Pergamon

Tetrahedron Letters 41 (2000) 9527–9531

TETRAHEDRON LETTERS

Enantioenriched acid, ester, and ketone β-phenyl homoenolate synthetic equivalents from *N*-Boc-*N*-(*p*-methoxyphenyl)cinnamylamine†

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Received 26 September 2000

Abstract

Oxidation of the β-substituted highly enantioenriched aldehydes obtained by hydrolysis of the 3,3-disubstituted enecarbamates affords enantioenriched β-substituted acids and esters. Lithiation of enantioenriched 3,3-disubstituted enecarbamates and subsequent reaction with electrophiles provides vinylically substituted enecarbamates. The use of benzyl and alkyl halide electrophiles affords α-substituted enecarbamates, which can be hydrolyzed to provide enantioenriched β-substituted ketones. Reaction of the lithiated intermediate with ketones affords oxazolidinones, which can be reductively ring-opened with DIBAL and hydrolyzed to provide enantioenriched β-substituted, α′-hydroxy ketones. These transformations demonstrate that the enantioselective lithiation of *N*-Boc-*N*-(*p*-methoxyphenyl)cinnamylamine provides a reactive intermediate which can be a ketone, acid, or ester homoenolate synthon. © 2000 Published by Elsevier Science Ltd.

Homoenolate synthons (**1**) allow electrophilic substitution β to a carbonyl group and are of increasing value as a synthetic tool in organic chemistry.[1] Since homoenolates are umpoled synthons, the carbonyl group is often masked as a heterovinyl group.[2] Highly enantioenriched, formally dipole stabilized carbanions,[3] produced by enantioselective deprotonation of allylic alcohol and amine derivatives, have been used primarily as aldehyde homoenolate synthetic equivalents (**1**, $R_2 = H$).[4–6] The reaction of *N*-Boc-*N*-(*p*-methoxyphenyl)cinnamylamine **2** with *n*-BuLi/(−)-sparteine followed by electrophilic substitution to afford enecarbamates **3** and **4** with high enantioenrichment is exemplary (Scheme 1).[5] Treatment of **3** or **4** with 6 M HCl in $CHCl_3$ provides β-substituted enantioenriched aldehydes **5** and **6**.

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† Dedicated to Harry H. Wasserman, an esteemed scientist and remarkable scholar, on the occasion of his 80th birthday.

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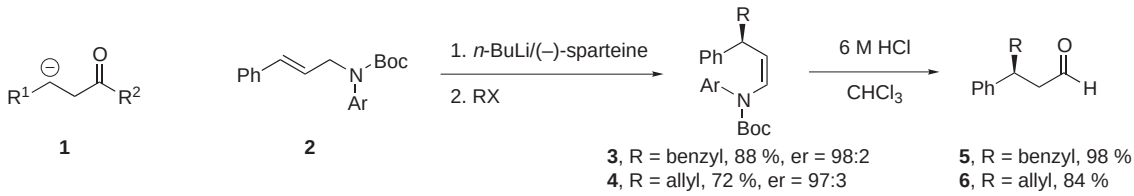
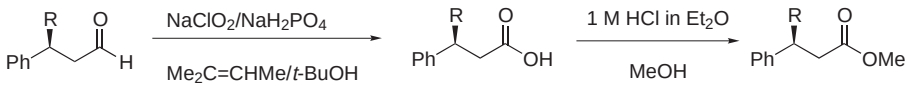
PII: S0040-4039(00)01663-4



Scheme 1.

In this communication, we report that the aldehydes resulting from hydrolysis of enecarbamates **3** and **4** can undergo mild oxidation to acids followed by esterification to afford enantioenriched esters in good yields. Previously, enantioenriched ester (**1**, $R_2 = OR$) homoenolate equivalents have been prepared by treatment of β-iodoalanine with a zinc–copper couple,[7] by direct metallation of (*S*)-3-iodo isobutyrate with activated zinc, or by reductive cyclization of (*S*)-3-bromo isobutyrate followed by ring opening with $ZnCl_2$.[8] We also describe the α-lithiation and substitution of **3** and **4** to give enecarbamates which can be hydrolyzed to enantioenriched ketones. In this methodology, the choice of electrophile allows for the incorporation of a variety of R_2 groups. Enantioenriched ketone (**1**, R_2 = alkyl or aryl) homoenolate equivalents have been reported from chiral auxiliary-mediated lithiation of allylic amines[6] and (–)-sparteine-mediated lithiation of *O*-allyl carbamates[4] for cases in which the R_2 group is present in the starting material.

