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A NOVEL METHOD FOR COPPER(I)-CATALYZED COUPLING REACTIONS OF TRIFLATES WITH GRIGNARD REAGENTS

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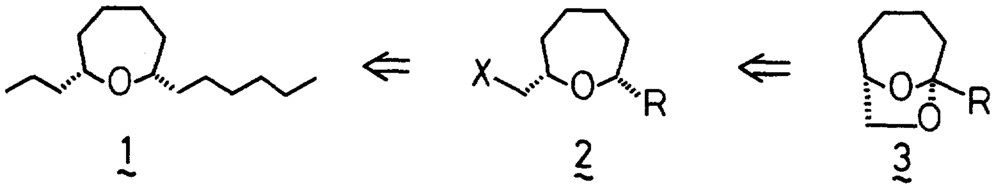
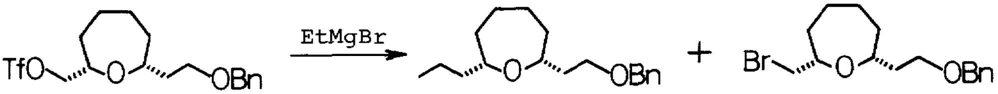
Abstract: A variety of triflates containing a β-oxygen functionality were efficiently reacted with Grignard reagents in the presence of CuBr to afford the corresponding coupling products.

We have recently described a strategy for preparing cis- or trans-disubstituted tetrahydropyran derivatives in optically active form via stereoselective reduction of bicyclic ketals.[1] In the course of our studies to extend this methodology to the larger-sized ether rings, we became interested in the synthesis of an isolaurepinnacin skeleton 1[2] from a bicyclic ketal 3 (Scheme I). For the completion of our project it has been necessary to develop an efficient and convenient method for the elongation of the side chain in 2 with some Grignard reagents. However, such nucleophilic *displacement reactions under the usual conditions prove to be difficult due* to the electron-withdrawing β-oxygen.[3] In fact, initial attempt of coupling reaction of the corresponding bromide (X=Br) or tosylate (X=OTs) with EtMgBr in the presence of Li_2CuCl_4[4] was unsuccessful.[5] Consequently, the triflate (X=OTf) was chosen as a candidate because of its powerful leaving property.[6]

Scheme I

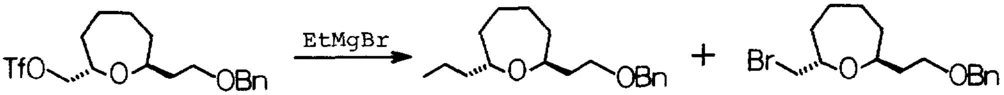


The coupling reaction of triflates 4 and 5 with EtMgBr in the presence of Li_2CuCl_4 (0.2 equiv) indeed proceeded, but a bromine substitution was observed as an important side reaction in both cases (Eqs 1 and 2). In attempting to improve these results, we found the use of CuBr as catalyst



(1)

4	Li_2CuCl_4, rt, 15 h	10 %	72 %
	CuBr, 0 °C, 0.5 h	82 %	—



(2)

5	Li_2CuCl_4, rt, 25 h	26 %	26 %
	CuBr, 0 °C, 1 h	88 %	—

(0.2 equiv) gave excellent results without any formation of by-products. Herein we report on our study of the generality of this potentially useful coupling reactions.

The results are summarized in Table I. In each case a variety of triflates, which were readily prepared from the starting alcohols by treatment with $(CF_3SO_2)_2O$ (1.5 equiv) in pyridine, were reacted with several Grignard reagents to afford the coupling products in good yields. Apparently, in the absence of CuBr the method had less synthetic utility (entry 2). Interestingly, even in the case of ditriflate 9 the desired reaction was achieved in moderate yields (entries 8 and 9). Although the reason is unclear, the reactions with allylmagnesium bromide were best performed in ether (entries 4 and 9).

