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A Highly Stereoselective Synthesis of Tri- and Tetrasubstituted Olefins via Ynolates

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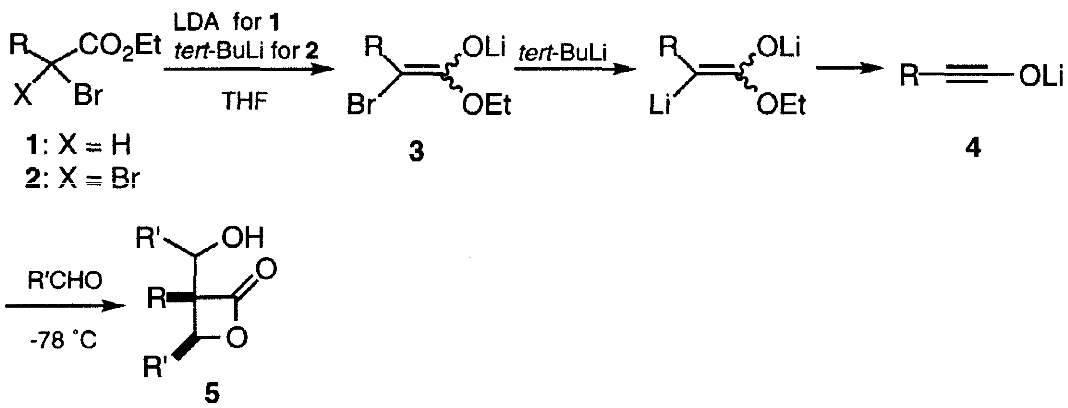
Abstract: A highly stereoselective synthesis of tri- and tetrasubstituted olefins has been accomplished by the reactions of ynolates with aldehydes and ketones.

Recently, we have reported a new and convenient method for the generation of lithium ynolate (**4**) via the cleavage of ester dianions (**3**) prepared from α-bromo (**1**)[1] or α,α-dibromo esters (**2**).[2] Herein we describe that the ynolates react with aldehydes and ketones at room temperature to afford trisubstituted and tetrasubstituted olefins with extremely high *E* selectivity.[3]



Scheme 1.

In the previous papers,[1,2] we have also reported that *alkyl*-substituted ynolates (**4**) react with two equivalents of aldehydes to give trisubstituted β-lactones (**5**) (Scheme 1). In order to investigate the synthetic utility of these products, **5a** was treated with *tert*-butyllithium at -78 °C. We expected the more useful 3,4-disubstituted β-lactone to be generated via retro-aldol reaction of the alkoxides (**5a'**). Although nothing happened at -78 °C, as the mixture was allowed to warm to room temperature, the β-lactone (**5a**) disappeared, and (*E*)-α-butylcinnamic acid (**6a**) was obtained in 50% yield as a *single* isomer (Scheme 2). This product is