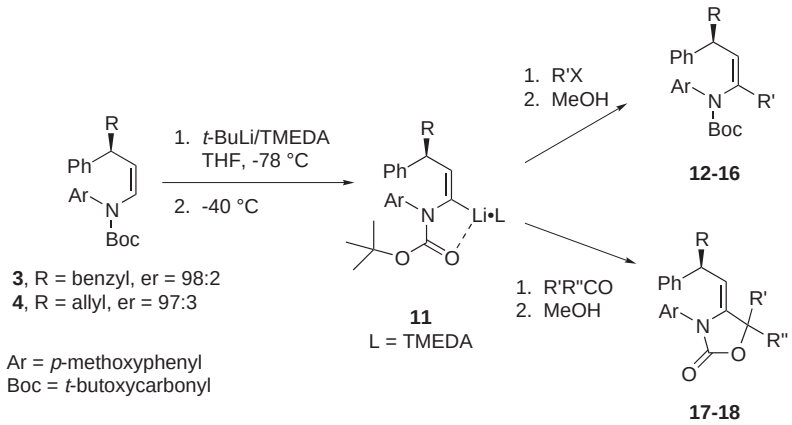
Enantioenriched β-substituted acids and esters can be isolated in high yield upon derivatization of aldehydes **5** and **6**. Oxidation of **5** and **6** with sodium chlorite[9] affords acids **7** and **8** in high yield.[10] Esterification of the carboxylic acids with 1 M HCl in diethyl ether and methanol provides esters **9** and **10** in good yields (Scheme 2). Alternate approaches to esterification with Cs_2CO_3 and iodomethane[11] provide the desired ester in slightly lower yields.



Scheme 2.

Enantioenriched β-substituted ketones can be accessed by further elaboration of the enecarbamates **3** and **4**. Directed α-lithiation/substitution sequences of **3** and **4** provide α-substituted enecarbamates (Scheme 3).[12] Treatment of **3** or **4** with *t*-BuLi/TMEDA at −78°C followed by warming to −40°C provides the putative lithiated intermediate **11**, which reacts with alkyl (Table 1, entries 1–4) or benzyl (Table 1, entry 5) halides to afford vinyl substituted products **12**–**16** in moderate to good yields. Ketones (Table 1, entries 6 and 7) react with the lithiated intermediate and cyclize with the Boc protecting group to provide oxazolidinones **17** and **18** in moderate yields.

Ease of removal of the masking group to provide a β-substituted carbonyl compound is important to the synthetic utility of a masked homoenolate methodology. In the cases of the *O*-allyl carbamates, cleavage of the masking group is difficult.[4] In the present work, removal of the heterovinyl mask by treatment of the α-substituted enecarbamates with 6 M HCl in $CHCl_3$ proceeds cleanly and quickly to afford β-substituted enantioenriched ketones in good yields. As

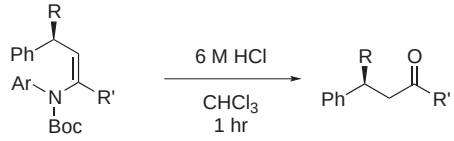


Scheme 3.