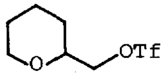
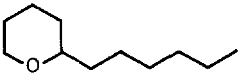
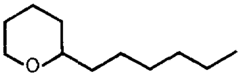
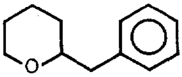
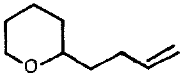
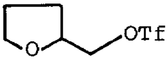
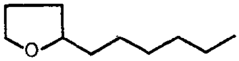
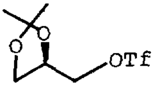
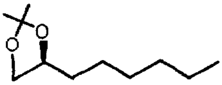
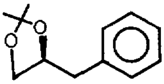
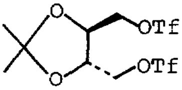
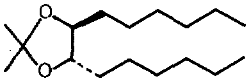
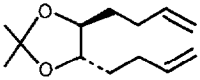
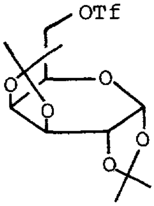
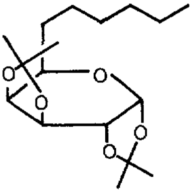
The existing method for the elongation of the side chain in large-sized ether ring systems such as 2 relies on a Wittig-type olefination after conversion to the corresponding aldehydes.[7] However, the main disadvantage of this method is the stereochemical confusion at the stage of aldehyde through an equilibration. The procedure described above has no such problem and therefore is particularly favorable for our purpose. Moreover, due to its simplicity the procedure will be widely applicable for the synthesis of chiral compounds from simple chiral sources such as 8, 9, and 10.

In conclusion, an efficient coupling reaction of triflates containing a β-oxygen with Grignard reagents has been realized by using CuBr as catalyst.

Typical procedure: Preparation of 2-hexyltetrahydropyran.

To a mixture of tetrahydropyran-2-methanol(210 mg,1.8 mmol) and 0.44 ml of pyridine in 5 ml of dry CH_2Cl_2 was added dropwise $(CF_3SO_2)_2O$ (762 mg, 2.7 mmol) in 2 ml of dry CH_2Cl_2 at -15 °C and the solution was stirred for 20 min at this temperature under N_2. After dilution with 5 ml of CH_2Cl_2, the mixture was treated conventionally and evaporation of the solvent (below 25

Table I. CuBr-Catalyzed Coupling Reactions of Triflates with Grignard Reagents at 0 °C[a]

Entry	Substrate	RMgX[b]	Reacn time, h	Product[c]	Overall yield, %[d]
1	 6	$C_5H_{11}MgBr$	2		84
2[e]	6	$C_5H_{11}MgBr$	18		37
3	6	C_6H_5MgBr	1		63
4[f]	6	$CH_2=CHCH_2MgBr$	3		66(29)
5	 7	$C_5H_{11}MgBr$	1		86
6	 8	$C_5H_{11}MgBr$	2		70
7	8	C_6H_5MgBr	3		62
8	 9	$C_5H_{11}MgBr$	1		56
9[f]	9	$CH_2=CHCH_2MgBr$	4		56(14)
10	 10	$C_5H_{11}MgBr$	3		69

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[a] Unless otherwise noted THF was used as solvent. [b] Used as an ether solution. [c] Satisfactory spectral data were obtained for all new compounds. [d] Overall yield of chromatographed pure product from the starting alcohol. [e] Without CuBr catalyst and at room temperature. [f] The reaction was conducted in ether. The yield in THF is given in parentheses.

°C) gave the crude product, which was dried azeotropically with toluene and then used immediately for the next reaction.

To an ice cooled suspension of CuBr(60 mg, 0.42 mmol) in 5 ml of dry THF was added an ether solution of $C_5H_{11}MgBr$ (4 ml, 2.7 mmol) followed by introduction of a THF(3 ml) solution of the above obtained triflate. During the reaction a black insoluble substance was gradually deposited. After being stirred for 2 h at 0 °C, the mixture was quenched by addition of satd NH_4Cl. The usual workup and a purification by flash chromatography afforded 2-hexyltetrahydropyran (257 mg, 84 %); bp 102-104 °C/21 mmHg(lit.[8] bp 105-110 °C/22 mmHg).

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References and Notes

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