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Widely Applicable Synthesis of Enantiomerically Pure Tertiary Alkyl-Containing 1-Alkanols by Zirconium-Catalyzed Asymmetric Carboalumination of Alkenes and Palladium- or Copper-Catalyzed Cross-Coupling

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Abstract: A highly enantioselective and widely applicable method for the synthesis of various chiral 2-alkyl-1-alkanols, especially those of feeble chirality, has been developed. It consists of zirconium-catalyzed asymmetric carboalumination of alkenes (ZACA), lipase-catalyzed acetylation, and palladium- or copper-catalyzed cross-coupling. By virtue of the high selectivity factor (*E*) associated with iodine, either (*S*)- or (*R*)-enantiomer of 3-iodo-2-alkyl-1-alkanols (**1**), prepared by ZACA reaction of allyl alcohol, can be readily purified to the level of ≥99% *ee* by lipase-catalyzed acetylation. A variety of chiral tertiary alkyl-containing alcohols, including those that have been otherwise difficult to prepare, can now be synthesized in high enantiomeric purity by Pd- or Cu-catalyzed cross-coupling of (*S*)-**1** or (*R*)-**2** for introduction of various primary, secondary, and tertiary carbon groups with retention of all carbon skeletal features. These chiral tertiary alkyl-containing alcohols can be further converted into the corresponding acids with full retention of the stereochemistry. The synthetic utility of this method has been demonstrated in the highly enantioselective (≥99% *ee*) and efficient syntheses of (*R*)-2-methyl-1-butanol and (*R*)- and (*S*)-arundic acids.

Keywords: asymmetric synthesis · cross-coupling · enzyme catalysis · homogeneous catalysis

Introduction

Recent major advances in the synthesis of chiral tertiary alkyl-containing compounds including a large number of those with biologically and medicinally important properties, for example, isoprenoids, deoxypolypropionates, and others,[1] have been made through the development of catalytic asymmetric alkene hydrogenation,[2] epoxidation,[3] carboalumination,[4] and so on. Those that have been synthesized by our group include vitamin E,[5a] vitamin K,[5a,b] siphonarienolone,[5c] 4,6,8,10,16,18-hexamethyldocosane,[5d] (+)-scyphostatin,[5e,f] and (−)-spongidepsin[5g] (Figure 1). These target compounds containing two or more asymmetric carbon atoms have been synthesized with high stereoisomeric purity, even if each stereogeneric process is of less than satisfactory stereoselectivity (<98%) by exploitation of the statistical enantiomeric amplification principle (Table 1).

An efficient route to compounds containing a single stereogenic carbon center has also been developed by us through the synergy of zirconium-catalyzed asymmetric carboalumination of alkenes (ZACA) and lipase-catalyzed acetylation.[5b] In all of the examples reported in our previous papers,[5b,g,6] β-chiral 1-alcohols of at least 98% *ee* were pre-

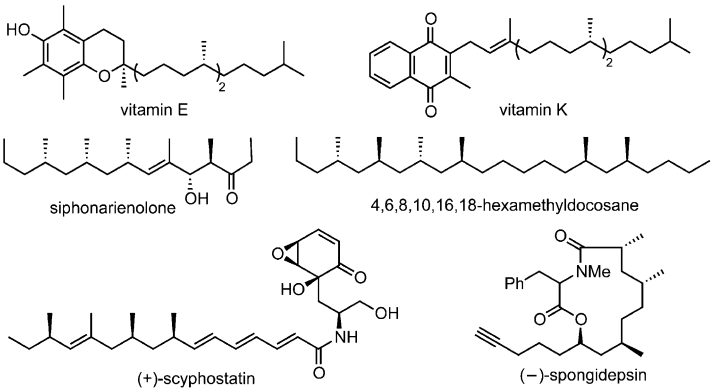

Figure 1. Some naturally occurring chiral tertiary alkyl groups of biological and medicinal importance.

