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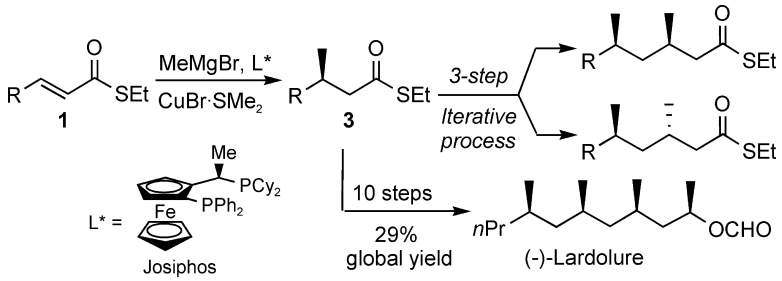

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An Iterative Catalytic Route to Enantiopure Deoxypropionate Subunits: Asymmetric Conjugate Addition of Grignard Reagents to α,β-Unsaturated Thioesters

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The occurrence of polydeoxypropionate chains in numerous biologically relevant compounds has stimulated the development of methods for their stereocontrolled synthesis.[1] Most of the reported procedures are based on iterative chiral auxiliary strategies (i.e., enolate alkylations, conjugate additions, and allylic alkylations),[2] although, very recently, an attractive iterative catalytic asymmetric procedure was disclosed by Negishi and co-workers.[3] Despite these important advances, the development of simple, enantioselective methods for the construction of these units with absolute stereocontrol and high synthetic flexibility continues to be a particularly desirable goal.

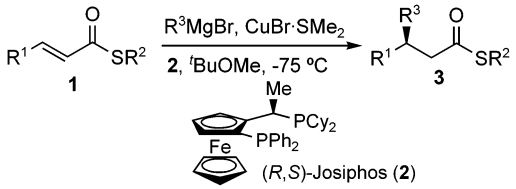
Recently, we reported a highly enantioselective conjugate addition (CA) of Grignard reagents to α,β-unsaturated esters.[4] Unfortunately, despite the scope of the method, the poor results obtained in the 1,4-additions of the less reactive MeMgBr impeded the development of catalytic iterative methodology for 1,3-dimethyl arrays. To address this issue, we focus our attention on the more reactive but equally readily accessible α,β-unsaturated thioesters.[5] The reduced electron delocalization in the thioester moiety,[6] compared to oxoesters, results in a higher reactivity toward CA reactions,[7,8] while the presence of the thioester in the chiral product offers additional synthetic versatility.[9] Herein, we report the implementation of this strategy, which results in a practical method for the addition of methyl Grignard reagents and a highly efficient and enantioselective iterative catalytic protocol for the synthesis of deoxypropionates.

Preliminary investigations involving unsaturated thioester **1a** revealed the feasibility of this approach. Indeed, the in situ prepared complex from CuBr·SMe_2 (5 mol %) and Josiphos (**2**, 6 mol %) catalyzed the 1,4-addition of MeMgBr, providing complete conversion to **3a** in 2 h at −75 °C (Table 1, entry 1). Importantly, these conditions afforded an excellent enantioselectivity of 96% for this CA.[10] The scope of the new method was next investigated, and it can be seen from Table 1 that a range of thioesters are suitable substrates for the CA, furnishing exclusively the 1,4-addition products **3** with excellent yields, high enantioselectivity, and complete regioselectivity.

Particularly noteworthy, the additions of MeMgBr proceed with equally high selectivity when the catalyst loading is reduced to only 1 mol %, providing the methylated 1,4-addition products with 92−96% ee and isolated yields of 88−94% (entries 2−8). The CA to substrate **1f**, bearing a protected hydroxyl group, and to the aryl-substituted unsaturated thioester **1g** proceeded with excellent 95% ee (entries 7, 8), further demonstrating the scope and potential of the method. Only substrate **1e**, bearing a smaller ethyl group at the alkene, gave a slightly lower 92% ee (entry 6).