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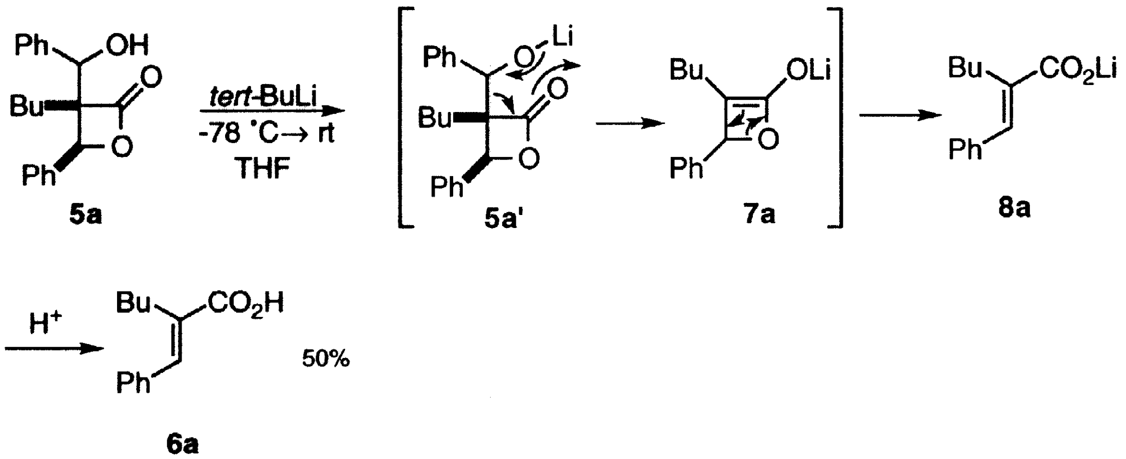
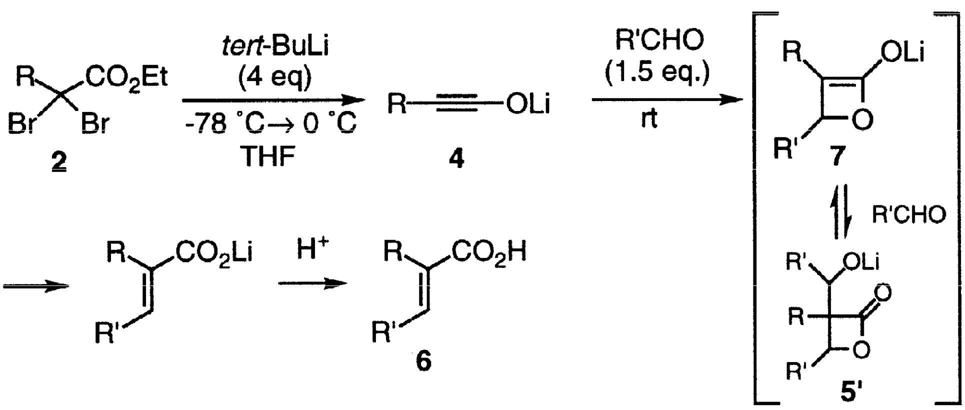
thought to arise from the retro-aldol reaction of the alkoxide (**5a'**), followed by ring-opening of the resulting β-lactone enolate (**7a**).



Scheme 2.

On the basis of this result, we focused on a one-pot synthesis of trisubstituted olefins via ynolates without isolation of the intermediates. This process is exemplified by the following: a solution of **2** (1.0 mmol) in THF was treated with *tert*-BuLi (4.0 mmol) at -78 °C. After the reaction mixture was stirred at -78 °C for 3 h and then at 0 °C for 30 min, it was treated with benzaldehyde (1.5 mmol) at room temperature. After being stirred for 30 min, the reaction mixture was quenched with sat. NH_4Cl aq. and extracted with CH_2Cl_2. The organic phase was extracted with 5% NaOH solution and then the aqueous layer was acidified with conc. HCl aq., followed by extraction with CH_2Cl_2. The organic layer was washed with brine, dried and evaporated *in vacuo* to afford almost pure α-butylcinnamic acid (**6a**) in 73% yield (Table 1, Entry 1). Judging from ^{1}H-NMR spectroscopic data, only the (*E*)-olefin was generated.[4] As shown in Table 1, **6a~6f** were obtained in excellent *E*/*Z* ratio. In the case of **6g**, an E/Z ratio of 5:1 was achieved, despite the steric hindrance of this *E*-olefin. This one-pot synthesis of the trisubstituted olefins appears to be general for a variety of **4**, including primary, secondary, or tertiary R groups, and starting aldehydes. The monobromoesters (**1**), as starting materials in place of **2**, also gave similar results (e. g. Table1, Entry 7) The stereoselectivity of the olefin synthesis is comparable to that of classical[5] and non-classical[6] Horner-Wadsworth-Emmons-type reactions and Lewis acid-catalyzed coupling of ynol ether and aldehydes.[7]

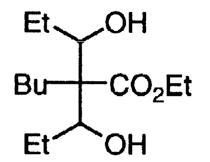


Scheme 3.

