Construction of a quaternary carbon at the carbonyl carbon of the cyclohexane ring†

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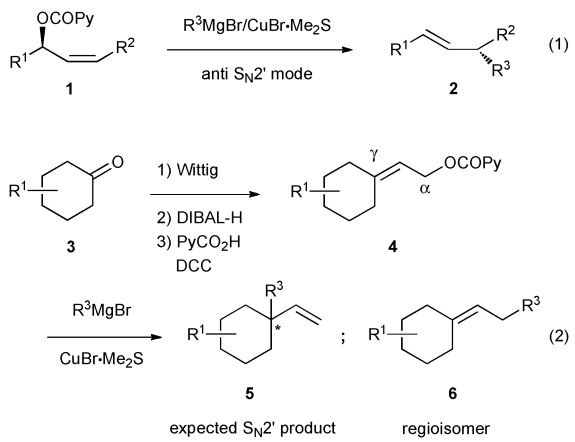
High S_N2' selectivity in the allylic substitution of cyclohexylidene ethyl picolinates with copper reagents prepared from RMgBr and CuBr·Me_2S was realized by addition of ZnX_2 (X = I, Br, Cl). Furthermore, ZnX_2 accelerated the reaction with the bulky *i*Pr reagent.

Addition of two alkyl groups to the carbonyl group of the cyclohexanones would be a convenient strategy for formation of a quaternary carbon on the cyclohexane ring, and provides an access to several kinds of biologically important natural compounds such as the steroids, morphine, taxol, *etc*. Previously, this concept was investigated by using a sequence of reactions, which consists of addition of CH_2=CHMgBr to 4-*tert*-butyl-cyclohexanone and a nickel-catalyzed allylic substitution of the resulting allylic alcohol with MeMgBr, producing 4-*tert*-butyl-1-methyl-1-vinylcyclohexane.[1] Although the stereoselectivity is quite high (*ca*. 95%), the reaction suffers from somewhat low regioselectivity (81–86%), indicating difficulty in controlling the reaction site of the π-allylnickel intermediates. Furthermore, according to the authors, this method is not applicable to Grignard reagents possessing a β-hydrogen.[2,3] Recently, we found highly regio- and stereoselective substitution of allylic picolinates with classes of organocopper reagents to afford the *anti* S_N2' products **2** (Scheme 1, eqn (1)).[4] With this substitution in mind, we envisioned a sequence of reactions shown in eqn (2) though the regioselectivity at the γ carbon over the α carbon in the allylation of picolinates **4** was uncertain as the γ and α carbons are, respectively, more and less congested than the substrates examined in eqn (1). Furthermore, the influence of the substituent(s) attached to the cyclohexane ring on stereoselectivity was unprecedented. In practice, regioselectivity with the original reagent system (R^3MgBr, CuBr·Me_2S) was low or reverse, whereas reaction in the presence of a zinc halide was found to be highly regioselective. On the other hand, stereoselectivity was high irrespective of zinc halides. Herein, we report the results of the investigation.



Scheme 1 The previous (eqn (1)) and the present investigation (eqn (2)). Py = 2-pyridyl.