Table 1. Statistical enantiomeric amplification.

ee of each stereogenic center [%]	Overall *ee* [%]		
	Two stereogenic centers	Three stereogenic centers	Four stereogenic centers
90	**99.4**	**ca. 100**	**ca. 100**
80	97.6	**99.7**	**ca. 100**
70	94.0	98.9	**99.8**

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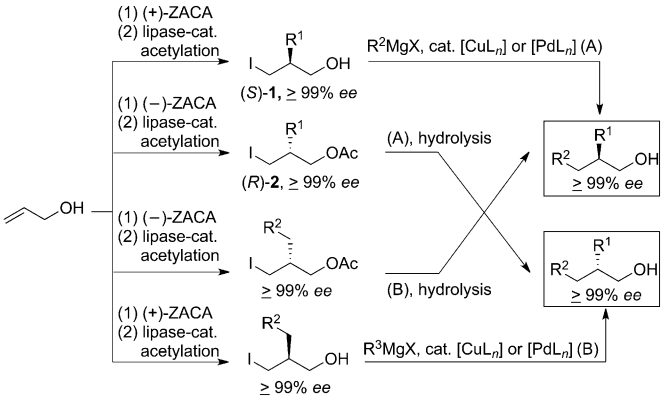
pared by the ZACA reaction of 1-alkenes ($R^1CH{=}CH_2$) to produce the final β-chiral 1-alcohols ($R^1R^2CHCH_2OH$) of mostly 70–85% *ee*, which were then enantiomerically purified to the level of at least 98% *ee* by resorting to sufficiently high selectivity factors (*E*)[7] associated with the R^1 or R^2 group of the desired compounds $R^1R^2CHCH_2OH$ containing proximal π bonds or heterofunctional groups. However, in cases where 1) the initial enantiomeric excess of the crude product is low, 2) the two carbon groups R^1 and R^2 are structurally similar, and/or 3) the selectivity factors (*E*) are not sufficiently high, enantiomeric purification of the obtained crude products, that is, $R^1R^2CHCH_2OH$, can be difficult and synthetically impractical, representing a major deficiency to be overcome. Consider, for example, the preparation of (*R*)- and (*S*)-2-methyl-1-butanol. Whereas the (*S*)-isomer is commercially available at relatively low cost as a ≥98% isomerically pure compound,[8] the (*R*)-isomer is not. In fact, a number of research groups have reported the syntheses of (*R*)-2-methyl-1-butanol.[9–12] One frequently employed route is to convert isomerically pure and commercially available methyl (*S*)-3-hydroxy-2-methylpropionate into (*R*)-2-methyl-1-butanol, typically in several steps.[9] While the enantiomeric purity of (*R*)-2-methyl-1-butanol thus obtained is satisfactory (≥98% *ee*), this method requires rather expensive (*S*)-3-hydroxy-2-methylpropionate, which seriously compromises the practical value of this strategy.[10] Brown developed an asymmetric hydroboration–one-carbon homologation–reduction–oxidation route[11] to provide (*R*)-2-methyl-1-butanol efficiently and selectively (≥99% *ee*). However, the entire process is non-catalytic, requiring stoichiometric quantities of chiral reagents. Moreover, its scope, as reported, is limited to the use of symmetrically substituted alkenes, such as *cis*-2-butene, to avoid the formation of regioisomeric mixtures. Lipase-catalyzed acetylation of enantiomeric mixtures of (*R*)- and (*S*)-2-methyl-1-butanols has also been reported.[12] Due to the low *E* factor, (*R*)-2-methyl-1-butanol of only 90% *ee* was obtained in a disappointingly low recovery of 30% after multiple rounds of lipase-catalyzed acetylation of a racemic mixture.

We report herein a widely applicable and highly enantioselective (≥99% *ee*) method for the synthesis of various chiral 2-alkyl-1-alkanols, including those that have been otherwise very difficult to prepare, by exploitation of 1) generally facile purification of $ICH_2CH(R)CH_2OH$ (**1**) to the level of ≥99% *ee* owing to the high *E* factor associated with iodine[4f] proximal to the chiral center and 2) full retention (>99%) of all carbon skeletal features of (*S*)-**1** or (*R*)-**2** in palladium- or copper-catalyzed cross-coupling reactions,[4h,13] which eliminates the limitations discussed above. The desired chiral 2-alkyl-1-alkanols of ≥99% *ee*, even in cases where R^1 and R^2CH_2 lacking any proximal π bonds or heterofunctional groups are structurally similar, have been readily prepared by substituting iodine with various primary, secondary, and tertiary carbon groups via Pd- or Cu-catalyzed cross-coupling of (*S*)-**1** or (*R*)-**2** without epimerization (Scheme 1).



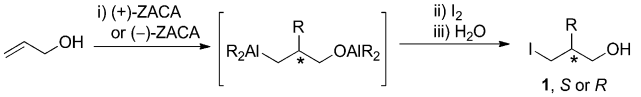
Scheme 1. Strategy for the synthesis of feebly chiral 2-alkyl-1-alkanols. $R^3CH_2{=}R^1$; R^1 and R^2CH_2 are structurally similar.

