Stereoselective Heteroatom-Assisted Allylic Alkylation of Cyclic Ethers with Grignard Reagents. A Convenient Route to Enantiomerically Pure Carbocycles

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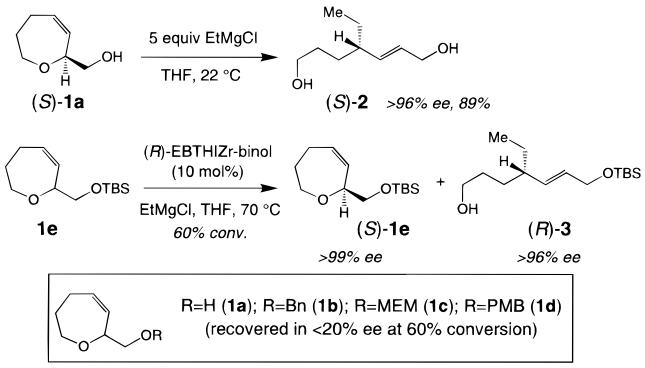
Addition reactions of Grignard reagents with carbonyl groups are among the most well-established protocols for C−C bond formation. In contrast, unactivated alkenes, including allylic ethers, do not typically react with alkylmagnesium halides in the absence of a metal catalyst:[1] these transformations do not represent a reliable and general approach in regio- and stereoselective synthesis. Previous studies, notably by Eisch,[2] Felkin,[3] and Richey,[4] have illustrated that olefin substrates with a suitably disposed internal Lewis base (hydroxyl groups),[5] at elevated temperatures (80−120 °C) and with extended reaction times (days), react with certain Grignard reagents. These transformations are not particularly efficient however; only allyl- and crotylmagnesium halides give rise to C−C bond formation. Liotta and Maryanoff have more recently reported a hydroxyl-directed conjugate addition of alkylmagnesium halides to the more electronically activated oxidoenones.[6] Complementing our efforts in the area of transition-metal-catalyzed addition of alkylmagnesium halides to cyclic allylic ethers,[7] herein we report an efficient, stereoselective, and heteroatom-assisted allylic substitution reaction that involves addition of Grignard reagents to unsaturated heterocycles; these processes proceed readily at ambient temperature. Together with the Zr-catalyzed kinetic resolution,[8] the present technology allows access to a range of optically pure chiral materials.

Scheme 1



As depicted in Scheme 1, when (*S*)-**1a** (>99% ee) is subjected to 5 equiv of EtMgCl at 22 °C (THF), C−C bond formation proceeds with complete asymmetric induction: (*S*)-**2** is obtained in >96% ee in 89% yield after silica gel chromatography (^{19}F NMR analysis of derived MTPA (α-methoxy-α-trifluoromethylphenylacetic acid) esters). It is noteworthy that, whereas silyl ether **1e** is resolved efficiently, compounds **1a**−**d** are not; the latter substrates were recovered after 55−60% conversion with 15−20% ee. Subsequent control experiments indicated that, in contrast to **1e**, **1a**−**d** cannot be resolved efficiently because they react with EtMgCl in the absence of the chiral metal catalyst. The lack of reactivity of **1e** toward Grignard reagents (without a catalyst), together with the facile uncatalyzed transformations of **1a**−**d**, suggests that the presence of an accessible Lewis basic heteroatom is critical to the success of C−C bond formation. Hence, reaction precursor can be prepared optically pure by the Zr-catalyzed alkylation and subsequently alkylated to afford a range of products with high enantiopurity (**1e** → (*S*)-**1e** → (*S*)-**1a** → (*S*)-**2**).

As illustrated in Table 1 (entries 1 and 2), when *n*-BuMgCl or *i*-BuMgBr are used, products are isolated in excellent yield and with outstanding levels of optical purity. In connection with the facility of these olefin alkylations, it is important to note that the asymmetric Zr-catalyzed alkylations with longer chain alkylmagnesium halides are more sluggish than those involving EtMgCl. Furthermore, when catalytic additions do occur, the corresponding branched products are obtained; that is, with *n*-PrMgCl and *n*-BuMgCl, *i*-Pr and *sec*-Bu addition products are formed, respectively.[7d] The uncatalyzed allylic substitution described here thus complements the enantioselective Zr-catalyzed protocol.

Stereoselective processes depicted in entries 2−9 of Table 1 illustrate that, in contrast to previous reports,[2−3] allylic ethers are effective promoter groups: the allylic substitution event does not require the highly Lewis basic resident Mg alkoxide. The corresponding benzyl (entries 2−5), 2-methoxyethoxymethyl (MEM) (entry 6), and *p*-methoxybenzyl (entry 7) ethers direct the C−C bond formation without diminution in yield or stereoselectivity. The remarkable difference in efficiency of reactions when Grignard reagents **8** and **9** are used is striking (entries 4 and 5). Contrary to reactions with **9**, with alkylmagnesium halide **8**, under identical reaction conditions, <2% product is obtained. This dramatic rate difference may suggest that, in the former case, intramolecular Mg−O chelation[9] preempts association of the metal with the Lewis basic alkoxy group and/or the C−C π cloud, a factor that may be critical to the success of the olefin alkylation. Reaction outcomes depicted in entries 8 and 9 of Table 1 illustrate that these stereoselective transformations are not limited to seven-membered heterocycles.[10]

