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Zirconium-Catalyzed Asymmetric Carboalumination of Alkenes: ZACA–Lipase-Catalyzed Acetylation Synergy

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This paper is dedicated to Professor Masakatsu Shibasaki on the occasion of his 60th birthday.

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Abstract: ZACA–lipase-catalyzed acetylation tandem reactions provide highly efficient and selective routes to either (*R*)- or (*S*)-2-methyl-1-alkanols, making, for the first time, the ZACA-based asymmetric synthesis of 2-methyl-1-alkanols widely applicable and satisfactory.

Keywords: Amano PS lipase; lipase-catalyzed acetylation; 2-methyl-1-alkanols; porcine pancreas lipase (PPL); ZACA reaction (Zr-catalyzed asymmetric carboalumination of alkenes)

Lipase-catalyzed selective acetylation of (*S*)-2-alkyl-1-alkanols has been used for the purification of 2-alkyl-1-alkanols.[1] Virtually all previous works on this topic have, however, dealt with purification of the racemic mixtures of 2-alkyl-1-alkanols.[1] As such, the lipase-catalyzed acetylation method suffers from two serious limitations. A useful theoretical prediction[2] reliably predicts that it would be virtually impossible to obtain enantiomerically pure ($\geq$98% *ee*) (*S*)-2-alkyl-1-alkanols by lipase-catalyzed selective acetylation of racemic mixtures even if the selectivity factor *E* is 100, where *E* (enantiomeric ratio) = ln[(1−*C*)(1−*ee*)]/ln[(1−*C*)(1+*ee*)], *C* and *ee* being the extent of conversion and the enantiomeric excess of the unreacted alcohols, respectively, expressed in fractions. The other well-known and obvious limitation is that the yields of the enantiomerically pure ($\geq$98% *ee*) *R* isomers are limited to $\leq$50% ($\leq$25% if *E* = 10, $\leq$35% if *E* = 20, and $\leq$ 45% if *E* = 100).[2]

The Zr-catalyzed asymmetric carboalumination of alkenes (ZACA reaction hereafter), discovered during the 1995–1996 period,[3] is a prototypical, controlled, asymmetric carbon-carbon bond-formation reaction of unactivated alkenes of "one-point binding", which does not require any other functional group. It is catalytic in both Zr and chiral auxiliaries and is therefore potentially economical. In cases where the chiral target molecules contain two or more asymmetric carbon centers, statistical enantiomeric amplification *via* kinetic resolution is operative, and an average stereoselectivity of 90% (or 80% *ee*) is minimally sufficient for producing enantiomerically pure ($\geq$99% or $\geq$98% *ee*) compounds containing two asymmetric carbon centers.[4,5] The presence of three or more asymmetric centers will further lower the minimally required average stereoselectivity level. These favorable features have provided a foundation for our recent development of the ZACA-based protocols for the synthesis of deoxypolypropionates[5–7] featuring (i) an unprecedentedly high efficiency attained through the development of a "one-pot" ZACA–Pd-catalyzed cross-coupling tandem process[5d] and (ii) a previously unrecognized facile diastereomeric purification by ordinary column chromatography (silica gel, EtOAc-hexanes) of a wide variety of 2,4-dimethyl-1-hydroxybutyl fragments.[5] As attractive and satisfactory as the ZACA reaction is for the synthesis of deoxypolypropionates and some other compounds containing two or more asymmetric centers,[8] its applicability to the synthesis of chiral organic compounds containing either a single asymmetric carbon center or two or more asymmetric carbon centers that do not effectively interact for facile diastereomeric separation has been less satisfactory, representing a major deficiency to be overcome.

We now report that the ZACA reaction of $\geq$70–80% *ee* (or $\geq$85–90% stereoselectivity) followed by the lipase-catalyzed acetylation with vinyl acetate indeed eliminates the limitations discussed above, rendering, for the first time, the ZACA-based asymmetric synthesis of stereoisomerically pure ($\geq$99%) 2-methyl-1-alkanols widely satisfactory.[9] The ready access to enantiomerically pure (*S*)-2-alkyl-1-alkanols

in practically useful yields is based on the above-mentioned kinetic theory permitting compilation of Table 1, which indicates that the maximum yield attainable for the preparation of (*S*)-2-alkyl-1-alkanols through lipase-catalyzed acetylation of racemic mixture is $\leq 2\%$, even if *E* is 100. On the contrary, useful yields of $\geq 80\%$ can be attainable, if the initial mixture is $\geq 60\%$ *ee* and if *E* is 100, and the higher the initial *ee*, the lower can be the threshold *E* value.

