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Efficient Synthesis of α-Quaternary α-Hydroxy-β-amino Esters via Silyl Glyoxylate-Mediated Three-Component Reactions

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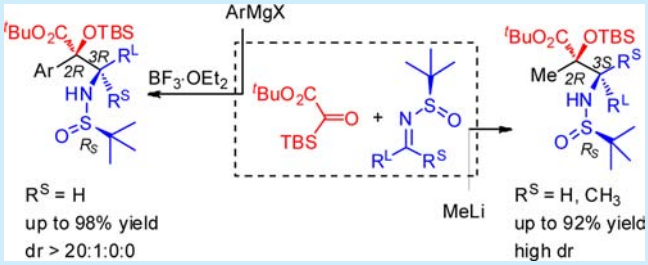
Supporting Information

ABSTRACT: An efficient method has been developed for the enantioselective synthesis of fully protected α-quaternary α-hydroxy-β-amino esters via the coupling of three components: aryl Grignard reagents (or methyllithium), silyl glyoxylate, and *N*-*tert*-butanesulfinyl imines. This protocol enables successive formation of two C−C bonds and two adjacent chiral carbons with high stereocontrol in a one-pot operation.

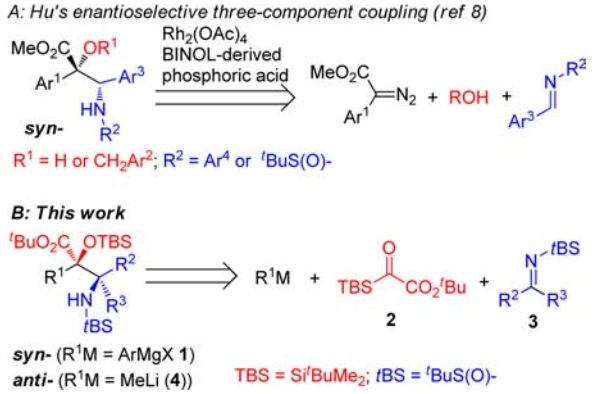


α-Hydroxy-β-amino acids and their congeners are important building blocks in natural products and biologically active agents.[1] Representative examples are taxoid-based anticancer agents, such as paclitaxel (Taxol), docetaxel, and cabazitaxel, all of which carry (2*R*, 3*S*)-3-phenylisoserine on C-13.[2] The success of these anticancer agents has stimulated tremendous efforts to develop efficient methods to synthesize this side chain.[3] In addition, preliminary SAR studies of taxoids with structurally different side chains suggest that installing a methyl group at the 2-position on the side chain without changing its absolute configuration of (2*R*, 3*S*) enhances cytotoxic activity.[4]

General and straightforward methods for enantioselective synthesis of β-amino acids derivatives bearing an α-tertiary carbinol center are relatively scarce.[5−7] Nevertheless, Hu and co-workers recently described an impressive synthetic protocol using $Rh_2(OAc)_4$-catalyzed three-component coupling of diazo compounds, alcohols, and imines.[8] This approach can be used to construct enantioenriched *syn*-α-aryl-α-hydroxy-β-amino esters in the presence of a catalytic amount of chiral phosphoric acid with high enantioselectivity (Scheme 1, pathway A). As part of our continuing investigations into multicomponent transformations,[9] we have developed an analogous synthetic method for constructing α-quaternary α-hydroxy-β-amino esters in which the three components that undergo coupling are aryl Grignard reagents **1** (or methyllithium **4**), silyl glyoxylate **2**, and *N*-*tert*-butanesulfinyl imine **3** (Scheme 1, pathway B).[10]

The compound *tert*-butyl 2-(*tert*-butyldimethylsilyl)-2-oxoacetate **2**, a member of the family of silyl glyoxylates known for their usefulness as conjunctive reagents,[11] works effectively as a linchpin reagent in the coupling of nucleophiles and electrophiles at a glycolic acid junction. This coupling has allowed the synthesis of a range of α,α-disubstituted glycolic acid derivatives.[12] The success of these silyl glyoxylate-mediated coupling reactions sometimes requires careful selection of coupling partners.[9a,12d,h] For example, activated imines such as

