Synthetic Methods

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Zinc-Catalyzed Enantiospecific sp^3–sp^3 Cross-Coupling of α-Hydroxy Ester Triflates with Grignard Reagents**

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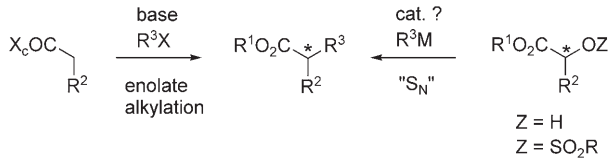
Skeleton-expanding operations that provide control of all levels of selectivity are among the most valuable transformations in organic synthesis.[1] One important example is the alkylation of ester or amide enolates which requires either a chiral auxiliary or stoichiometric amounts of a chiral base in order to control the absolute configuration of the final alkylation product.[2–5]

As an alternative, one might start from an α-hydroxy ester derivative (Scheme 1), a number of which are available in enantiomerically pure form from the chiral pool or are readily



Scheme 1. Syntheses of enantiopure α-alkylesters.

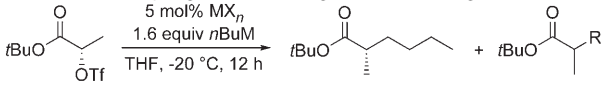
prepared from either α-amino acids (vide infra) or enzymatically generated chiral cyanohydrins.[6] Thus, the transformation of the hydroxy function into a leaving group followed by an sp^3–sp^3 cross-coupling reaction with an organometallic nucleophile could become an attractive alternative if the reaction occurs with control of the stereochemistry.

Unfortunately, known cross-coupling protocols employing stereogenic secondary electrophiles occur as stereorandom processes.[7–14] An elegant solution to this problem is to use racemic substrates in combination with a chiral nickel catalyst in order to achieve good levels of enantioselectivity.[15,16] To the best of our knowledge the stereoselective sp^3–sp^3 cross-coupling of α-hydroxy ester derivatives is restricted to the use of stoichiometric amounts of transition-metal salts, employing cuprate reagents.[17,18] The stereochemical outcome corresponded to complete inversion of configuration. Unfortunately, yields were low owing to side reactions arising from electron-transfer processes.

To find an improved and widely applicable method for the synthesis of optically active α-alkylcarbonyl compounds on a large scale and under mild conditions, we examined the reaction of organometallic reagents with secondary alkyl electrophiles. We report herein the development of a zinc-catalyzed cross-coupling reaction of Grignard reagents with α-hydroxy ester triflates.

Initial investigations of the reaction between lactic acid derived triflate **1a**[19] and a Grignard reagent in the absence of any catalyst resulted in a low yield of coupling product **2a** as a result of competitive side reactions such as the formation of chloride **3** (Table 1, entry 1). Adding an iron catalyst led to the formation of homocoupling product **4**, while the presence of a copper salt[20] resulted in only a slightly higher yield of **2a** as well as the reduction of the triflate to ester **5** (Table 1, entry 3). Finally, the addition of a catalytic amount of $ZnCl_2$ resulted in a quantitative yield of **2a** with complete inversion of configuration (Table 1, entry 4).[21,22] When *n*-butylmagnesium bromide was used instead of the corresponding chloride, only low yields of the desired product could be obtained (Table 1, entry 5). The presence of magnesium salts proved critical, as Mg-free systems were ineffective (Table 1, entry 6).

Table 1: Cross-coupling of **1a** with organometallic reagents.



(−)-**1a** (+)-**2a** **3**: R = Cl; **4**: R = $CH(Me)CO_2tBu$; **5**: R = H

Entry	Cat. MX_n	nBu-M	**2a** [%][a]	Conv. [%][b]
1	–	*n*BuMgCl	46	62
2	$[Fe(acac)_3]$	*n*BuMgCl	0	>99
3	Li_2CuCl_4	*n*BuMgCl	56	>99
4	$ZnCl_2$	*n*BuMgCl	>99	>99
5	$ZnCl_2$	*n*BuMgBr	11	>99
6	$ZnCl_2$	*n*BuLi	0	>99

[a] Yield determined by GC with an internal standard. [b] Determined by ^1H NMR spectroscopy.