Table 1 Synthesis of Trisubstituted Olefins (6) via Ynolates

Entry	R	R'	Product		
			6	E:Z[a]	Yield (%)
1	Bu	Ph	**6a**	>99:1	73
2	Bu	(*E*)-CH_3CH=CH	**6b**	>99:1	71
3	Bu	(*E*)-PhCH=CH[b]	**6c**	>99:1	74
4	Bu	*tert*-Bu	**6d**	>99:1	51
5	Bu	Et	**6e**	>99:1	24[c]
6	cyclohexyl	Ph	**6f**	>99:1	62
7	cyclohexyl[d]	Ph	**6f**	>99:1	45
8	cyclohexyl	*tert*-Bu	**6g**	5:1	(44)[e]
9	*tert*-Bu	Ph	**6h**	20:1	58

a) See notes 4. b)1.0 eq of aldehyde was used. c) **5e** (28%) and **9** (42%) were isolated as by-products. d) The ynolate was prepared from α-bromo-ester (**1**). e)The yields of the corresponding methyl ester, generated by diazomethane and **6**.



9

It is not clear whether the lithium alkoxide (**5'**) was generated as an intermediate in this procedure. Since the efficiency of the retro-aldol reaction (**5a'** → **7a**) was not so good as shown in Scheme 2, although the yield of **6a** was over 70%, it might be possible that most of β-lactone enolate (**7a**) was directly converted to the carboxylate (**8a**) without the intervention of aldol (**5a'**) (Scheme 3). In the case of propionaldehyde (Table 1, Entry 5), **5e** and **9**, generated by the addition of LiOEt to **5e'**, were isolated in 28% and 42% yield, respectively. This result suggests that the formation of **5'** reduces the yield of **6**.

Next, we tried the stereoselective formation of tetrasubstituted olefins using ketones as electrophiles. When α-tetralone (**10i**) was used, the desired olefin (**11**) was obtained with good *E* selectivity in 77% yield

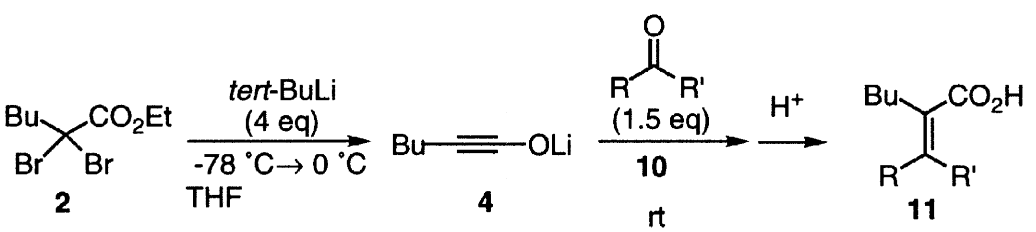


Table 2 Synthesis of Tetrasubstituted Olefins (11) via Ynolate

Entry	Ketone			Product		
		R	R'		E:Z	Yield (%)
1	**10i**	α-tetralone		**11i**	7:1	77
2	**10j**	Ph	Me	**11j**	6:1	82
3	**10k**	Ph	Et	**11k**	4:1	71

(Table 2, Entry 1). Acetophenone (**10j**) and propiophenone (**10k**) also gave the corresponding olefins (**11j**, **11k**) in which *E*-forms were predominant (Table 2, Entry 2, 3). These results indicate that this olefin synthesis is applicable to a stereoselective construction of tetrasubstituted olefins, which are reagarded as very difficult to achieve with high stereoselectivity.[8]

Although a possible explanation for the mechanism of this conversion might be a concerted, electrocyclic thermal ring-opening of the β-lactone enolate, additional investigation is needed to clarify the details.[9]

In conclusion, we have developed an efficient and highly stereoselective construction of tri- and tetrasubstituted olefins via the reaction of ynolates with aldehydes and ketones. This one-pot procedure is an operationally simple and useful alternative to the classical Horner-Wadsworth-Emmons reactions, taking into account the common precursors, α-bromo esters.

Acknowledgment

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References and Notes

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