Scheme 1. Three-Component Reactions to Construct α-Tertiary α-Hydroxy β-Amino Esters



N-*tert*-butanesulfinyl aldimine **3**[9a] have proven to be good electrophilic trapping reagents in three-component couplings in the presence of lithium aza-enolates.[13] We speculated that suitable organometallic reagents might also initiate similar transformations that would efficiently generate α-quaternary α-hydroxy-β-amino esters.

We began our investigation by employing phenylmagnesium bromide **1a** as a nucleophilic initiator to react with silyl glyoxylate **2** and (R_S)-*N*-*tert*-butanesulfinyl aldimine **3a** (Table 1, entry 1). To our delight, treating **2** with **1a** and **3a** at −78 °C gave the expected, fully protected α-phenyl α-hydroxy-β-amino ester **4a** with excellent diastereoselectivity (dr >20:1:0:0) and moderate yield (70%). The moderate yield was due to incomplete conversion of *t*BS-imine **3a**. This problem was overcome by introducing 3.0 equiv of boron trifluoride etherate

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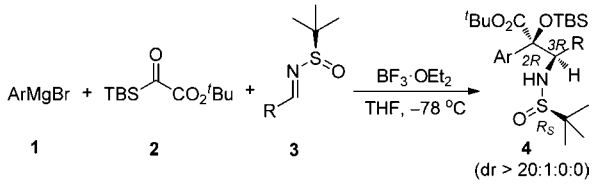
Table 1. Synthesis of α-Aryl-α-hydroxy-β-amino Esters via Three-Component Coupling[a]



entry	1 (Ar)	3 (R)	products	yield (%)[b]
1	**1a** (Ph)	**3a** (4-BrC_6H_4)	**4a**	98 (91)[c]
2	**1a** (Ph)	**3b** (2-BrC_6H_4)	**4b**	67
3	**1a** (Ph)	**3c** (3-BrC_6H_4)	**4c**	73
4	**1a** (Ph)	**3d** (4-$MeOC_6H_4$)	**4d**	61
5	**1a** (Ph)	**3e** (Ph)	**4e**	82
6	**1a** (Ph)	**3f** (2-thienyl)	**4f**	93
7	**1a** (Ph)	**3g** (*trans*-PhCH=CH)	**4g**	85
8	**1a** (Ph)	**3h** (*trans*-MeCH=CH)	**4h**	82
9	**1a** (Ph)	**3i** (Et)	**4i**	76
10	**1a** (Ph)	**3j** (*i*-Pr)	**4j**	45
11	**1b** (2-naphthyl)	**3a** (4-BrC_6H_4)	**4k**	70
12	**1c** (4-FC_6H_4)	**3a** (4-BrC_6H_4)	**4l**	63 (98)[d]
13	**1d** (4-$Me_2NC_6H_4$)	**3a** (4-BrC_6H_4)	**4m**	69
14	**1e** (cyclohexyl)	**3a** (4-BrC_6H_4)	**4n**	67

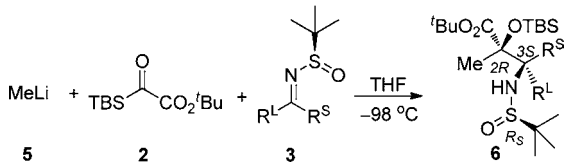
[a]All reactions were carried out in THF with 3.05 equiv of **1** and 3.0 equiv of **2** at −78 °C unless otherwise noted; see the Supporting Information for details. The dr was determined by ^{1}H NMR of the crude reaction mixture. [b]Isolated yield after silica gel chromatography. [c]1 g scale reaction. [d]5.0 equiv of **1c** and 5.0 equiv of **2** were used.

in the reaction, which increased the isolated yield of **4a** to 98% without reducing the dr.[14] Using these optimized reaction conditions, we scaled up the reaction to 1 g and obtained a 91% yield. Notably, performing the reaction at temperatures above −20 °C in the absence of boron trifluoride etherate reduced the dr. In fact, adding the imine **3a** to the reaction at −78 °C and then quickly warming the mixture to room temperature led to inversion of diastereoselectivity (dr = 1:4:0:0). The reason for the observed inverted diastereoselectivity is unclear.