Furthermore, other linear Grignard reagents, such as EtMgBr, *n*PrMgBr, and *n*BuMgBr, also participate in the CA, providing

Table 1. Enantioselective CA of Grignard Reagents (R^3MgBr) to α,β-Unsaturated Thioesters (**1**)[a,b]



entry	**1**	R^1	R^2	Grignard (R^3)	yield (**3**) (%)[c]	ee (%)[d]	
1	**a**	*n*Pent	Et	MeMgBr	90 (**a**)	96	
2[e]	**a**	*n*Pent	Et	MeMgBr	90 (**a**)	96	
3[e]	**b**	*n*Pent	Me	MeMgBr	93 (**b**)	96	
4[e]	**c**	*n*Bu	Et	MeMgBr	93 (**c**)	95	(*R*)[f]
5[e]	**d**	*n*Pr	Et	MeMgBr	92 (**d**)	96	(*R*)[f]
6[e]	**e**	Et	Et	MeMgBr	92 (**e**)	92	(*R*)[f,g]
7[e]	**f**	$BnO(CH_2)_3$	Et	MeMgBr	94 (**f**)	95	(*R*)[f]
8[e]	**g**	Ph	Et	MeMgBr	88 (**g**)	95	(*S*)[f]
9	**a**	*n*Pent	Et	EtMgBr	89 (**h**)	86	
10	**b**	*n*Pent	Me	EtMgBr	91 (**i**)	87	
11	**e**	Et	Et	*n*PrMgBr	87 (**j**)	85	
12	**h**	Me	Et	*n*BuMgBr	90 (**c**)	90	(*S*)[f]
13	**a**	*n*Pent	Et	*i*PrMgBr	93 (**k**)	25	
14	**a**	*n*Pent	Et	*i*BuMgBr	80 (**l**)	15	

[a] Conditions: **1** (1.0 equiv), R^3MgBr (1.2 equiv), CuBr·SMe_2 (5 mol %), **2** (6 mol %), in ^{t}BuOMe (0.1 M), −75 °C, 2−5 h, unless otherwise noted. [b] All conversions > 98% (GC−MS). [c] Isolated yield. [d] Regio- and enantioselectivity determined by chiral GC or HPLC.[11] [e] With 1 mol % CuBr·SMe_2, 1.2 mol % **2**. [f] Absolute configuration determined by correlation with known compounds.[11] [g] Enantiomeric excess determined on the oxoester.[4,11]

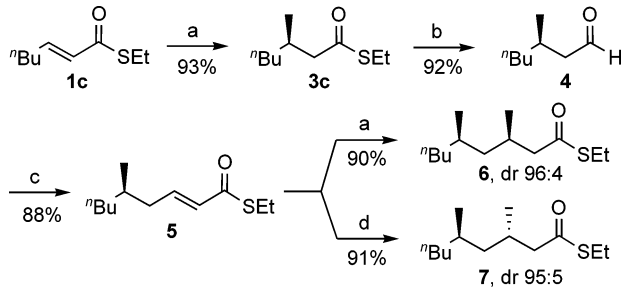
enantioselectivities in the range of 85−90% (entries 9−12). Bulky Grignard reagents, such as *i*PrMgBr and *i*BuMgBr, however, gave poor enantioselectivities under these conditions (entries 13, 14).

The drastically higher yields obtained for the methyl adducts from α,β-unsaturated thioesters, compared to the oxoester analogues,[4] are most probably due to their inherent electronic properties which are closer to those of enones (vide supra).[6c] However, a possible positive effect arising from a coordination of the active catalyst to the sulfur atom may not be ruled out.

Once the new, practical, and effective procedure for the enantioselective CA of MeMgBr to unsaturated acid derivatives was developed, an iterative method to provide access to optically active *syn*- and *anti*-1,3-dimethyl arrays was pursued.[12] The approach, based on sequential enantioselective CAs to unsaturated thioesters, is shown in Scheme 1. The first stereogenic center was created in 95% ee by the addition of MeMgBr to **1c**, using Josiphos **2**. The resulting thioester **3c** was efficiently converted in one step into the corresponding aldehyde **4** (Et_3SiH, 10 mol % Pd/C, 92% yield),[13] which subsequently underwent a Wittig reaction to give the desired Michael acceptor **5** in 88% yield. Finally, a second catalytic (1 mol %) CA using Josiphos **2** or its enantiomer *ent*-**2** afforded with

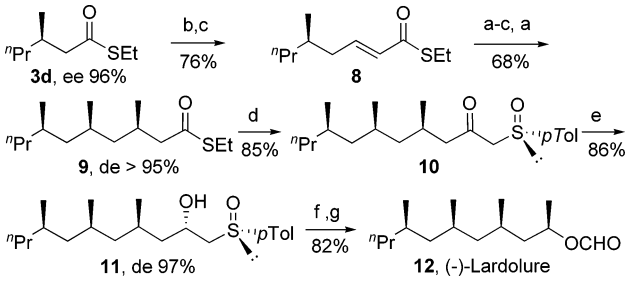
10.1021/ja053020f CCC: $30.25

Scheme 1 [a]