Initially, MeMgBr and CuBr·Me_2S were mixed in a 2 : 1 ratio at 0 °C for 30 min to prepare the copper reagent of the supposed structure, $Me_2CuMgBr{\cdot}MgBr_2$, which (1.5 equiv.) was subjected to reaction with 4-*tert*-butylcyclohexylidene derivative **4A** at 0 °C for 1 h according to the published procedure[4a,b] to afford the regioisomer **6a** as the major product (Table 1, entry 1). We supposed that the chelation of the picolinoxy group to $MgBr_2$, one of the effective activations, is insufficient for the present substrate. We then directed our attention to zinc halides. Fortunately, $ZnBr_2$ (1.5 equiv.) was found to afford the desired product **5a** with 95% regioselectivity by ^{1}H NMR spectroscopy (entry 2). Reaction at lower temperatures resulted in higher regioselectivity (99%, entry 3). Use of $ZnBr_2$ in larger quantity (4 equiv.) provided a similar selectivity (entry 4), whereas insufficient selectivity was obtained with 0.5 equiv. of $ZnBr_2$ (entry 5). High efficiency was also observed with ZnI_2 and $ZnCl_2$ (entries 6 and 7). In contrast to $Me_2CuMgBr{\cdot}MgBr_2$, another copper reagent, $MeCu{\cdot}MgBr_2$, (1.5 equiv.) was 89% S_N2' selective (entry 8). However, the selectivity was not improved by $ZnBr_2$ (1.5 equiv.), which rather retarded the reaction (entry 9 and footnote *e*). In addition, leaving groups other than the picolinoxy group were examined. The *o*-$(PPh_2)C_6H_4CO_2$, $C_6F_5CO_2$, and AcO leaving groups showed no reactivity, while the $MeOCO_2$ group gave **5a** in <24% yield.

Next, the above protocol was applied to $Et_2CuMgBr{\cdot}MgBr_2$ and $Bu_2CuMgBr{\cdot}MgBr_2$. Different from $Me_2CuMgBr{\cdot}MgBr_2$, these reagents as such were of slight S_N2' selectivity, which was substantially improved by addition of ZnI_2 to produce **5b** and **5c** in good yields (entries 11 and 13 *vs*. entries 10 and 12).

The *cis* stereochemistry regarding the *t*Bu and the vinyl group of **5a** was unambiguously established by comparison of the ^{13}C NMR spectrum with the literature data for the *cis* and *trans* isomers.[1] The assignment indicates that the stereochemical course of the reaction depicted by heavy arrow **A** in Fig. 1 is controlled to avoid the steric interaction with the axial hydrogens in the chair conformation. This consideration is

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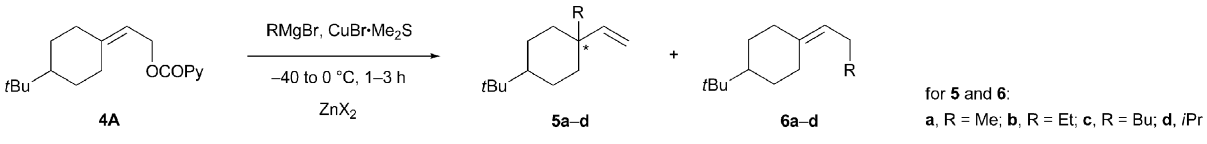
† Electronic supplementary information (ESI) available: The details of the results of Chart 1, full experimental detail, spectroscopic data, stereochemical correlation, and copies of NMR spectra. See DOI: 10.1039/c0cc00653j