Table 1
Lithiation/substitution sequences of **3** and **4**

Entry	Substrate	Electrophile	R′	R″	Product	Yield (%)
1	**3**	MeI	Me	–	**12**	85
2	**3**	EtI	Et	–	**13**	72
3	**4**	*n*-BuBr	*n*-Bu	–	**14**	31
4	**4**	CH_2=$CHCH_2Br$	CH_2CH=CH_2	–	**15**	83
5	**4**	$PhCH_2Br$	$PhCH_2$	–	**16**	79
6	**3**	$(CH_2)_5CO$	–$(CH_2)_5$–		**17**	62
7	**4**	$(CH_3)_2CO$	Me	Me	**18**	52

Table 2
Hydrolysis of α-substituted enecarbamates



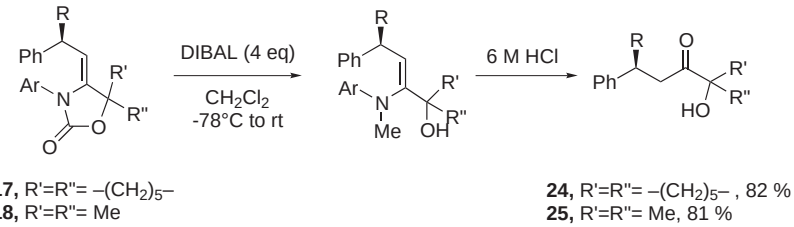
12-16 **19-23**

Entry	Substrate	R′	Product	Yield (%)
1	**12**	Me	**19**	70
2	**13**	Et	**20**	85
3	**14**	*n*-Bu	**21**	96
4	**15**	CH_2CH=CH_2	**22**[a]	70
5	**16**	CH_2Ph	**23**	69

[a] Upon standing, the double bond isomerizes to the conjugated product, R′ = –CH=$CHCH_3$.

evidenced in Table 2, alkyl (entries 1–4) and benzyl (entry 5) groups can be incorporated into the ketone.

α′-Hydroxy ketones are accessible in one pot from the oxazolidinones that were prepared by reaction of the lithiated intermediate **11** with ketone electrophiles (vide supra). Treatment of the oxazolidinone **17** or **18** with DIBAL at −78°C followed by warming to rt affords a ring-opened enamine.[13] The enamine is treated in situ with 6 M HCl to provide the enantioenriched β-substituted, α′-hydroxy ketone **24** or **25** in good yield (Scheme 4).



17, R'=R"= –$(CH_2)_5$–
18, R'=R"= Me

24, R'=R"= –$(CH_2)_5$– , 82 %
25, R'=R"= Me, 81 %

Scheme 4.

In summary, the present work demonstrates that the (−)-sparteine complexed, lithiated intermediate from *N*-Boc-*N*-(*p*-methoxyphenyl)cinnamylamine **2** can be developed as a β-phenyl acid, ester, and ketone homoenolate equivalent. The approach should be easily extended to other β-aryl systems and is being investigated for β-alkyl groups.

Acknowledgements

This work was supported by a grant from the National Institute of Health (GM-18874). We are grateful for this support.

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10. Purification of the aldehydes is recommended in order to remove the by-product ArNHBoc. Otherwise, oxidation of the crude aldehyde mixture also generates impurities, which are difficult to separate from the desired carboxylic acid.
11. On average, the yields were ~5% lower for each substrate. (a) Parrish, J. P.; Dueno, E. E.; Kim, S.-I.; Jung, K. W. *Synth. Commun*. **2000**, *30*, 2687–2700. (b) Kruizinga, W. H.; Strijtveen, B.; Kellogg, R. M. *J. Org. Chem*. **1981**, *46*, 4321–4323.
12. *Representative procedure*: to a stirring solution of **4** (122 mg, 0.734 mmol) and TMEDA (68 μL, 0.321 mmol) in dry THF (6 mL, 0.054 M) at −78°C under N_2 was added *t*-BuLi (1.45 M, 0.24 mL, 0.385 mmol). The dark yellow solution was stirred for 45 min before warming to −40°C, whereupon the mixture turned dark green. After stirring at −40°C for 1 h, allyl bromide (56 μL, 0.642 mmol) was added and the reaction was stirred for 2 h. The solution was then quenched with MeOH, warmed to rt, poured into 50 mL H_2O, and extracted with ether (3×25 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to provide the crude product as a yellow oil. The oil was purified by column chromatography (90:10, petroleum ether:EtOAc) to give pure **15** as a colorless oil (112 mg, 83%).
13. The α-hydroxy enamines can be isolated after treatment of the oxazolidinones with DIBAL.