[a] Conditions: (a) MeMgBr (1.2 equiv), **2** (1.2 mol %), CuBr·SMe_2 (1 mol %), ^{t}BuOMe, −75 °C, 2 h; (b) 10% Pd/C (5 mol %), Et_3SiH, CH_2Cl_2, rt, 20 min; (c) $Ph_3PCHCOSEt$, CH_2Cl_2, reflux; (d) MeMgBr (1.2 equiv), *ent*-**2** (1.2 mol %), CuBr·SMe_2 (1 mol %), ^{t}BuOMe, −75 °C, 3 h.

Scheme 2 [a]



[a] Conditions: (a−c) see Scheme 1 caption; (d) (*S*)-MeSO*p*Tol, LDA, THF, −78 °C; (e) DIBAL-H, $ZnBr_2$, THF, −78 °C; (f) Raney-Ni, EtOH, rt; (g) HCOOH, 65 °C.

excellent yields and selectivity the 1,3-dimethyl derivatives (3*R*,5*R*)-**6** (90% yield, dr 96:4) and (3*S*,5*R*)-**7** (91% yield, dr 95:5). The high diastereoselectivities obtained in this simple three-step iterative protocol demonstrate the efficiency of the chiral catalyst to control the configuration at the new stereocenter, independently of the absolute configuration of the chain.[14]

The synthetic utility of the iterative sequence and the versatility of β-methyl-substituted thioesters are further demonstrated in the asymmetric total synthesis of (−)-lardolure,[15] the aggregation pheromone of the acarid mite *Lardoglyphus konoi* (Scheme 2).

The route starts with the enantiopure thioester **3d**, obtained in 92% yield and 96% ee from the 1,4-addition of MeMgBr to **1d**. The iterative sequence shown in Scheme 2 provided the polydeoxypropionate derivative **9** in 52% yield over six steps from **3d**. Importantly, the second and third 1,4-addition proceed with excellent diastereoselectivities (dr 97.5:2.5 and 98:2, respectively) at the newly formed stereocenter, affording **9** with an overall de > 95%. For the introduction of the final stereogenic center, the stereocontrolled reduction of enantiopure β-ketosulfoxides, a well-established method for preparing enantiomerically pure alcohols, was employed.[16]

The synthesis of the sulfinyl ketone **10** was efficiently achieved by condensation of thioester **9** with the lithium anion of (*S*)-methyl-*p*-tolylsulfoxide.[17] Notably, the purification of **10** allowed the increase of the diastereomeric purity above 97%. Subsequent reduction with DIBAL-H in the presence of $ZnBr_2$ afforded the β-hydroxysulfoxide **11** in 86% yield and with excellent diastereoselectivity (dr 98.5:1.5) at the new stereocenter. Finally, desulfurization of **11** followed by formylation of the resulting alcohol led to (−)-lardolure **12** in 82% yield (two steps).[18]

In summary, we have developed a highly enantioselective (up to 96% ee) CA of Grignard reagents, in particular, MeMgBr, to α,β-unsaturated thioesters and demonstrated its application in a diastereo- and enantioselective iterative route to both *syn*- and *anti*-1,3-dimethyl arrays and deoxypropionate chains. The versatility of the method is illustrated in the synthesis of (−)-lardolure, a multimethyl-branched insect pheromone, obtained in 12 steps and 26% overall yield from commercial available (*E*)-hex-2-enoic acid.

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Supporting Information Available: Experimental procedures and spectroscopic data of the reaction products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) Thioesters can be efficiently obtained in one step from the corresponding oxoesters, aldehydes, carboxylic acids, anhydrides, or acyl chlorides.[11]

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(14) On the basis of the mass action law, and considering the absence of internal asymmetric induction, a reliable ee > 99.9% for (3*R*,5*R*)-**6** and (3*S*,5*R*)-**7** can be predicted. See ref 3b.

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(17) To the best of our knowledge, this is the first example of the use of a thioester for this reaction, further demonstrating their synthetic versatility.

(18) NMR properties (^{1}H and ^{13}C), optical rotation, and mass spectrometry data of **12** were identical to those reported for the natural pheromone.

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