Under optimized reaction conditions, the cross-coupling reaction of triflate **1a** or nonaflate **1b** at 0 °C with 1.4 equivalents of chloromagnesium reagent and 2.5 mol% of zinc catalyst resulted in a quantitative yield of the coupling product after 3 h (Scheme 2). Reducing the amount of either

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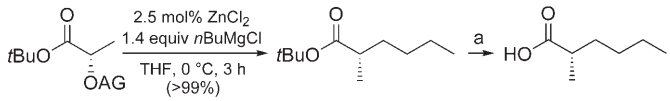


(−)-**1a** AG = Tf >99% *ee* (+)-**2a** >99% *ee* (+)-**6** >99% *ee*
(−)-**1b** AG = Nf >99% *ee*

Scheme 2. Determination of the absolute configuration of **2a**. a) TFA (trifluoroacetic acid), CH_2Cl_2, RT, >99%. Tf = trifluoromethanesulfonyl, Nf = nonafluorobutanesulfonyl.

the Grignard reagent or $ZnCl_2$ led to the formation of small amounts of chloride **3** (Table 2, entries 1 and 4). The absolute configuration of ester **2a** was determined by its conversion to

Table 2: Optimization of the reaction conditions for the cross-coupling of **1a** with *n*BuMgCl.

Entry	*n*BuMgCl	$ZnCl_2$ [mol%]	**2a** [%][a]	**3** [%]
1	1.1 equiv	5.0	98	2
2	1.4 equiv	5.0	>99	–
3	1.4 equiv	2.5	>99	–
4	1.4 equiv	1.0	96	4

[a] Combined quantitative yield; ratio was determined by ^{1}H NMR spectroscopy.

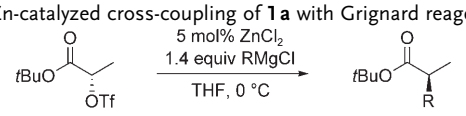
the known carboxylic acid **6**, an important building block of the high-potency sweetener NC-00637.[23] This proved the course of the transformation to proceed by inversion of configuration.

Using the optimized conditions, we next investigated the reaction of **1a** with a variety of organomagnesium nucleophiles to explore the scope and generality of this process (Table 3). Not only primary (entries 1, 3, 4, 7, and 8), but also secondary acyclic (entries 2 and 5), secondary cyclic (entry 6), and functionalized (entries 9–11) Grignard reagents were found to be suitable coupling partners, affording the target compounds **2a–k** in excellent yields and with complete inversion of configuration.

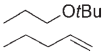
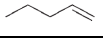
Thus, enantiospecific carbon–carbon bond formation proceeds smoothly with **1a** and an array of different alkyl chloromagnesium reagents under mild conditions.[24] The generality of this cross-coupling reaction makes **1a** an important building block in organic synthesis,[25] as it is easily prepared and stable, and it can be stored at −20 °C for several months.

After having examined different variations of the nucleophilic partner in the zinc-catalyzed cross-coupling reaction with lactic acid derived triflate **1a**, we turned our attention to other electrophiles, investigating several structurally diverse α-hydroxy ester derivatives. Starting from inexpensive and commercially available α-amino acids **7a–f** we obtained the α-hydroxy acids **8a–f** by a known diazotization protocol (Scheme 3).[26] Subsequent straightforward conversions of **8a–f** to α-hydroxy ester triflates **9a–f**[19] yielded the electrophilic coupling partners in enantiopure form. Substrate **9g** was obtained directly from L-malic acid.

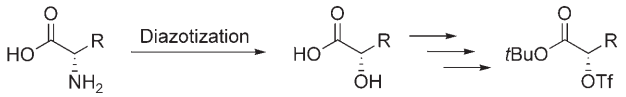
Table 3: Zn-catalyzed cross-coupling of **1a** with Grignard reagents.



(−)-**1a** >99% *ee* (+)-**2a-k**

Entry	R[a]	Product	Yield [%][b]	*ee* [%][c]	CT [%][d]
1	Et	(+)-**2b**	>99	>99	100
2	*i*Pr	(+)-**2c**	98	>99	100
3	*n*Bu	(+)-**2a**	>99	>99	100
4	*i*Bu	(+)-**2d**	>99[e]	>99	100
5	*s*Bu	(+)-**2e**	96[f]	>99[g]	100
6	Cy	(+)-**2f**	90[h]	>99	100
7	Oct	(+)-**2g**	>99	>99[i]	100
8	lauryl	(+)-**2h**	>99	>99[i]	100
9	Bn	(+)-**2i**	>99	>99[j]	100
10		(+)-**2j**	94[k]	>99	100
11		(+)-**2k**	>99	>99	100

