ORGANIC LETTERS

2003
Vol. 5, No. 12
2111−2114

Highly Stereoselective Anti S_N2' Substitutions of (*Z*)-Allylic Pentafluorobenzoates with Polyfunctionalized Zinc–Copper Reagents

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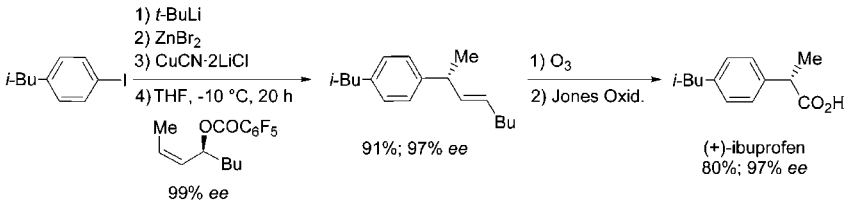
Received March 26, 2003

ABSTRACT



Allylic substitution reactions of zinc–copper organometallics on (*Z*)-allylic pentafluorobenzoates proceed with very high regioselectivity and excellent anti selectivity. The high fidelity in transfer of stereochemical information allowed a short synthesis of (+)-ibuprofen (97% ee).

Absolute stereocontrol in acyclic systems is an important synthetic problem.[1] Especially useful are stereoselective synthetic methods involving the formation of a new C−C bond. Among various substitution reactions, palladium-catalyzed allylic substitutions have been used with considerable success.[2] However, the narrow range of nucleophiles (only stabilized nucleophiles can be used) as well as the low regioselectivity observed in nonsymmetrical allylic systems have hampered the general use of this reaction. On the other hand, copper-catalyzed allylic substitutions do not suffer from these limitations.[3] They proceed usually with anti S_N2' selectivity in cyclic and acyclic systems.[4] The chiral information can be contained either in the allylic electrophile[5] or in a chiral copper catalyst.[6] This last approach, although the ultimate solution, suffers also from generality since the chiral ligand−copper complex has to be optimized for each class of allylic substrates.[6i] The diastereoselective synthesis in which a chiral allylic electrophile is used is more appealing

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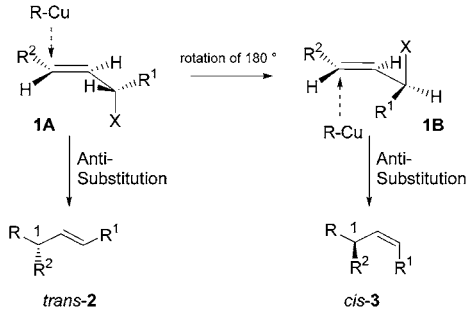
10.1021/ol034525i CCC: $25.00
Published on Web 05/14/2003

and should be generally applicable since allylic alcohols can be readily prepared in optically enriched form by several asymmetric syntheses.[1,7,8] Herein, we wish to report a general synthetic method allowing a highly diastereoselective anti S_N2' substitution in open-chain systems using functionalized zinc−copper reagents.[9]

Allylic substrates of type **1** can undergo anti S_N2' substitution via two conformations (**1A** and **1B**), either of them allowing an anti parallel arrangement of the copper reagent and the leaving group (Scheme 1). The substitution via

Scheme 1

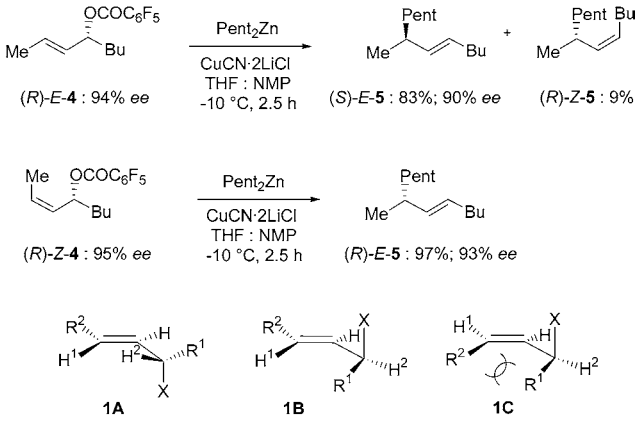


conformer **1A** would afford the *trans*-alkene substitution; reaction via the conformer **1B** would result in the formation of *cis*-alkene (cis-**3**).