Table 1 Reactions under various conditions



Entry	Copper reagent[a] Formula	Equiv.	Additive ZnX_2	Equiv.	Temp.,°C	Regioselectivity (**5**:**6**)[b]	Stereoselectivity of **5**[b,c]	Yield, %[d]
1	$Me_2CuMgBr{\cdot}MgBr_2$	1.5	—	—	0	22:78	98:2	nd
2	$Me_2CuMgBr{\cdot}MgBr_2$	1.5	$ZnBr_2$	1.5	0	95:5	93:7	nd
3	$Me_2CuMgBr{\cdot}MgBr_2$	1.5	$ZnBr_2$	1.5	−40 to −10	99:1	97:3	94
4	$Me_2CuMgBr{\cdot}MgBr_2$	1.5	$ZnBr_2$	4.0	−40 to 0	99:1	98:2	88
5	$Me_2CuMgBr{\cdot}MgBr_2$	1.5	$ZnBr_2$	0.5	−40 to 0	59:41	98:2	nd
6	$Me_2CuMgBr{\cdot}MgBr_2$	1.5	ZnI_2	1.5	−40 to −10	100:0	100:0	85
7	$Me_2CuMgBr{\cdot}MgBr_2$	1.5	$ZnCl_2$	1.5	−40 to −10	98:2	98:2	86
8	$MeCu{\cdot}MgBr_2$	1.5	—	—	0	89:11	94:6	nd
9	$MeCu{\cdot}MgBr_2$	1.5	$ZnBr_2$	1.5	0 to rt[e]	85:15	94:6	nd
10	$Et_2CuMgBr{\cdot}MgBr_2$	1.5	—	—	−40 to 0	56:44	99:1	81
11	$Et_2CuMgBr{\cdot}MgBr_2$	1.5	ZnI_2	1.5	−40 to 0	98:2	98:2	86
12	$Bu_2CuMgBr{\cdot}MgBr_2$	1.5	—	—	−40 to −10	62:38	100:0	nd
13	$Bu_2CuMgBr{\cdot}MgBr_2$	1.5	ZnI_2	1.5	−40 to −10	99:1	100:0	94
14	$iPr_2CuMgBr{\cdot}MgBr_2$	1.5	—	—	−40 to −10	—	—	0[f]
15	$iPr_2CuMgBr{\cdot}MgBr_2$	3.0	ZnI_2	3	−40 to 0	99:1	99:1	93

[a] The copper reagents were prepared from RMgBr (R = Me, Et, Bu, *i*Pr) and CuBr·Me_2S in 2:1 and 1:1 ratios, respectively. [b] Determined by ^{1}H NMR spectroscopy. [c] For **5a** (R = Me) the *cis* relation regarding the *t*Bu and the vinyl groups is confirmed by ^{13}C NMR spectroscopy, while the same stereochemistry was assigned for **5b–d** by analogy. [d] Isolated, combined yields of **5** and **6**. nd: Not determined. [e] 18 h at rt. [f] The corresponding alcohol and **4A** were obtained in 75 and 25% yields, respectively.

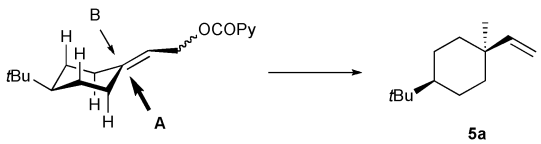


Fig. 1 Stereochemical course and the assigned stereochemistry of **5a**.

later proved to be applicable to other cases. The same stereochemistry was assigned to **5b–d** by analogy.

Allylation with a bulky copper reagent derived from $iPr_2CuMgBr{\cdot}MgBr_2$ disclosed another effect of ZnX_2. In the absence of a zinc halide, the S_N2' reaction was suppressed apparently by the steric reason. Alternatively, attack at the carbonyl carbon of the picolinoxy group took place to produce the corresponding alcohol (entry 14 and footnote *f*). In contrast, ZnI_2 (3 equiv.) led the S_N2' allylation to completion, giving **5d** in high yield with high regio- and stereoselectivities (entry 15). It should be noted that ZnX_2 accelerated the reaction with the cuprate ($iPr_2CuMgBr{\cdot}MgBr_2$) or retarded the reaction with the copper reagent ($MeCu{\cdot}MgBr_2$).

The S_N2' allylation optimized above with ZnX_2 was further examined by using a variety of substrates and reagents to establish the generality of the reaction. Substrate–product relationship, regioselectivity (rs), stereoselectivity (ss) and yields (y) are summarized in Chart 1, in which the selectivities were determined by ^{1}H NMR spectroscopy. In the cases of **5i** and **5k**, yields were somewhat low due to the volatile property. The details of the results and those carried out without ZnX_2 are presented in Table S1 in the electronic supplementary information (ESI†). 4-Phenyl derivative **4B** showed similar reactivity and selectivity to 4-*t*-butyl substrate **4A**. Thus, the S_N2 (α) selectivity (**5e**/**6e** = 1:99) observed with the Me reagent was inverted to S_N2' selective by addition of ZnX_2 (X = I, Br) (rs 95% and 100%, respectively). The low level of S_N2' preference with Et and Bu reagents (rs 82%, 70%) was substantially improved (rs 100% both cases), while >95% ss was recorded independent of ZnX_2 (X = I, Br). Reaction with the *i*Pr reagent afforded a mixture of the regioisomer **6h**, the corresponding alcohol and **4B** in a 29:61:10 ratio, whereas $ZnBr_2$ accelerated the S_N2' allylic substitution selectively to produce **5h** as observed in the case of **4A**. ZnI_2 gave a similar result.

