1) and **11cC** (3:2). [c]The *trans* stereochemistry of **11** was assigned by ^{1}H NMR of the derived ketones (see the text). [d]Determined by ^{1}H NMR analysis of the unpurified reaction mixtures. [e]Isolated, combined yields of **11** and **12**.

Table 1. Allylic Substitution of 1a[a]



1a 9aA–aC 10aA–aC 6a

entry	reagent (equiv)	additive (equiv)	9/10/6a/1a[b]	9/10	yield (%)[c]
1	MeCu·LiBr (2.5)	$MgBr_2$ (3.1)	90:7:3:0	93:7	90
2	MeCu·$MgBr_2$ (1.5)		88:6:6:0	94:6	89
3	$Me_2CuMgBr{\cdot}MgBr_2$ (1.5)		6:78:8:8	7:93	
4	BuCu·LiBr (2.9)	$MgBr_2$ (3.0)	94:3:2:1	97:3	82
5	$Bu_2CuMgBr{\cdot}MgBr_2$ (1.7)		13:81:6:0	14:86	
6	PhCu·LiBr (3.0)	$MgBr_2$ (3.0)	53:35:12:0	60:40	
7	PhCu·$MgBr_2$ (1.4)		46:54:0:0	46:54	
8	$Ph_2CuMgBr{\cdot}MgBr_2$ (1.5)		3:97:0:0	3:97	
9	PhCu·MgBr(acac) (1.5)		80:18:2:0	82:18	
10	$Ph_2CuMgBr{\cdot}MgBr$(acac) (1.5)[d]	ZnI_2 (1.5)[e]	84:7:5:4	92:8	81

[a]Reactions were performed at 0 °C for 1−2 h to produce **9aA**/**10aA** (R = Me), **9aB**/**10aB** (R = Bu), and **9aC**/**10aC** (R = Ph). [b]Determined by ^{1}H NMR analysis of the unpurified reaction mixtures. [c]Isolated, combined yields of **9** and **10**. [d]At −40 °C for 12 h. [e]**9aC**/**10aC** = 22:78 without ZnI_2.

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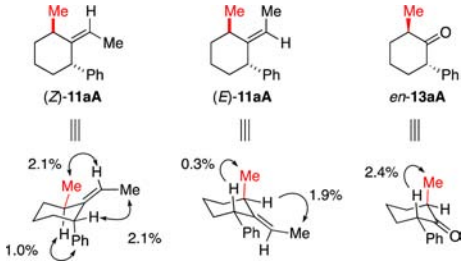


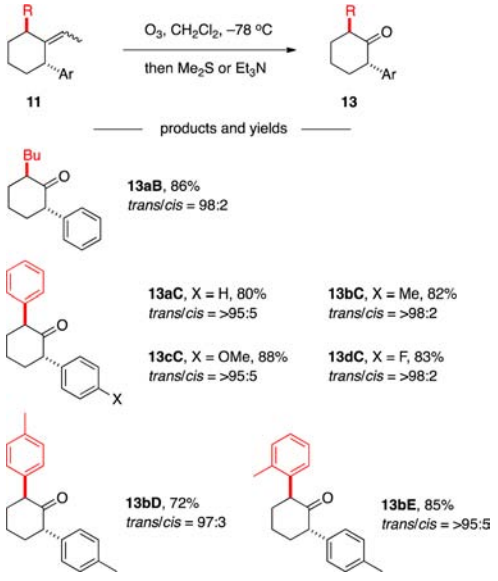
Figure 1. NOE analysis of (*Z*)- and (*E*)-**11aA** and *en*-**13aA**.

produced a mixture of the regioisomers (entry 2). Similarly, substitution of **2a** with BuCu·LiBr produced **11aB** with 98% regioselectivity in 85% yield (entry 3).

Next, phenyl addition of **2a** was examined. To our delight, PhCu·LiBr and PhCu·$MgBr_2$ afforded **11aC** with 95 and 96% regioselectivities, respectively, in good yields (entries 4 and 6; cf. entry 5), demonstrating higher S_N2' preference for the secondary picolinate **2a** than that of the primary picolinate **1a** (Table 1, entries 6 and 7). In a similar way, substitution of **2b** (Ar = 4-MeC_6H_4) with PhCu·LiBr and 4-MeC_6H_4Cu·X (X = $MgBr_2$, MgBr(acac)) produced **11bC** and **11bD**, respectively, with 95% regioselectivity in good yields (entries 7−9). A sterically congested reagent, 2-MeC_6H_4Cu·$MgBr_2$, lowered the regioselectivity and yield of **11bE** (entry 10). In addition, upon reaction with PhCu·LiBr, **2c** (Ar = 4-$MeOC_6H_4$) and **2d** (Ar = 4-FC_6H_4) produced **11cC** and **11dC**, respectively (entries 11 and 12).