Notice that the configuration at the carbon atom C(1) is the opposite in products trans-**2** and cis-**3** (Scheme 1). Allylic substitutions with zinc−copper reagents were known with allylic halides,[9,10] but we needed to perform this study with allylic alcohol derivatives, since these molecules can be readily obtained in optically enriched form contrary to allylic halides. Preliminary experiments show that zinc−copper reagents do not react with allylic acetates or benzoates, but a high-yield substitution is obtained with allylic pentafluorobenzoates that are readily prepared from the corresponding alcohols (C_6F_5COCl, pyridine, DMAP, CH_2Cl_2, 0 °C, 1−4 h). Thus, the reaction of the (*E*)-allylic pentafluorobenzoate ((*E*)-**4**, >99% (*E*)-; 94% ee)[11] with $Pent_2Zn$ and CuCN·2LiCl[12] in a 2:1 THF/NMP mixture at −10 °C for 2.5 h produces the expected (*S*)-(*E*)-7-methyl-5-dodecene ((*E*)-**5**) in 83% yield with an enantiomeric excess of 90% ee as well as ca. 9% yield of (*Z*)-7-methyl-5-dodecene ((*Z*)-**5**). The absolute stereochemistry of (*S*)-(*E*)-**5** was established by ozonolytic cleavage and in situ Jones oxidation providing (*S*)-2-methylheptanoic acid.[13]

This demonstrates unambiguously that zinc−copper reagents react with anti selectivity. The absolute configuration of the minor product (*R*)-(Z)-**5** was not established, but an independent synthesis[14] indicates that its structure was indeed the (*Z*)-alkene-**5**.[15] The formation of (*Z*)-**5** results from an anti substitution of the zinc−copper reagent via a conformation of type **1B** (Scheme 1). By comparing the allylic 1,3-strain[16] of the two possible conformations (**1A** and **1B**) that can undergo an anti S_N2' substitution, we noticed a higher allylic 1,3-strain (between H^1 and R^1) in conformer **1B** (Scheme 2) disfavoring the substitution reaction via this

Scheme 2



conformer. To disfavor this conformation further, we have envisioned using the (*Z*)-allylic pentafluorobenzoate (*Z*)-**4**. With such a substrate, the disfavored conformation of type **1C** will now display considerable allylic 1,3-strain.[16] This was confirmed by experiments. The allylic pentafluorobenzoate (*Z*)-**4** (95% ee) reacted smoothly with $Pent_2Zn$ in the

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(9) Knochel, P.; Millot, N.; Rodriguez, A. L.; Tucker, C. E. *Org. React.* **2001**, *58*, 417.

(10) Sekiya, K.; Nakamura, E. *Tetrahedron Lett.* **1988**, *29*, 5155.

(11) The allylic alcohol derived from *trans*-**4** was prepared by a Sharpless kinetic resolution; see ref 8 and Supporting Information.

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(14) (*Z*)-allylic alcohol ((*Z*)-**5**; (5*Z*)-7-methyl-5-dodecene) was prepared by Lindlar reduction of the corresponding alkyne (7-methyl-5-dodecyne); see Supporting Information.

(15) Assuming that an anti substitution via the conformer **1B** will lead to the (*R*)-configuration for (*Z*)-**5**. Since only 9% of this isomer was formed, it was not possible to establish its enantiomeric purity by GC analysis.

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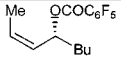
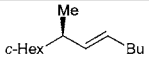
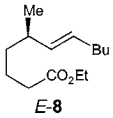
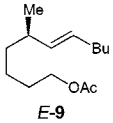
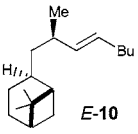
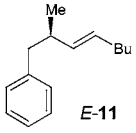
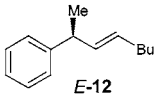
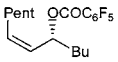
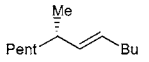
presence of CuCN·2LiCl (1.2 equiv) providing only (7*R*,5*E*)-7-methyl-5-dodecene ((*R*)-(*E*)-**5**) in 97% yield and 93% ee as indicated by GC analysis.

Remarkably, this behavior is rather general and various diorganozincs react with chiral (*Z*)-allylic pentafluorobenzoates (*Z*)-**4** and (*Z*)-**6** furnishing the S_N2' substitution products **5** and **7**−**12** with the (*E*)-stereochemistry in 89−95% ee (Table 1).