2-Methyl substrate **4C**, prepared as a 4:1 mixture of the *E*/*Z* isomers, was subjected to reaction with the Me and Bu reagents. High selectivity was observed as well to produce the S_N2' products **5i** and **5j**, respectively. The results indicate that stereocontrolled synthesis or separation of the olefin isomers of the substrate is not a requirement for attaining high selectivity, thus demonstrating another advantage of the present strategy. The stereochemistry of **5i** was established as drawn in Chart 1 by transformation to the known acid, 1,2-dimethylcyclohexanecarboxylic acid,[5] by oxidation of the double bond (see ESI†). The outcome was consistent with the stereochemical course illustrated in Fig. 1.

Next, ZnI_2-assisted reaction of 3-methyl and 3,5,5-trimethyl derivatives **4D** and **4E** with the Et and Bu reagents afforded the corresponding S_N2' products **5k–m** with similarly high selectivities (rs >99%, >97%). ZnI_2-assisted substitution of the 2-methoxy derivative **4F** with the Bu reagent proceeded similarly to furnish the S_N2' product **5n** in 70% yield. The S_N2' selectivity (100%) was not diminished by the Lewis basic MeO group. The piperidine derivative **4G**, chosen as a heterocyclic substrate, upon reactions with the Me and Bu reagents produced the S_N2' products **5o** and **5p** with high selectivities