Next, the second step of the strategy illustrated in Scheme 1 was investigated. Ozonolysis of **11aB** (Ar = Ph, R = Bu) at −78 °C followed by reductive workup afforded *trans*-2,6-disubstituted cyclohexanone **13aB** in 86% yield with a 98:2 *trans*/*cis* ratio (Scheme 3), and exposure of this ketone to *t*-BuOK in

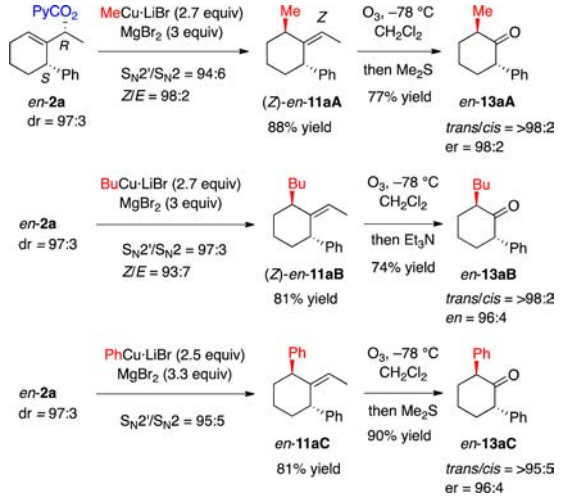
Scheme 3. Synthesis of 2,6-Disubstituted Cyclohexanones



THF afforded the *cis* isomer in 73% yield with an 81:19 *cis*/*trans* ratio determined by ^{1}H NMR spectroscopy. Similarly, ozonolysis of other olefins **11** provided *trans*-ketones **13** with high stereoselectivity (Scheme 3), which was determined by comparison with the *cis* isomers synthesized by isomerization. In the case of **13aC**, the ^{1}H NMR spectrum was consistent with that reported for the *trans* isomer.[2f]

The present method culminated in the synthesis of ketones in enantiomerically enriched forms. As delineated in Scheme 4,

Scheme 4. Synthesis of Enantiomerically Enriched Cyclohexanones[a]

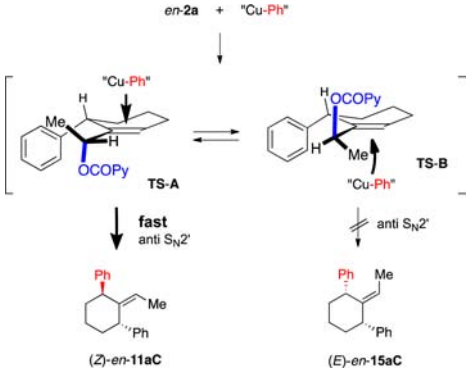


[a]THF, 0 °C, 1 h for the first step.

substitution of enantiomerically enriched picolinate *en*-**2a** with MeCu·LiBr produced (*Z*)-*en*-**11aA** with 98% *Z* selectivity.[11] This product was subsequently oxidized to ketone *en*-**13aA** with a >98:2 *trans*/*cis* ratio and a 98:2 er. The *trans* stereochemistry was confirmed by comparing the ^{1}H and ^{13}C NMR spectra with those reported for the *trans* isomer[3f] and by NOE analysis, as well (Figure 1). This result indicates that the *R* chirality at the *α* carbon of the allylic moiety is transferred to the *Z* olefin, whereas the stereochemical course of the reaction is determined independently of this chirality. This indication was also observed in the production of (*Z*)-*en*-**11aB** with 93% Z selectivity and then *en*-**13aB** with a >98:2 *trans*/*cis* ratio. Similarly, transformation of *en*-**2a** with PhCu·$MgBr_2$ furnished *en*-**13aC** with a >98:2 *trans*/*cis* ratio and 96:4 er. In addition, ozonolysis of *en*-**9aB** (R = Bu) derived from *en*-**1a** produced *en*-**13aB** selectively (equation not shown).

Taking the anti-S_N2' pathway into consideration for the substitution of allylic picolinates with copper reagents, **TS-A** and **TS-B** were conceived as transition state models for the reaction of *en*-**2a** with PhCu (Scheme 5), in which the Ph

Scheme 5. Pathway Analysis for the Substitution of *en*-2a



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group is projected to the pseudoequatorial space with a perpendicular angle to the cyclohexenyl ring by the steric reason. Among these models, the severe steric repulsion is conceived between the Ph group and Cu−Ph that approaches the olefin from the α side to form the π complex, thus disfavoring **TS-B**. Consequently, **TS-A** is the predominant pathway to produce (*Z*)-*en*-**11aC**. This consideration is consistent with the fact that the present substitution selectively afforded **11** with the *trans* stereochemistry between the R and Ar (Table 2). Thus, stereodefined construction of the chirality on the α carbon possessing $PyCO_2$ is unnecessary for the purpose of this two-step synthesis of the 2,6-disubstituted ketones in enantiomerically enriched form from *en*-**2a**.[12]

In summary, we developed a stereoselective method to obtain *trans*-2,6-disubstituted cyclohexanones. Furthermore, we clarified that (1) high anti-S_N2' selectivity is secured with the Me group, and (2) the stereochemical course is definitely dictated by the pre-existing chirality on the ring.[13]

■ ASSOCIATED CONTENT

Supporting Information

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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Notes

The authors declare no competing financial interest.

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(10) The α regioselectivity observed with the cuprates (Table 1, entries 3, 5, and 8) might stem in part from the increased nucleophilicity of the reagents, which prefer reaction at less sterically congested carbon.

(11) Substitution of the diastereomer of *en*-**2a** is predictable on the basis of the results of the substitutions using *en*-**2a** (Scheme 4) and **2a** (Table 1, entry 1).

(12) Allylic substitution of picolinate **II** (Ar = Bu, R^2 = Me) with PhCu afforded a mixture of the products, among which the desired S_N2' product was confirmed by ^1H NMR spectroscopy.

(13) Substitution of the cyclopentenyl picolinate corresponding to **2a** with $PhCu{\cdot}MgBr_2$ proceeded with 95% regioelectivity and 80% stereoselectivity.