Prompted by these encouraging theoretical predictions, enantiomeric purification of 2-methyl-1-alkanols of 76–90% *ee* containing a phenyl group in the 2-, 3-, or 4-position obtained by the ZACA reaction of the corresponding 1-alkenes was carried out, and the results are summarized in Table 2. The originally sluggish ZACA reaction of inexpensive styrene[3] ($ 1/mol) has been significantly accelerated by addition of H_2O, MAO,[10] or IBAO,[4b] where MAO is methylaluminoxane and IBAO is isobutylaluminoxane, to give, after oxidation with O_2, an 85% yield of (*R*)- or (*S*)-2-phenyl-1-propanol (**1**) of 89–90% *ee*. Although a widely used and highly acclaimed, Amano PS lipase from *Pseudomonas cepacia* ($ 78.30/50 g from Aldrich) was disappointingly ineffective (entries 1 and 2), less expensive porcine pancreas lipase (PPL) ($ 95.70/500 g from Aldrich) was found to be highly effective, producing (*R*)-2-phenyl-1-propanol of 98% *ee* in 78% recovery (entry 3) or of 99% *ee* in 62% recovery (entry 4). Furthermore, the acetate of (*S*)-2-phenyl-1-propanol of $\geq 98\%$ *ee* was also obtained in 72% yield from a 95/5 mixture (90% *ee*) of (*S*)- and (*R*)-2-phenyl-1-propanol (entry 5). Hydrolysis of the acetate provided nearly quantitatively pure (*S*)-2-phenyl-1-propanol ($\geq 98\%$ *ee*). Thus, either enantiomer of 2-phenyl-1-propanol is now readily obtainable as an enantiomerically pure compound of $\geq 98\%$ *ee* in 61–66% overall yield from styrene in an unprecedentedly efficient, satisfactory, and potentially economical manner.

Curiously, Amano PS lipase proved to be not only satisfactory but significantly superior to PPL in the purification of (*R*)-2-methyl-3-phenyl-1-propanol [(*R*)-**2b**, $n=1$][1a,3a] obtained in 85% yield and in 76% *ee* in one step from allylbenzene (entries 6–8). On the other hand, PPL is somewhat more favorable than Amano PS lipase in the purification of (*R*)-2-methyl-4-phenyl-1-butanol [(*R*)-**2c**, $n=2$] (entries 9–11). Its *S* isomer was also obtained *via* its acetate that was obtained in 70% yield and in 97% *ee* (entry 12). Other commercially available lipases, such as Amano PF, Amano F-AP15, and Fluka PFL, were also used in these cases, but it was not readily feasible to obtain enantiomerically pure ($\geq 98\%$ *ee*) compounds with these lipases. Despite the unexpectedly favorable results observed with 2- and 4-phenyl-substituted 2-methyl-1-alkanols, PPL has been generally less satisfactory than Amano PS lipase. As amply demonstrated below, it does appear reasonable to initially choose Amano PS lipase in the absence of information indicating otherwise. Significantly, the results obtained with 2-phenyl-1-propanol are in striking contrast with the previously reported rather poor results obtained with racemic 2-aryl-1-propanols containing phenyl, naphthyl, and thienyl groups, for which low *E* value of ≤ 9 was reported.[1d–f] On the contrary, the *E* value for 2-phenyl-1-propanol observed in its PPL-catalyzed acetylation in THF was 42 ($C=23.1\%$, 28.3% *ee*).

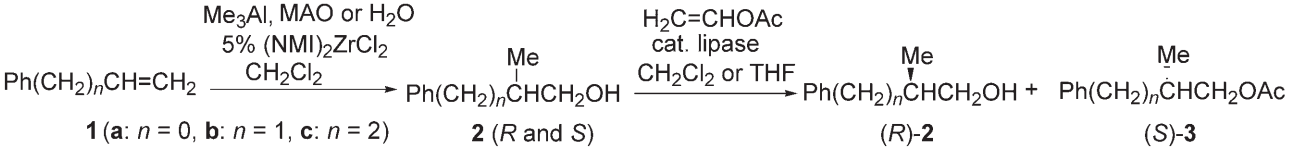
The favorable results presented above further prompted us to apply the ZACA–lipase-catalyzed acetylation protocol to the synthesis of other classes

Table 1. The maxinally attainable yields of (*S*)-2-alkyl-1-alkanols of $>98\%$ *ee* from the racemic and enantiomerically enriched mixtures (this table was compiled according to Ref.[2]).