Studies of the scope of this three-component coupling reaction (Table 1) revealed that *t*BS-imines derived from various aryl aldehydes (entries 1−6), α,β-unsaturated aldehydes (entries 7 and 8), or unbranched and branched alkyl aldehydes (entries 9 and 10) can couple with **1a** and **2** to furnish the desired products **4a**−**h** in yields of 45−98%. However, attempts to extend this method to acetophenone-derived *t*BS-imines were unsuccessful. In addition to phenylmagnesium bromide **1a**, other aryl Grignard reagents **1b**−**d** and cyclohexylmagnesium bromide **1e** were well tolerated under the reaction conditions, allowing easy generation of diverse substitutions at the 2-position in product **4** (Table 1, entries 11 and 13). Phenyllithium, on the other hand, did not react as desired in this coupling protocol, giving rise to an uncharacterizable complex. In the particular case of synthesizing **4l** (entry 12), increasing the amount of **1c** and **2** from 3.0 to 5.0 equiv improved the yield from 63% to 98%. In all reactions in Table 1, only one diastereomer was observed (dr >20:1:0:0). The absolute configuration of compound **4e** was established to be (2*R*, 3*R*, R_S) by single-crystal X-ray analysis.[15] The configuration of the other products was assigned by analogy.

We then applied this synthetic strategy to the construction of α-methyl-α-hydroxy-β-amino esters. The reaction of MeMgBr with **2** and **3a** proceeded smoothly at −78 °C and led to a mixture of two inseparable diastereomers (**4o**, dr = 5.5:1:0:0) in 96% yield. When methyllithium was used to initiate the three-component reaction (Table 2, entry 1), coupling product **6a**

Table 2. Synthesis of α-Methyl-α-hydroxy-β-amino Esters via Three-Component Coupling[a]



entry	3 (R^L, R^S)	products	yield (%)[b]	dr[c]
1	**3a** (4-BrC_6H_4, H)	**6a**	92	>20:1:0:0
2	**3b** (2-BrC_6H_4, H)	**6b**	71	>20:1:0:0
3	**3c** (3-BrC_6H_4, H)	**6c**	55	>20:1:0:0
4[d]	**3e** (Ph, H)	**6d**	90	>20:1:0:0
5	**3k** (4-MeC_6H_4, H)	**6e**	75	>20:1:0:0
6	**3l** (2-furyl, H)	**6f**	61	>20:1:0:0
7	**3m** (3-pyridine, H)	**6g**	81	15:1:0:0
8	**3i** (Et)	**6h**	41	>20:1:0:0
9[e]	**3n** (Ph, Me)	**6i**	89	>20:1:0:0
10[e]	**3o** (4-BrC_6H_4, Me)	**6j**	89	>20:1:0:0
11	**3p** (4-$MeOC_6H_4$, Me)	**6k**	87	>20:1:0:0

[a]All reactions were carried out in THF with 2.1 equiv of **5** and 2.0 equiv of **2** unless otherwise noted; see the Supporting Information for details. [b]Isolated yield after silica gel chromatography. [c]Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [d]3.0 equiv of **5** and 3.0 equiv of **2** were used. [e]2.5 equiv of **5** and 2.5 equiv of **2** were used.

was generated in 92% yield with excellent diastereoselectivity.[16] The absolute stereochemistry of **6a** was assigned to be (2*R*, 3*S*, R_S) by single-crystal X-ray analysis of its desilylation product **7**,[15] which differed from that of **4o**.