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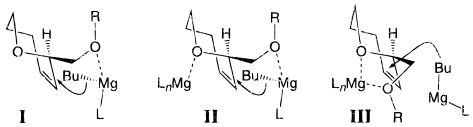
Table 1

entry	substrate	alkylating agent	product	ee; yield (%) [e]
1	(*S*)-**1a** R=H	*n*-BuMgCl	(*S*)-**4**	>96; 93 [b]
2	(*S*)-**1b** R=Bn	*i*-BuMgBr	(*R*)-**5**	>96; 87 [c]
3	(*S*)-**1b** R=Bn	Ph, MgBr **6**	(*S*)-**7**	>96; 88 [d]
4	(*S*)-**1b** R=Bn	MgBr **8**	NO REACTION	
5	(*S*)-**1b** R=Bn	MgBr **9**	(*S*)-**10**	>96; 89 [c]
6	(*S*)-**1c** R=MEM	Ph, MgBr **6**	(*S*)-**11**	>96; 78 [b]
7	(*S*)-**1d** R=PMB	BrMg **12**	(*S*)-**13**	>99; 99 [d]
8	(*R*)-**14**	*n*-BuMgCl	(*R*)-**15**	>96; 67 [c]
9	(*R*)-**14**	*i*-BuMgCl	(*S*)-**16**	>96; 71 [c]

[a] Conditions: 5 equiv of Grignard reagent, 22 °C, THF, 12−24 h. [b] Ratio established by analysis of derived (*R*)-MTPA ester, in comparison with authentic materials (400 MHz ^{19}F NMR). [c] Same as *b*, except ^{1}H NMR used. [d] Ratio established by chiral HPLC (Chiralcel OB/H column), in comparison with authentic materials. [e] Isolated yields after silica gel chromatography.

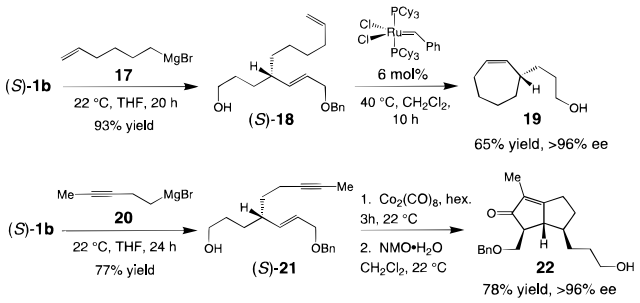
Scheme 2



Three possible modes of heteroatom association with the alkylating agent are tentatively depicted in Scheme 2; detailed understanding of various mechanistic aspects of the heteroatom-assisted alkylation process must await extensive studies. A number of related observations are, however, worthy of mention: (1) The presence of an internal Lewis base (on the side chain) is required for the diastereoselective C−C bond formation (minor isomer never detected); silyl ether **1e** and heterocycles with 2-alkyl substituents are inert to the reaction conditions. (2) In contrast to reactions of oxidoenones,[6] use of the corresponding dialkylmagnesium reagents leads to significantly less product formation (<10%). This observation suggests that the presence of Lewis acidic magnesium halide salts is critical, favoring the modes of addition represented by **II** and **III** in Scheme 2. (3) Similar to heteroatom-directed reactions of oxidoenones, allylic substitutions only proceed when THF is used as solvent; <5% reaction is detected in Et_2O. (4) Contrary to reactions of oxidoenones,[6] additives such as HMPA or DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone) are not required and the nature of the halide group of the Grignard reagent (RMgBr vs RMgCl) makes little, if any, difference in reaction efficiency.

(10) Initial studies indicate that the related five- and six-membered heterocycles do not undergo uncatalyzed allylic substitution; as a result, they are readily resolved by the Zr-catalyzed protocol (ref 8).

Scheme 3



The diastereoselective uncatalyzed C−C bond forming process, in conjunction with the Zr-catalyzed kinetic resolution,[8] promises to be of notable utility in synthesis; it might be used to rapidly construct a variety of carbocycles in the enantiomerically pure form. Various functional groups can be imported as part of the alkylmagnesium halide, such that subsequent functionalization procedures lead to a range of useful organic molecules in the nonracemic form. The examples put forth in Scheme 3 are illustrative. Addition of an alkene- or alkyne-bearing Grignard agent (Scheme 3; **17** and **20**, respectively), followed by an appropriate cyclization process leads to the formation of optically pure carbocycles. Thus, ring-closing metathesis[11] of **18** leads to the extrusion of the methoxybenzyl directing group, to afford **19** in >96% ee and 65% yield after silica gel chromatography. Similarly, with alkyne-containing alkylation product **21** as the starting material, optically pure and highly functionalized bicyclic enone **22** is formed through a diastereoselective Pauson−Khand reaction (78% overall yield from **20**).[12]

In brief, we report a highly stereoselective heteroatom-assisted C−C bond forming reaction, where the starting material can be synthesized through the Zr-catalyzed kinetic resolution protocol. Allylic substitution products can be obtained in excellent enantiomeric purity and be subjected to additional functionalization to afford a number of carbocyclic adducts in the optically pure form. Studies in connection to the ability of other alkylmetals and alkene substrates to undergo related C−C bond forming reactions, mechanistic details of such processes, and their applications to the total synthesis of medicinally important agents are in progress.

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Supporting Information Available: Experimental procedures and spectral and analytical data for all reaction products (17 pages). See any current masthead page for ordering and Internet access instructions.

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