[a] Cy = cyclohexyl, Bn = benzyl. [b] Yield of isolated product. [c] Determined by GC on a chiral phase. [d] The chirality transfer (CT) was calculated as CT = [*ee*(**2**)/*ee*(**1**)] × 100%. [e] 20 mol% $ZnCl_2$. [f] Combined yield of a 1:1 mixture of diastereomers. [g] Each diastereomer is enantiopure. [h] 10 mol% $ZnCl_2$. [i] The enantiomeric excess was determined after conversion of the reduced ester to the acetate. [j] Determined by HPLC on a chiral phase. [k] 2.3 equiv of Grignard reagent led to a quantitative yield.



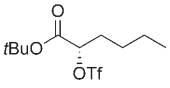
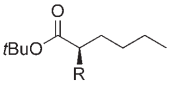
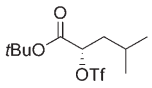
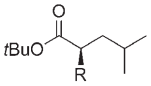
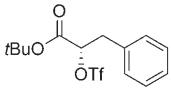
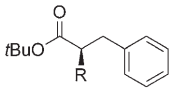
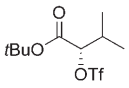
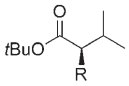
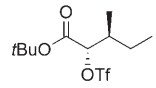
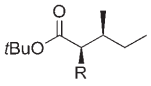
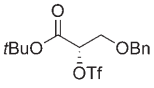
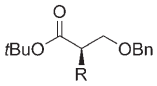
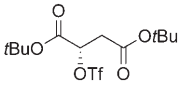
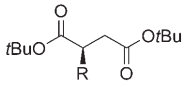
(−)-**7a-f** (−)-**8a-f** (−)-**9a-f**

Scheme 3. Synthesis of enantiopure α-hydroxy ester triflates **9a–f** from α-amino acids **7a–f**.

The zinc-catalyzed cross-coupling is general and can be extended to a wide variety of substrates, generating the coupling products with complete inversion of configuration. α-Hydroxy ester derived electrophiles with a linear alkyl chain (**9a**), a β-branched alkyl chain (**9b**), or a benzyl substituent (**9c**) in the α position could be coupled with primary Grignard reagents to quantitatively yield the corresponding products (Table 4, entries 2, 5, and 8). When less-reactive MeMgCl was used, the cross-coupling proceeded sluggishly and an excess of Grignard reagent had to be used to minimize competing side reactions (Table 4, entries 1, 4, and 7). The cross-coupling with secondary Grignard reagents resulted in very good yields (Table 4, entries 3, 6, and 9) but was accompanied by the formation of small amounts of the corresponding reduction products.

Even more challenging β-substituted α-hydroxy ester triflates **9d** and **9e** could be coupled quantitatively with EtMgCl (Table 4, entries 11 and 14), although an excess of *n*BuMgCl was required to drive the reaction to complete conversion (entries 12 and 15). In the case of MeMgCl an increase of the reaction temperature to 20 °C, an excess of organomagnesium reagent, and higher catalyst loading were needed to ensure complete conversion and a good yield (Table 4, entries 10 and 13).

Table 4: Zn-catalyzed cross-coupling of α-hydroxy ester triflates **9a–g** with Grignard reagents.[a]

Entry	Substrate	Product	R	$ZnCl_2$ [mol%]	Yield [%][b]	*ee* [%][c]	CT [%][d]
1	 (−)-**9a**, 99% *ee*		(−)-**2a**, R = Me	20	92[e]	99	100
2			(−)-**10a**, R = Et	5	> 99	99	100
3			(−)-**10b**, R = *i*Pr	15	88	99	100
4	 (−)-**9b**, >99% *ee*		(−)-**2d**, R = Me	20	81[e]	> 99	100
5			(−)-**11a**, R = Et	10	> 99	> 99	100
6			(−)-**11b**, R = *i*Pr	15	79	> 99	100
7	 (−)-**9c**, 98% *ee*		(−)-**2i**, R = Me	20	72[e]	98[f]	100
8			(−)-**12a**, R = Et	5	> 99	98[f]	100
9			(−)-**12b**, R = *i*Pr	20	84	98[f]	100
10	 (−)-**9d**, >99% *ee*		(−)-**2c**, R = Me	50	76[g]	> 99	100
11			(−)-**13a**, R = Et	15	> 99	> 99	100
12			(+)-**10b**, R = *n*Bu	20	> 99[h]	> 99	100
13	 (−)-**9e**, 99% *de*, >99% *ee*		(−)-**2e**, R = Me	50	73[g]	99[i]	100
14			(−)-**14a**, R = Et	20	> 99	99[i]	100
15			(+)-**14b**, R = *n*Bu	20	> 99[j]	99[i]	100
16	 (−)-**9f**, 97% *ee*		(−)-**15**, R = Et	20	95[k]	97[f]	100
17	 (−)-**9g**, >99% *ee*		(−)-**16**, R = Me	20	74[e]	> 99	100