We were able to extend the methyllithium-initiated cascade transformation to several different *t*BS-imines bearing a variety of aryl and heteroaryl substituents (Table 2, entries 1−7). In particular, the fully protected (2*R*, 3*S*)-α-methyl-α-hydroxy-β-amino ester **6d** (entry 4) should be an appropriate precursor for the side chain of 2′-methyl-taxoids.[4] Linear alkyl *t*BS-imine **3i** participated in the coupling reaction to give a relatively low yield of product with excellent diastereoselectivity (entry 8). Using *t*BS-imines derived from acetophenones (entries 9−11) led to α-hydroxy-β-amino esters possessing vicinal stereogenic quaternary carbon centers in good yields with excellent diastereocontrol (dr >20:1:0:0). Rather than with methyl lithium, a similar coupling reaction could not be initiated by lithium hydride even at elevated temperatures. Instead, the starting materials **2** and **3a** were intact. Attempts to extend the described coupling reaction to a sterically hindered lithium reagent (*t*BuLi) were unsuccessful. In this case, no three-component coupling products were obtained.

The stereochemical outcome for product **4** was consistent with Ellman's chelated 6/4-membered bicyclic transition state **TS-1** in the chair conformation[17] (Scheme 2). In this pathway, mixing aryl Grignard reagent **1** with silyl glyoxylate **2** leads to 1,2-silyl migration from carbon to oxygen, preferentially forming (*Z*)-glycolate enolate **8**.[12g] The observed stereoselectivity of **6** may be rationalized by invoking Aitken's 6/6 chelated bicyclic chairlike transition state **TS-2**, or a non-

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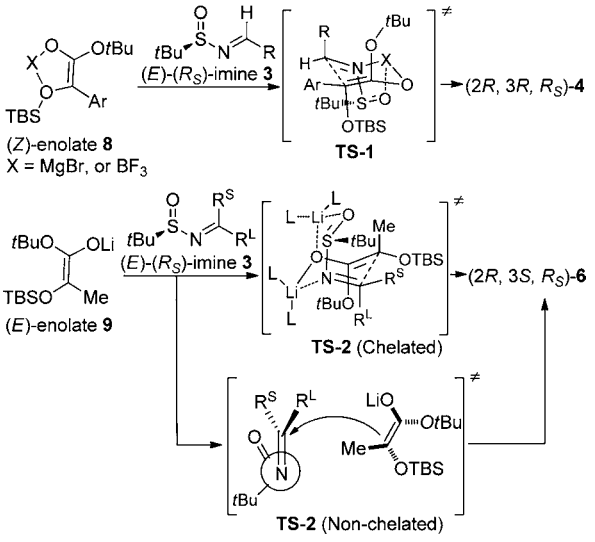
Scheme 2. Model for Diastereoselection



chelated open transition state **TS-3**.[18] In this scheme, mixing methyllithium to **2** is proposed to yield (*E*)-lithium glycolate enolate **9** exclusively.[19]

In summary, we have developed an efficient protocol for synthesizing fully protected α-aryl or α-methyl α-hydroxy-β-amino esters via three-component coupling of aryl Grignard reagents or methyllithium, *tert*-butyl 2-TBS-2-oxoacetate, and *N*-*tert*-butanesulfinyl imines. This method allows rapid, highly stereocontrolled construction of diverse, enantioenriched α-quaternary α-hydroxy-β-amino esters.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(15) See the Supporting Information for details.
(16) Notably, the usage of methyllithium was essential for high diastereoselectivity in this transformation. Poor diastereoselectivity was observed when methyllithium was replaced with *n*-butyllithium in the three-component coupling reaction with **2** and **3a**.
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(19) Preferential formation of (*Z*)-lithium glycolate enolates is normally assumed in Brook rearrangements of silyl glyoxylates that are initiated by lithium enolates or lithium aza-enolates. See refs 9a and 12g.

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