Initial ee_o (%)	*E*[a]	Max. yield (%)[a,b]	Initial ee_o (%)	*E*[a]	Max. yield (%)[a,b]
0 (racemic)	100	<2	70	100	<85
	90	0		50	~80
				30	~60
20	100	<35		20	~25
	80	~20		10	0
	60	0			
			80	100	<90
50	100	<70		30	~85
	50	~55		20	~70
	40	~25		10	0
	30	0			
			90	100	<95
60	100	<80		20	<95
	50	~65		10	80
	30	~25		5	0
	20	0			

[a] See text.
[b] Based on the extent of conversion (*C*).

Table 2. ZACA–lipase-catalyzed acetylation tandem processes for the synthesis of ω-phenyl-2-methyl-1-alkanols.



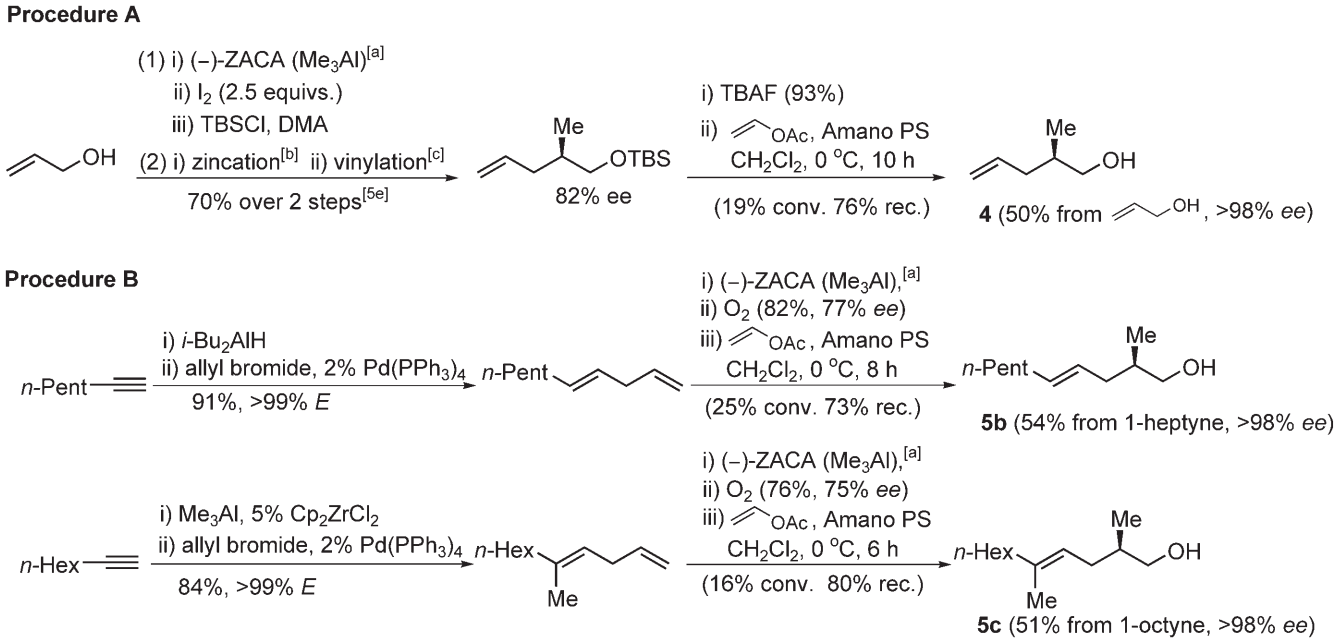
Entry	*n*	**1**	**2** Yield[a] [%]	**2** *R* or *S*[b]	**2** Purity [% *ee*]	Ref.	Lipase	Conversion *C* [%]	Recovery or yield [%]	Purity [% *ee*]
1	0	$PhCH=CH_2$	85	*R*	89 – 90	[5d,10]	Amano PS	22	68	93
2							Amano PS	50	49	96
3							**PPL**	**14**	**78**	**98**
4							**PPL**	**31**	**62**	**99**
5	0	$PhCH=CH_2$	85	*S*	89 – 90	[5d,10]	**PPL**	**80**	**72**[c]	**98**
6	1	$PhCH_2CH=CH_2$	85	*R*	76	[3a]	Amano PS	30	69	96
7							**Amano PS**	**40**	**59**	**99**
8							PPL	48	51	77
9	2	$Ph(CH_2)_2CH=CH_2$	85	*R*	78	[8]	**Amano PS**	**38**	**56**	**99**
10							**PPL**	**20**	**79**	**98.5**
11							**PPL**	**30**	**64**	**99**
12	2	$Ph(CH_2)_2CH=CH_2$	85	*S*	78	[8]	**Amano PS**	**75**	**70**[c]	**97**