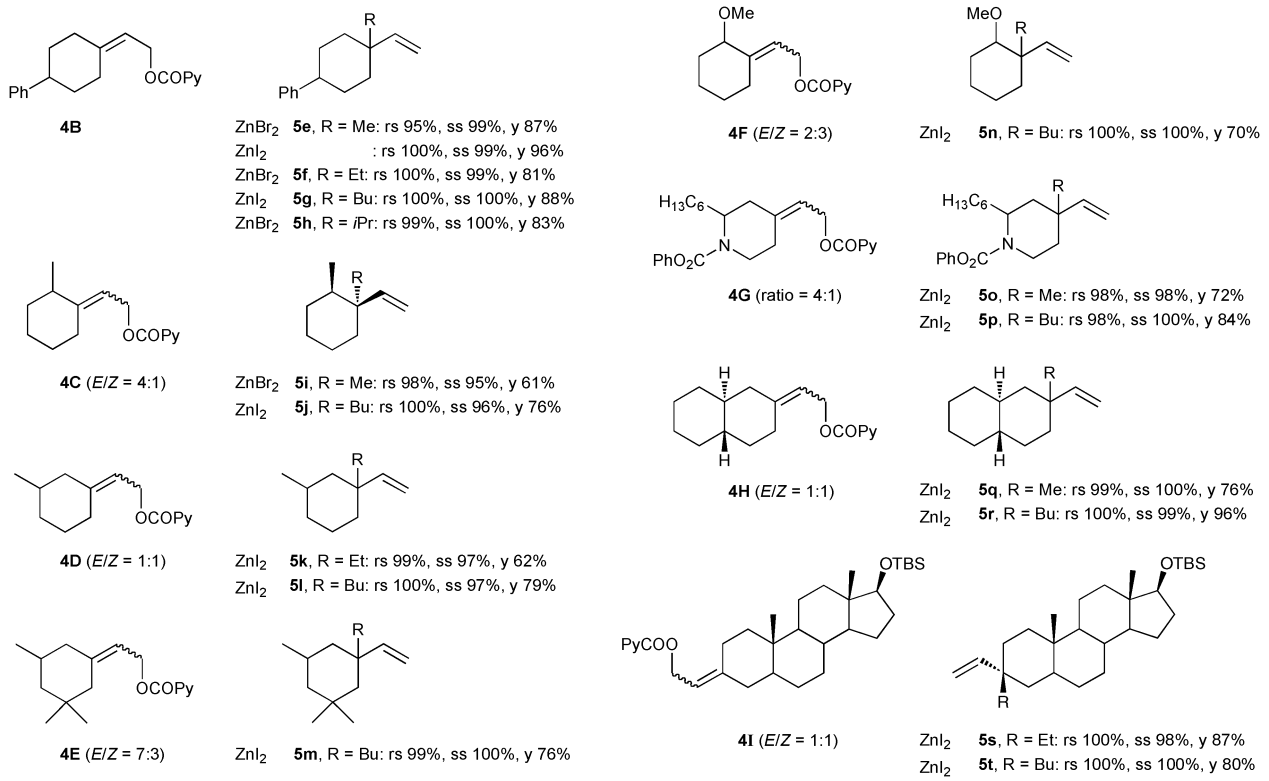


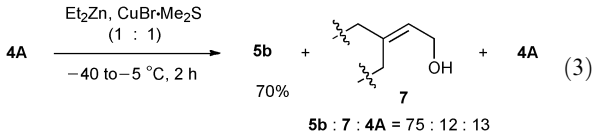
Chart 1 Substrates, products, regio- and stereoselectivities (rs, ss) and yields.

(rs 98%, ss >98%). It should be noted that high regio- and stereoselectivities were independent of the *E*/*Z* stereochemistry of **4D–4G** as in the case of **4C**.

The allylation was applied to the *trans* decaline derivative **4H**, which was prepared from the corresponding ketone[6] as a 1 : 1 mixture of the olefin isomers. The methylation without a zinc halide was moderately S_N2 selective (**5q**/**6q** = 25 : 75), whereas reaction in the presence of ZnI_2 was S_N2' selective, giving **5q** with rs 99% and ss 100%. Substitution with the Bu reagent afforded **5r**.

Finally, the protocol established above (with ZnX_2) was applied to the steroid derivative **4I** (*E*/*Z* = 1 : 1), which afforded **5s** and **5t** upon reaction with the Et and Bu reagents, respectively. The regio- and stereoselectivities (rs 100%, ss >98%) were as high as those recorded with other picolinate derivatives. Once again, the stereochemistry of **5t**, confirmed by derivation to the known compound[7] (see ESI† for the transformation), is consistent with the model depicted in Fig. 1.

A copper reagent derived from Et_2Zn and $CuBr{\cdot}Me_2S$ in a 1 : 1 ratio upon reaction with **4A** afforded **5b** with a similarly high regioselectivity, indicating $Et_2Cu(ZnBr)$ is also an effective reagent to give **5b** in 70% yield though the reagent suffers from the co-production of alcohol **7** as shown in eqn (3).



(3)

5b : **7** : **4A** = 75 : 12 : 13

The data obtained with ZnX_2 and $ZnEt_2$ suggest that stronger coordination of the picolinoxy group to more acidic Zn^{2+} activates the leaving group effectively for the reaction to proceed at the γ carbon.

In conclusion, the S_N2' selective allylation of **4** was attained by adding ZnX_2 (X = I, Br), and the generality of the reaction was established by sacrificing a number of the substituted cyclohexyl derivatives. In all cases, the stereoselectivity was at high levels and the stereochemical course of the reaction is now predictable by using the chair conformer of the cyclohexane ring. Furthermore, ZnX_2 was found to accelerate the allylation with the bulky *i*Pr reagent.

Notes and references

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