Table 1. Allylic Substitution Products (*E*)-**5** and (*E*)-**7**−**12** Obtained by the Reaction of (*Z*)-Allylic Pentafluorobenzoates ((*Z*)-**4** and (*Z*)-**6**) with Polyfunctional Diorganozinc Reagents

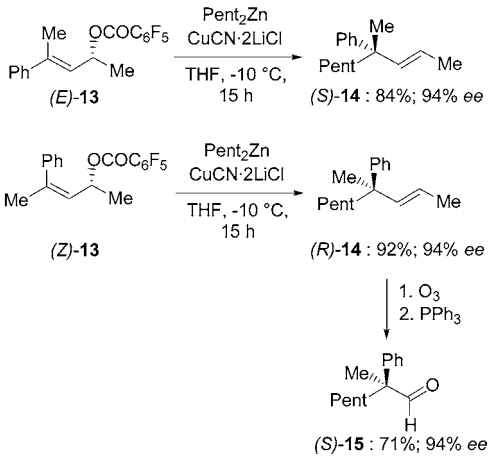
entry	allyl substrate	R_2Zn (R)	product of type **2**	yield (%)[e]	*ee* (%)[f]
1	 *Z*-**4**[a]	*c*-Hex	 *E*-**7**	79	95
2	*Z*-**4**[a]	$EtO_2C(CH_2)_3$	 *E*-**8**	68	95
3	*Z*-**4**[a]	$AcO(CH_2)_4$	 *E*-**9**	71	95
4	*Z*-**4**[a]		 *E*-**10**	80	92
5	*Z*-**4**[a]	$PhCH_2$[d]	 *E*-**11**	83	95
6	*Z*-**4**[b]	Ph	 *E*-**12**	74	93
7	 *Z*-**6**[c]	Me	 (*S*)-*E*-**5**	90	89

[a] Enantiomeric excess of (*Z*)-**4** was 98%. [b] Enantiomeric excess of (*Z*)-**4** was 95% in this case. [c] Enantiomeric excess of (*Z*)-**6** was 90%. [d] Reaction was carried out in THF/NMP (*N*-methylpyrrolidinone)/toluene 2:1:1. [e] Yield of analytically pure products. [f] Enantiomeric excess was determined using GC or HPLC analysis. In each case, the racemic product was prepared for calibration.

In all cases, no products derived from S_N2 substitutions could be detected and pure (*E*)-substitution products of type **2** were obtained (*E*:*Z* > 99:1). Various diorganozincs undergo the allylic substitution. Dicyclohexylzinc[17] leads to the desired product (*E*)-**7** in 79% yield and 95% ee within 12 h of reaction time (entry 1 of Table 1). Functionalized diorganozincs such as $(EtO_2C(CH_2)_3)_2Zn$ and $(AcO(CH_2)_4)_2Zn$ furnish the functionalized products in 68 and 71% yields and 95% ee (entries 2 and 3). Dimyrtanylzinc obtained after hydroboration of (−)-*β*-pinene[17] reacts somewhat slower (21 h) and leads to the substitution product ((*E*)-**10**) in 80% yield and 92% ee (entry 4). Dibenzylzinc[18] in toluene leads, after reaction for 17 h at −10 °C, to the substitution product (*E*)-**11** in 83% yield and 95% ee. Diphenylzinc obtained by transmetalation from PhLi with $ZnBr_2$ reacts also with high anti S_N2' selectivity leading to the chiral product (*E*)-**12** in 74% yield and 93% ee. Finally, the use of (*Z*)-5-pentafluorobenzoate-6-dodecene ((*Z*)-**6**) demonstrates the versatility of this method, since its reaction with Me_2Zn and CuCN·2LiCl provides the alkene (*S*)-(*E*)-**5** in 90% yield and 89% ee (compare entry 7 of Table 1 with Scheme 2). Thus, the two enantiomeric products are available either by changing the substituent stereochemistry of the double bond or by changing the configuration of the allylic alcohol.