[a] Isolated yields based on **1**.
[b] Configuration of the major enantiomer. *R*- or *S*-enriched products were obtained by using (−)- or (+)-$(NMI)_2ZrCl_2$, respectively.
[c] The product is (*S*)-**3**.

of 2-methyl-1-alkanols. Aside from the intrinsically limited product yields of 25–36%, some examples of lipase-catalyzed enantiopurification producing 4-alkenyl-2-methyl-1-alkanols of >96% *ee* from their racemic mixtures are known.[1b,d] Even so, rather modest *E* values of 10 and 13 were reported for the purification of 2-methyl-4-penten-1-ol (**4**) and (*E*)-2-methyl-4-hexen-1-ol (**5a**), respectively,[1d] although the latter case reported in another paper[1b] was claimed to be more favorable. We have recently reported two widely applicable routes to enantiomerically enriched (70–85% *ee*) 2-methyl-4-alken-1-ols (**5**), one involving a one-step synthesis of TBS-protected (*R*)- and (*S*)-3-iodo-2-methyl-1-propanols in 82% yield and 82% *ee* followed by Pd-catalyzed alkenylation and deprotection[5e] (Procedure A) and the other involving the synthesis of 1,4-dienes *via* Pd-catalyzed alkenyl-allyl coupling[11] followed by the ZACA reaction typically in 70–85% yields and 70–85% *ee*[12] (Procedure B). A few representative 2-methyl-4-alken-1-ols (**4**, **5b**, and **5c**) were accordingly prepared and subjected to the lipase-catalyzed acetylation using Amano PS lipase. As summarized in Scheme 1, all compounds were readily purified to ≥ 98% *ee* in 70–80% recoveries. The *E* value measured for racemic **5c** was 22 (*C* = 18.4%, 20.2% *ee*).

Somewhat less favorable but still satisfactory results have been obtained with 2-methyl-5-alken-1-ols (**6**), as indicated by the results shown in Scheme 2. Thus, **6a** and **6b** prepared by the ZACA reaction of the corresponding terminal alkenes in 76% and 77% yields and 75% and 78% *ee*, respectively, were purified by Amano PS lipase-catalyzed acetylation to 98% *ee* in 66% and 62% recoveries, respectively. In the case of **6b**, the acetate initially obtained was hydrolyzed with NaOMe in MeOH to give **6b** in 97% yield. Oxidation of **6a** with *N*-methylmorpholine *N*-oxide (NMO) produced aldehyde **7** which has recently been converted to the ethyl ester of the side-chain (**8**) of antifungal and cytotoxic stellettamide B[13] in one step in 71% yield, while the conversion of **6b** to the side-chain (**9**) of stellettamide A[14] was performed in two steps in 75% overall yield (Scheme 2). The results shown in Scheme 1 and Scheme 2 suggest that the ZACA–lipase-catalyzed acetylation tandem protocol provides an efficient and selective route to a variety of 4- and 5-alkenyl-substituted 2-methyl-1-alkanols, such as **4**, **5**, and **6** of ≥98% *ee*.

Despite an exceptional and puzzling claim to the preparation of the acetate of (*S*)-2-methyl-1-decanol of 98% *ee* in 39% yield from the racemic mixture,[1c] the great majority of the previously reported results