Results and Discussion

Asymmetric Synthesis of (*R*)- and (*S*)-3-Iodo-2-Alkyl-1-Alkanols (1)

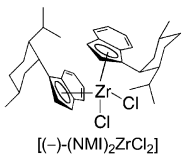
We began our study by asymmetric synthesis of (*R*)- and (*S*)-3-iodo-2-alkyl-1-alkanols (**1**) via ZACA reaction of allyl alcohol. Compounds (*S*)- and (*R*)-**1a** were prepared in 80% and 81% yields by treatment of allyl alcohol with Me_3Al (2.5 equiv), methylaluminoxane (MAO, 1 equiv), and [(+)-$(NMI)_2ZrCl_2$] or [(−)-$(NMI)_2ZrCl_2$] (5 mol%) in CH_2Cl_2,[14] followed by iodinolysis with I_2.[4f] Their enantiomeric purities were 82% *ee* and 84% *ee*, respectively (Table 2, entries 1 and 2). Similarly, the ZACA reaction of allyl alcohol with Et_3Al or $n-Pr_3Al$ was also performed. In

Table 2. Asymmetric synthesis of (*R*)- and (*S*)-3-iodo-2-alkyl-1-alkanols (**1**).



Entry	R	Protocol[a]	Product	Yield [%][b]	Purity of **1** *ee* [%][c]
1	Me	I	(*S*)-**1a**	80	82
2	Me	II	(*R*)-**1a**	81	84
3	Et	III	(*S*)-**1b**	60	87
4	Et	IV	(*R*)-**1b**	62	88
5	*n*Pr	III	(*S*)-**1c**	59	82
6	*n*Pr	IV	(*R*)-**1c**	60	80

[a] Protocol I: i) Me_3Al (2.5 equiv), MAO (1 equiv), 5 mol% [(+)-$(NMI)_2ZrCl_2$] ii) I_2 (2.5 equiv), THF. Protocol II: i) Me_3Al (2.5 equiv), MAO (1 equiv), 5 mol% [(−)-$(NMI)_2ZrCl_2$] ii) I_2 (2.5 equiv), THF. Protocol III: i) R_3Al (3.0 equiv), IBAO (1 equiv), 5 mol% [(+)-$(NMI)_2ZrCl_2$] ii) I_2 (6 equiv), Et_2O. Protocol IV: i) R_3Al (3.0 equiv), IBAO (1 equiv), 5 mol% [(−)-$(NMI)_2ZrCl_2$] ii) I_2 (6 equiv), Et_2O. [b] Yield of isolated product. [c] Enantiomeric excess determined by ^1H NMR spectroscopic analysis of Mosher esters.



[(−)-$(NMI)_2ZrCl_2$]

these reactions, however, isobutylaluminoxane (IBAO) was used in place of MAO, and after iodinolysis with I_2, (*S*)-**1b**, (*R*)-**1b**, (*S*)-**1c**, and (*R*)-**1c** of enantiomeric purities ranging from 80–88% *ee* were obtained in 59–62% yields (Table 2, entries 3–6).

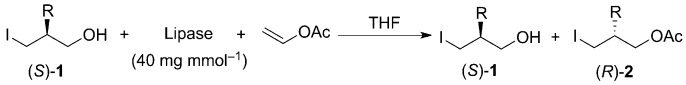
Lipase-Catalyzed Acetylation of (*S*)- and (*R*)-3-Iodo-2-Alkyl-1-Alkanols (1)

Amano PS lipase from *Pseudomonas cepacia* (Amano PS, purchase from Aldrich) or Amano AK lipase from *Pseudomonas fluorescens* (Amano AK, purchase from Aldrich) was generally satisfactory for purification of (*S*)- and (*R*)-3-iodo-2-alkyl-1-alkanols (**1**). Compound (*S*)-**1a** of ≥99% *ee* was prepared in 63% recovery by using Amano PS (Table 3, entry 1). In the purification of (*S*)-**1b**, Amano AK and Amano PS were comparatively effective (Table 3, entries 2 and 3). The (*S*)-**1b** of ≥99% *ee* was obtained in 60% recovery yield by using Amano AK (Table 3, entry 4).

Five commercially available lipases were tested for enantiomeric purification of (*S*)-**1c** (Table 3, entries 5–10). Amano AK proved to be the most satisfactory reagent for the purification of (*S*)-**1c**, producing (*S*)-**1c** of ≥99% *ee* in 58% recovery yield (Table 3, entry 7). Amano PS lipase was effective in providing (*S*)-**1c** of 92% *ee* in 74% recovery yield (Table 3, entry 8). However, lipase from porcine pancreas (PPL), lipase from *Rhizomucor miehei*, and lipase from *Candida rugosa* were disappointingly ineffective in selective acetylation of (*S*)-**1c** (Table 3, entries 5, 9, and 10).