The asymmetric preparation of quarternary centers is an important synthetic problem,[19] and this copper-mediated allylic substitution reaction provides a solution in the case of cinnamic alcohol derivatives. The (*E*)- and (*Z*)- pentafluorobenzoates ((*E*)- and (*Z*)-**13**) were prepared in 98% ee (see Supporting Information) and reacted with $Pent_2Zn$ and CuCN·2LiCl in THF at −10 °C for 16 h (Scheme 3). The

Scheme 3



two enantiomeric alkenes (*S*)- and (*R*)-**14** were obtained in 84−92% yield and 94% ee, showing the high synthetic potential of this method for the construction of quaternary centers otherwise difficult to prepare with high enantioselectivity.[19]

Interestingly, the olefin (*R*)-**14** can be converted by ozonolysis (reductive conditions: (1) O_3, −78 °C, CH_2Cl_2; (2) PPh_3, −78 °C to room temperature, 2 h) to the chiral aldehyde (*S*)-**15** in 71% yield and 94% ee. As an application of this method, we have prepared (+)-ibuprofen (**16**), an

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(18) Dibenzylzinc was prepared by reaction of benzylmagnesium bromide with diethylzinc.

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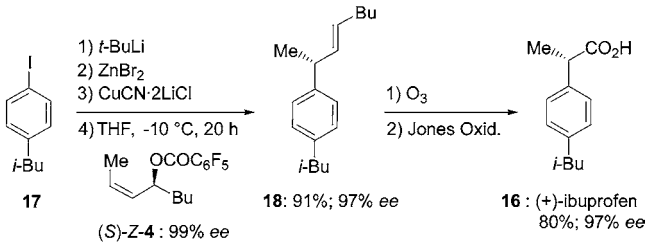
important antiinflammatory agent.[20] The reaction of aryl iodide **17** (1 equiv) with *t*-BuLi (2 equiv) followed by the transmetalation with $ZnBr_2$ (0.5 equiv) generates an intermediate zinc reagent that, in the presence of CuCN·2LiCl (0.25 equiv), reacts in THF with (S)-(*Z*)-**4** (99.3% ee)[21] to provide the allylic substitution product **18** in 91% yield and 97.2% ee. Ozonolysis followed by Jones oxidation gives (+)-ibuprofen (**16**) in 80% yield and 97.2% ee (Scheme 4).

Scheme 4



In summary, we have demonstrated that various functionalized zinc−copper reagents react with high anti S_N2' selectivity with (*Z*)-allylic pentafluorobenzoates allowing excellent stereocontrol for the synthesis of acyclic molecules. Quaternary centers can be created by this method with excellent transfer of the stereochemical information. Further applications of this method for the synthesis of natural products are currently underway.[22]

Acknowledgment. We thank the Deutsche Forschungsgemeinschaft (KN 347/6-1) and the Alexander von Humboldt-Foundation for financial support. M.I.C. thanks the European Community (Marie Curie Fellowship of the program "Improving Human Research Potential and the Socio-economic Knowledge Base" contract number HPM-FCT-2000-01024) for a fellowship. We thank the BASF AG (Ludwigshafen) and Chemetall GmbH (Frankfurt) for the generous gift of chemicals.

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

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(21) Although it is stated that the allyl pentafluorobenzoate (*S*)-(*Z*)-**4** has 99.3% ee, it contains 0.5% of the trans isomer (*S*)-(*E*)-**4**. As a result, the "real" ee for the pure cis compound (*S*)-(*Z*)-**4** would be 98.6% ee, so the loss of enantiomeric excess during the allylation reaction is even less important.

(22) **Typical Procedure: Preparation of (*R*)-(*E*)-5.** A flame-dried 25 mL flask equipped with a magnetic stirring bar, an argon inlet, and a septum was charged with a solution of CuCN·2LiCl (1 M solution in THF; 0.6 mL, 0.6 mmol) and cooled to −30 °C under an argon atmosphere. NMP was added as a cosolvent (overall ratio of THF/NMP = 2:1). $Pent_2Zn$ (5.1 M solution in THF, 0.24 mL, 1.2 mmol) was added dropwise, and the resulting mixture was stirred for 0.5 h at −30 °C. Then, the pentafluorobenzoate ester ((*R*)-(*Z*)-**4**) (160 mg, 0.5 mmol, 95% *ee*) was added dropwise as a solution in THF (0.8 mL), and the reaction mixture was allowed to warm to −10 °C and stirred for 2.5 h. Water (20 mL) was added followed by 25% aqueous ammonia solution (2 mL); then, the reaction mixture was stirred at 25 °C until the copper salts had dissolved. The mixture was extracted with Et_2O (3 × 20 mL). The combined extracts were washed with brine and dried over $MgSO_4$. Evaporation of the solvents and purification by column chromatography (SiO_2, pentane) afforded the desired alkene (*R*)-(*E*)-**5** as a colorless liquid (88 mg, 97%, 93% ee).