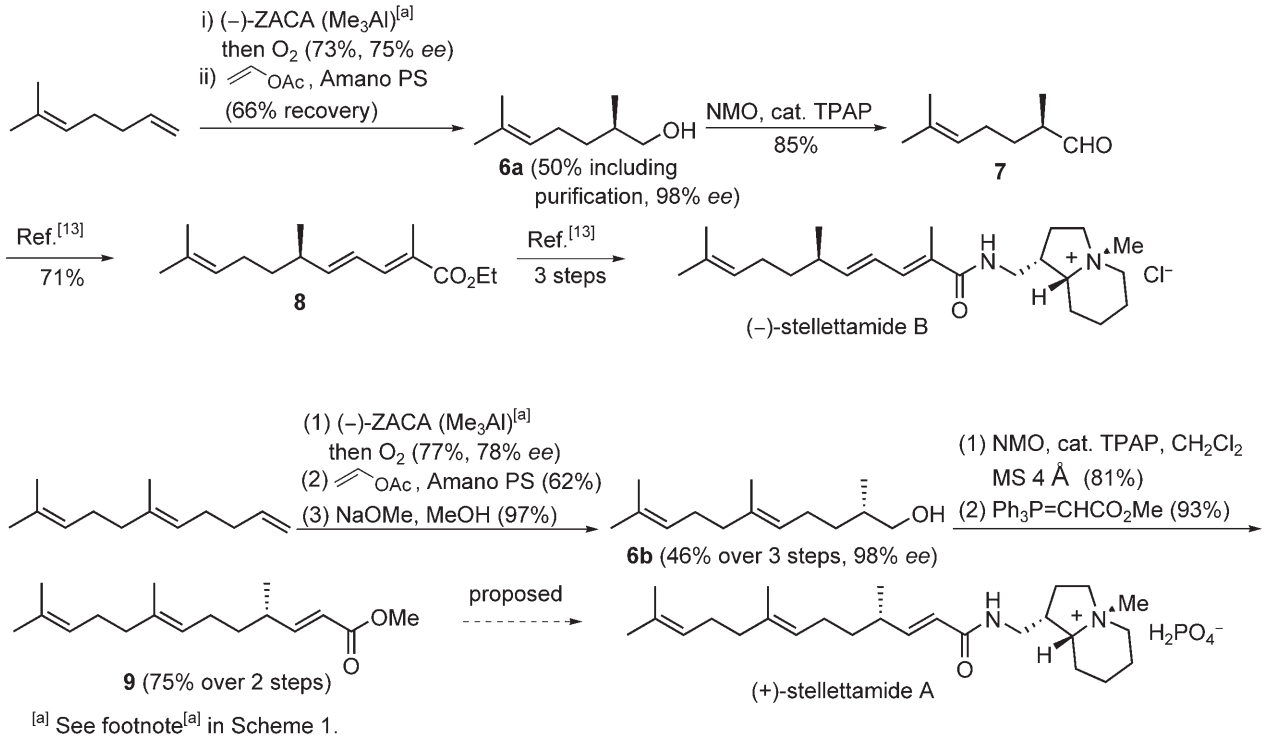


[a] (–)-ZACA (Me_3Al) = Me_3Al, 5% (–)-$(NMI)_2ZrCl_2$, CH_2Cl_2.

[b] zincation = *t*-BuLi (2.1 equivs.) at –78 °C then dry $ZnBr_2$ (0.6 – 1.0 equiv.).

[c] vinylation = Br, 2% $Pd(PPh_3)_4$, THF.

Scheme 1. Enantioselective synthesis of 2-methyl-4-alken-1-ols *via* ZACA–lipase-catalyzed acetylation tandem processes.



[a] See footnote[a] in Scheme 1.

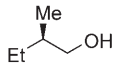
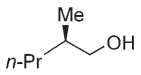
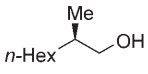
Scheme 2. ZACA–lipase-catalyzed acetylation route to enantiomerically pure 2-methyl-5-alken-1-ols pertinent to the synthesis of stellettamide A and B.

indicate that the purification of 2-methyl-1-alkanols lacking any proximal π-bonds or heterofunctional groups by lipase-catalyzed acetylation is generally more difficult than that of their proximally functionalized derivatives, their commonly reported *E* factors being $\leq$ 10.[1d,g] Under the conditions employed in this study, acetylation of racemic 2-methyl-1-decanol with 5 equivs. of vinyl acetate, Amano PS lipase in CH_2Cl_2 at 0 °C yielded an *E* factor of 6 (*C* = 14.8%, 11.9% *ee*). Even so, it is feasible to convert 1-alkenes with no additional unsaturation into the corresponding (*R*)-2-methyl-1-alkanols of $\geq$98% *ee via* the ZACA–lipase acetylation tandem process in $\geq$40% overall yields, as shown in Table 3.

The ZACA–lipase-catalyzed acetylation tandem process was applied to an efficient synthesis of (2*R*,6*R*)-2,6,10-trimethyl-1-undecanol (**10**), readily convertible to phytol and vitamins E and K,[4a] as shown in Scheme 3. In our previous synthesis,[4a] the preparation of **10** as a stereoisomerically pure substance was achieved *via* three-step purification process involving formation-repeated recrystallization-hydrolysis of a bisurethane derived from **10** and *p*-phenylene diisocyanate, which was rather laborious and of unpredictable applicability.