Thus, (*S*)-**1a**, (*S*)-**1b**, and (*S*)-**1c** are now readily obtainable as enantiomerically pure compounds of ≥99% *ee* in 50%, 36%, and 34% yields over two steps from allyl alcohol in a highly enantioselective, efficient, and satisfactory manner.

Table 3. Lipase-catalyzed acetylation of (*S*)-**1**.

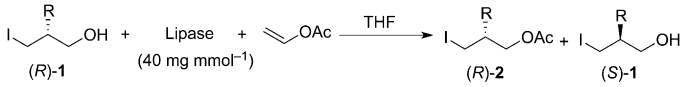


R = Me (**1a**), Et (**1b**), *n*Pr (**1c**)

Entry	Substrate	Initial purity of (*S*)-**1** *ee* [%]	Lipase	Conversion [%][a]	Recovery of (*S*)-**1** [%]	Purity of (*S*)-**1** *ee* [%][b]
1	(*S*)-**1a**	82	**Amano PS**	**33**	**63**	**≥99**
2	(*S*)-**1b**	87	Amano PS	23	72	96
3	(*S*)-**1b**	87	Amano AK	22	74	96
4	(*S*)-**1b**	87	**Amano AK**	**37**	**60**	**≥99**
5	(*S*)-**1c**	82	PPL	62	35	85
6	(*S*)-**1c**	82	Amano AK	24	74	94
7	(*S*)-**1c**	82	**Amano AK**	**39**	**58**	**≥99**
8	(*S*)-**1c**	82	Amano PS	22	74	92
9	(*S*)-**1c**	82	lipase from *Rhizomucor Miehei*	63	34	80
10	(*S*)-**1c**	82	lipase from *Candida rugosa*	37	59	83

[a] Conversion determined by ^{1}H NMR spectroscopy. [b] Enantiomeric excess determined by ^{1}H NMR spectroscopic analysis of Mosher esters.

Table 4. Lipase-catalyzed acetylation of (*R*)-**1**.



R = Me (**1a**), Et (**1b**), *n*Pr (**1c**)

Entry	Substrate	Initial purity of (*R*)-**1** *ee* [%]	Lipase	Conversion [%][b]	Yield of (*R*)-**2** [%]	Purity of (*R*)-**2** *ee* [%][e]
1	(*R*)-**1a**	84	**Amano PS**	**62**	**60**	**≥99**
2	(*R*)-**1b**	88	**Amano PS**	**56**	**52**	**≥99**
3	(*R*)-**1b**	88	Amano PS	67	64	98
4	(*R*)-**1b**	88	Amano PS	84	81	96
5	(*R*)-**1b**	96	**Amano PS**	**82**	**62**[c]	**≥99**
6	(*R*)-**1c**	80	**Amano AK**[a]	**53**	**50**	**≥99**
7	(*R*)-**1c**	80	Amano AK[a]	63	60	98
8	(*R*)-**1c**	80	Amano AK[a]	82	79	94
9	(*R*)-**1c**	94	**Amano AK**[a]	**83**	**60**[d]	**≥99**

[a] Toluene was used in place of THF. [b] Conversion determined by ^{1}H NMR spectroscopy. [c] Overall yield in two rounds of lipase-catalyzed purification (entries 4+5). [d] Overall yield in two rounds of lipase-catalyzed purification (entries 8+9). [e] Enantiomeric excess determined by ^{1}H NMR spectroscopic analysis of Mosher esters.

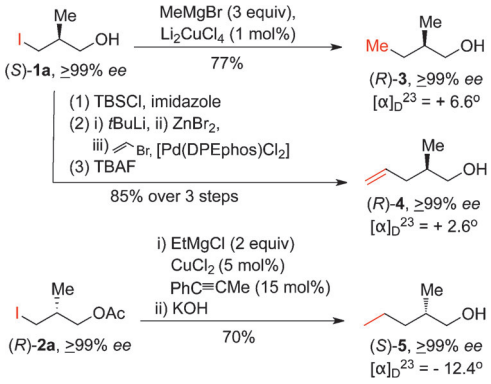
The results of lipase-catalyzed purification of (*R*)-**1** are summarized in Table 4. Compound (*R*)-**2a** of ≥99% *ee* was prepared in 60% yield by using Amano PS (Table 4, entry 1), while (*R*)-**2b** of ≥99% *ee* was obtained in 52% yield from a 94/6 mixture (88% *ee*) of (*R*)-**1b** and (*S*)-**1b** (Table 4, entry 2). We were further pleased to find that (*R*)-**2b** of ≥99% *ee* was also obtained by two rounds of lipase-catalyzed purification in 62% overall yield. Thus, (*R*)-**2b** of 96% *ee* was obtained in 81% yield (Table 4, entry 4). Hydrolysis of acetate (*R*)-**2b** (96% *ee*) without isolation, followed by the second round of lipase-catalyzed acetylation, provided (*R*)-**2b** of ≥99% *ee* (Table 4, entry 5).