[a] Unless otherwise noted, reactions were carried out on a 1 mmol scale in THF (0.3 M) with 1.4 equiv of a Grignard solution in THF (1.0–2.5 M) for 3 h at 0 °C. [b] Yield of isolated product. [c] Unless otherwise noted, determined by GC on a chiral phase. [d] The chirality transfer (CT) was calculated as CT = [*ee*(**2**)/*ee*(**1**)] × 100%. [e] 2.3 equiv MeMgCl. [f] Determined by HPLC on a chiral phase. [g] 5.0 equiv MeMgCl, slow addition (3 mL h^{-1}) of the Grignard reagent at 20 °C. [h] 4.5 equiv *n*BuMgCl. [i] *de*, > 99% *ee*. [j] 2.5 equiv *n*BuMgCl. [k] 2.0 equiv EtMgCl.

β-Functionalized α-hydroxy ester substrates, such as serine-derived triflate **9f** and malic acid derivative **9g** proved compatible with the cross-coupling reaction conditions as well, generating excellent yields of the coupling products (Table 4, entries 16 and 17) and thereby extending the scope of the reaction.[27] The zinc-catalyzed cross-coupling of chloromagnesium reagents with α-hydroxy ester triflates tolerates substantial variations in both reaction partners. The resulting coupling products can be used for further synthetic manipulations, making this methodology a valuable and practical tool in organic synthesis.

In summary, we have documented the first stereospecific zinc-catalyzed sp^3–sp^3 cross-coupling reaction employing Grignard reagents. As an ideal catalyst, inexpensive and nontoxic anhydrous zinc chloride was identified. Readily available α-hydroxy esters served as electrophilic coupling partners. They are available in enantiomerically pure form from the chiral pool either directly (L- and D-lactic acid, L-malic acid, etc.) or in a one-step protocol by the diazotization of the corresponding α-amino acids. This methodology offers an attractive alternative to enolate alkylation and features a reversal of polarity. This allows for the preparation of compounds having sterically crowded tertiary carbon centers in excellent yield and enantioselectivity that are not accessible by classical techniques.

Experimental Section

Typical procedure: (+)-**2a** (Table 2, entry 3): A solution of anhydrous $ZnCl_2$ (3.4 mg, 2.5 mol%) in dry THF (3 mL) at 0 °C was treated successively with triflate (−)-**1a** (278 mg, 1.00 mmol) and *n*BuMgCl (2.0 M in THF; 0.70 mL, 1.4 mmol, 1.4 equiv) in an argon atmosphere. After the reaction mixture had been stirred for 3 h at this temperature, it was diluted with *n*-pentane and quenched by the addition of a saturated aqueous NH_4Cl solution. The reaction mixture was then extracted three times with *n*-pentane, and the combined organic layers were applied directly to a pad of silica gel. The filter was rinsed with *n*-pentane, the product was eluted with a mixture of *n*-pentane/Et_2O (10:1), and the solvent was distilled off at atmospheric pressure

to give (+)-**2a** (186 mg, >99% yield, >99% *ee*). The enantiomeric excess was determined by GC on a chiral phase (Chiraldex G-TA column 30 m × 0.25 mm, 1.2 bar He, isothermal 40 °C); retention times: 69.9 min (minor *R* enantiomer) and 72.0 min (major *S* enantiomer). $[\alpha]_D^{20} = +11.5$ ($c = 0.83$, $CHCl_3$). The absolute configuration of the product was determined by converting (+)-**2a** to carboxylic acid (+)-**6** $[\alpha]_D^{20} = +18.1$ ($c = 0.84$, $CHCl_3$) and comparing with reported data:[28] $[\alpha]_D^{20} = +15.8$ ($c = 1.0$, $CHCl_3$).

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Keywords: alkylation · C–C coupling · chiral pool · Grignard reaction · zinc

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