Notable selectivity-enhancing effects of proximal heterofunctional groups have been observed with some 3-substituted 2-methyl-1-propanol derivatives containing furyl and thienyl groups[1f] as well as iodine[5e] in the C-3 position. With the goal of synthesizing spongidepsin (**11**)[15] in an efficient and selective manner, a ZACA–lipase-catalyzed acetylation route to enantiomerically pure (*R*)-4-(trialkylsilyloxy)-2-methyl-1-butanol (**12**) was sought. We first synthesized racemic $TBSO(CH_2)_2C(Me)HCH_2OH$ (**12a**) and $TBDPSO(CH_2)_2C(Me)HCH_2OH$ (**12b**) from the corresponding terminal alkenes **13a** and **13b** by their $(Ind)_2ZrCl_2$-catalyzed reaction with 3 equivs. of

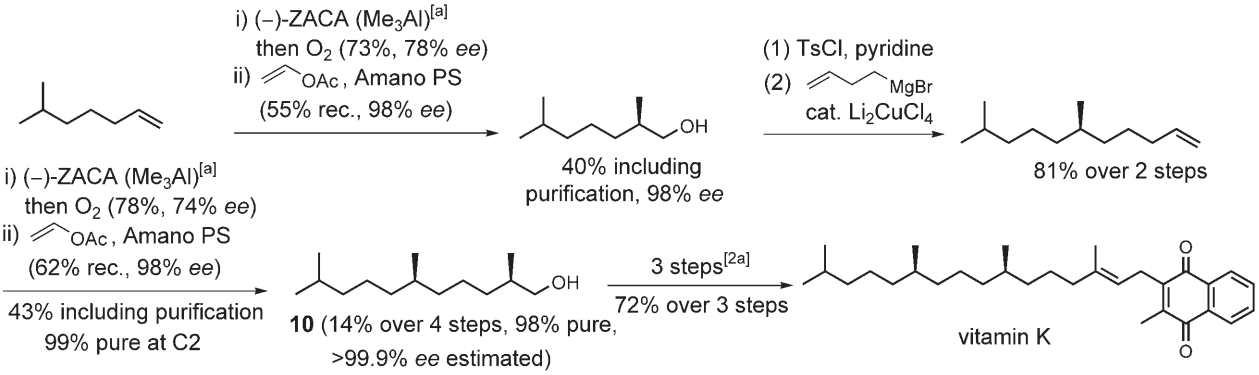
Table 3. Synthesis of saturated 2-methyl-1-alkanols *via* ZACA–lipase-catalyzed acetyaltion with Amano PS lipase.

Compound	ZACA			Lipase-catalyzed acetyaltion			Overall yield from 1-alkene
	Protocol[a]	Yield [%]	*ee* [%]	Conversion [%]	Recovery [%]	*ee* [%]	[%]
	II	71	84	[b]	[b]	[b]	[b]
	I	78	72				
	II	83	85	40	56	98	46
	III	60	83				
	I	71	72	38	60	98	43
	I	71	72	40[c]	55[c]	91[c]	

[a] Protocol I: $RCH{=}CH_2$ + Me_3Al (2 equivs.) and 5% (−)-$(NMI)_2ZrCl_2$. Protocol II: $MeCH{=}CH_2$ + R_3Al (1 equiv) and 5% (+)-$(NMI)_2ZrCl_2$. Protocol III: $H_2C{=}CH\text{-}CH_2OH$ + R_3Al (2-3 equivs.), MAO or IBAO (1 equiv), and 5% (−)-$(NMI)_2ZrCl_2$.

[b] Not yet purified to the $\geq$ 98% *ee* level.

[c] Fluka PFL lipase was used in place of Amano PS lipase.



[a] See footnote[a] in Scheme 1.

Scheme 3. ZACA–lipase-catalyzed acetylation route to (2*R*,6*R*)-2,6,10-trimethyl-1-undecanol and vitamin K.

Me_3Al in 74% and 89%, respectively. The lower yield of **12a** must be due, in part, to a partial deprotection of the TBS-protected alcohol. The *E* factors for the Amano PS lipase-catalyzed acetylation with vinyl acetates of **12a** and **12b** were 15.7 and 33.5, respectively. The presence of two Ph groups providing proximal π bonds and the greater steric requirement of the TBDPS group may be responsible for the higher *E* value for **12b**, as compared with that of **12a**. On the bases of both the yield of methylalumination and the higher *E* value, we chose **13b** and ran its ZACA–lipase catalyzed acetylation–methanolysis reaction to synthesize (*S*)-**12b** in 52% yield and 98% *ee*. After two-step conversion of **12b** into **14** in 77% overall yield, a two-step series consisting of (−)-ZACA-vinylation followed by (−)-ZACA-oxidation with O_2 provided, after chromatography (silica gel, AcOEt-hexanes), the desired **15** of ≥97% isomeric purity in 42% over 2 steps (Scheme 4). The yield of ≥97% pure **15** from **13b** over 5 synthetic steps, one lipase-catalyzed enantiomeric purification, and one chromatographic diastereomeric purification was 16%.

In summary, neither the ZACA reaction by itself nor the lipase-catalyzed acetylation of racemic 2-methyl-1-alkanols is a widely applicable and practically attractive asymmetric synthetic method. Nevertheless, their combination provides an unprecedentedly efficient, selective, widely applicable, and potentially economical asymmetric route to 2-methyl-1-alkanols that is catalytic in the chiral Zr complex.[16] Its application to other primary alcohols is currently being investigated.

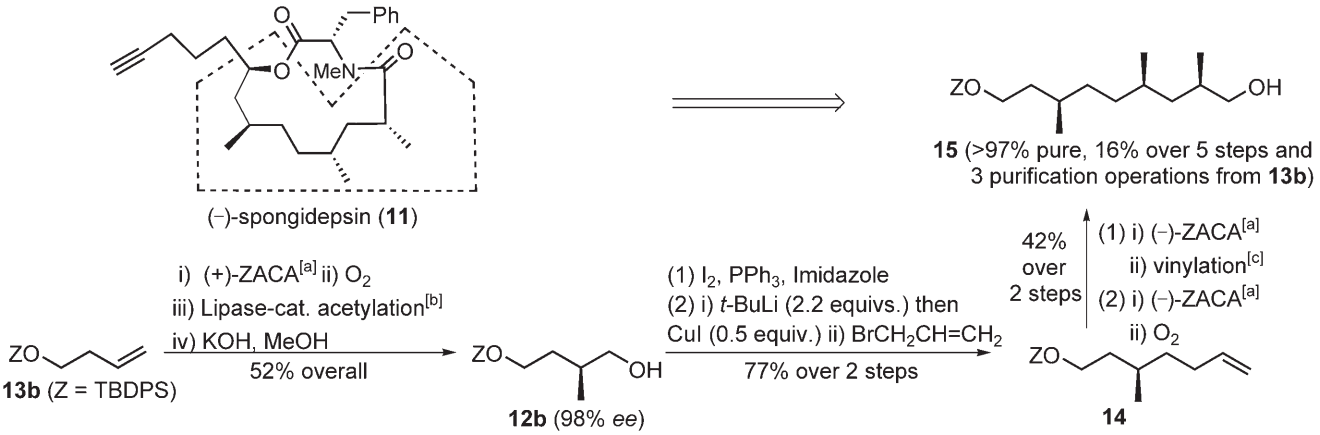
Experimental Section

The following two procedures for the preparation and enatiomeric purification by lipase-catalyzed acetylation of (*R*)-2-phenyl-1-propanol and (*S*)-4-*tert*-butyldiphenylsilyloxy-2-methyl-1-butanol are representative.

(*R*)-2-Phenyl-1-propanol[3a,10a]

To Me_3Al (0.96 mL, 10 mmol) in 20 mL of CH_2Cl_2 was added 1 molar equiv. of H_2O (0.18 mL, 10 mmol) at −50 °C, and the mixture was stirred at 23 °C for 1 h to generate MAO. This solution was transferred *via* cannula to a solution of (−)-$(NMI)_2ZrCl_2$ (0.335 g, 0.50 mmol), Me_3Al (1.92 mL, 20 mmol), and styrene (1.04 g, 10 mmol) in 20 mL of CH_2Cl_2. The resultant reddish mixture was stirred overnight at 23 °C for completion of the reaction. It was then treated with a stream of O_2 bubbled through a needle for 1 h at 0 °C, and stirred further for 5 h under O_2 atmosphere at 23 °C. The resultant mixture was treated at 0 °C with 2 N NaOH, and the organic layer was washed with water, dried over $MgSO_4$, and concentrated. Purification by column chromatography (silica gel, 90/10 hexanes-EtOAc) afforded 2-phenyl-1-propanol; yield: 0.99 g, (85%); approximately 90% *ee* by Mosher ester analysis.

To 136 mg (1 mmol) of the crude product obtained above in 5 mL of THF were added 0.90 mL (10 mmol) of vinyl acetate, 6 μL of H_2O, and 34 mg of PPL (porcine pancreas lipase). The resultant mixture was stirred for 7 h at 23 °C, at which time the substrate had been acetylated to the extent of 14%. It was filtered, washed with ether, concentrated, and purified by column chromatography (silica gel, 95/5 hexanes-EtOAc) to give 106 mg (78% recovery) of (*R*)-2-phenyl-1-propanol: ≥99% pure by ^{13}C NMR; ≥97% *ee* by HPLC analysis of the urethane obtained by treating the alcohol with (*R*)-1-naphthylethyl isocyanate; $[\alpha]_D^{23}$: 16.2° (*c* 1.0, $CHCl_3$).



[a] (+)-ZACA = Me_3Al (2.5 equivs.), (+)-$(NMI)_2ZrCl_2$ (1 mol %), IBAO (0.5 equiv.); (−)-ZACA = Me_3Al (2.5 equivs.), (−)-$(NMI)_2ZrCl_2$ (1 mol %), IBAO (0.5 equiv.).

[b] CH_2=CHOAc (5.0 equivs.), Amano PS lipase (30 mg/mmol).

[c] vinylation = $Zn(OTf)_2$ (1 equiv.), CH_2=CHBr (3 equivs.), $Pd(DPEphos)Cl_2$ (3 mol %), DIBAL-H (6 mol %).

Scheme 4. ZACA–lipase-catalyzed acetylation route to (2*R*,4*R*,7*R*)-9-*tert*-butyldiphenylsilyloxy-2,4,7-trimethyl-1-nonanol (**15**).

(2*S*)-4-*tert*-Butyldiphenylsilyloxy-2-methyl-1-butanol[17]

To 11.3 mL (45 mmol) of *i*-Bu_3Al in 45 mL of CH_2Cl_2 was added 0.81 mL (45 mmol) of H_2O at −50 °C, and the mixture was stirred at 23 °C for 1 h to give a solution of IBAO in CH_2Cl_2 (*Note*: although IBAO[4b] was used in this case, it may be substituted with MAO). To 602 mg (0.90 mmol) of (+)-$(NMI)_2ZrCl_2$ in 45 mL of CH_2Cl_2 were added 13 mL (135 mmol) of Me_3Al. To the resultant orange mixture were added *via* cannula 28.0 g (90 mmol) of 4-*tert*-butyldiphenylsilyloxy-1-butene in 90 mL of CH_2Cl_2 and the IBAO solution prepared above. After stirring for 5 h at 23 °C, the reaction mixture was treated with a vigorous steam of O_2 bubbled through a needle for 1 h at 0 °C, and stirred further for 5 h at 23 °C under O_2. The reaction mixture were quenched with 2 N NaOH, extracted with CH_2Cl_2, the organic phase was washed with water, dried and concentrated. Purification by column chromatography (silica gel, 90/10 hexanes-EtOAc) afforded the title compound mixed with its *R* isomer as a colorless oil; yield: 24.0 g (78 %); ≥ 98 % pure by ^{13}C NMR; 77 % *ee* by Mosher ester analysis.

To 24.0 g (70 mmol) of the crude product of 77 % *ee* obtained above in 200 mL of CH_2Cl_2 were added 2.1 g of Amano PS lipase (30 mg/mmol substrate) and 35 mL (350 mmol) of vinyl acetate. After stirring for 24 h at 23 °C, at which time 72 % of the substrate was acetylated, the reaction mixture was filtered, concentrated and purified by column chromatography (silica gel, 97/3 hexanes-EtOAc) to afford the desired acetate as a colorless oil; yield: 18.8 g (70 %).

To 18.8 g (49 mmol) of the acetate in 150 mL of CH_3OH were added 3.2 g (50 mmol) of KOH. After stirring for 2 h at 23 °C, the mixture was concentrated under vacuum, extracted with ether, washed with water, dried and concentrated again, and purified by column chromatography (silica gel, 90/10 hexanes-EtOAc) to afford the title compound; yield: 16.0 g (95 %); 98 % *ee* by Mosher ester analysis: $[\alpha]_D^{23}$: −6.95° (*c* 1.0, $CHCl_3$).

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