Similarly, the acetate of (*R*)-**1c** of ≥99% *ee* was obtained in 50% yield from a 90/10 mixture (80% *ee*) of (*R*)-**1c** and (*S*)-**1c** (Table 4, entry 6). Compound (*R*)-**2c** of ≥99% *ee* was also obtained by two rounds of lipase-catalyzed purification in 60% overall yield (Table 4, entries 8 and 9). As summarized in Table 4, (*R*)-**2a**, (*R*)-**2b**, and (*R*)-**2c** were all readily purified to ≥99% *ee* in 49%, 38%, and 36% overall yields from allyl alcohol.

Synthesis of (*S*)- and (*R*)-Chiral Tertiary Alkyl-Containing Alcohols

With six key intermediates, that is, (*S*)-**1a**, (*S*)-**1b**, (*S*)-**1c**, (*R*)-**2a**, (*R*)-**2b**, and (*R*)-**2c** of ≥99% *ee* in hand, our attention was then focused on establishing the feasibility of synthesizing feebly chiral 2-alkyl-1-alkanols of high enantiomeric purity by their Pd- or Cu-catalyzed cross-coupling reactions. The cross-coupling reaction of (*S*)-**1a** with methylmagnesium bromide (3 equiv) in the presence of 1 mol% of Li_2CuCl_4[13] gave (*R*)-2-methyl-1-butanol (**3**) of ≥99% *ee* in 77% yield. Thus, we have developed a highly selective and efficient route to the synthesis of (*R*)-2-methyl-1-butanol (**3**, ≥99% *ee*) in 39% yield from allyl alcohol over three steps via ZACA, lipase-catalyzed acetylation, and Cu-catalyzed cross-coupling.

Treatment of (*S*)-**1a** with TBSCl followed by Negishi coupling[4h] catalyzed by 5 mol% [Pd(DPEphos)Cl_2] with vinyl bromide and subsequent desilylation with tetrabutylammonium fluoride (TBAF), provided (*R*)-**4** in 85% yield over three steps (Scheme 2). Synthesis of (*S*)-**5** was achieved in

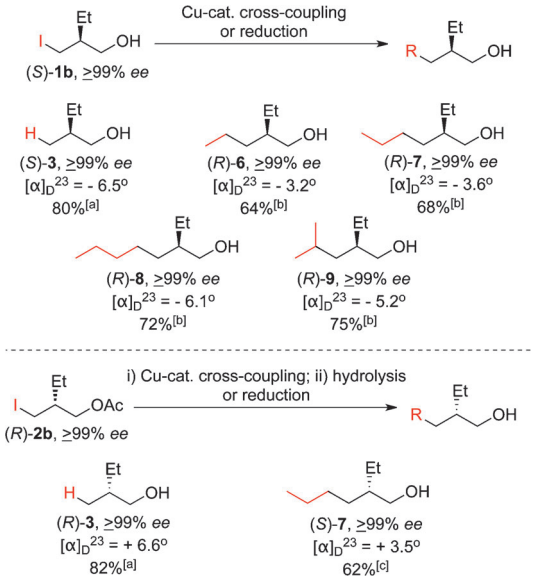


Scheme 2. Synthesis of chiral tertiary alkyl-containing 1-alcohols from (*S*)-**1a** and (*R*)-**2a**. DPEphos = bis[(2-diphenylphosphino)phenyl]ether, TBS = *tert*-butyldimethylsilyl.

70% yield by copper-catalyzed cross-coupling of (*R*)-**2a** with ethylmagnesium chloride (2 equiv) in the presence of 5 mol% $CuCl_2$ and 15 mol% 1-phenylpropyne[15] followed by hydrolysis of the acetate with KOH. As we expected, all three of these chiral alkanols were obtained with high enantiomeric purity of ≥99% *ee*.

Similarly, (*S*)-**1b** of ≥99% *ee*, prepared as described earlier, was converted into (*S*)-**3**, (*R*)-**6**, (*R*)-**7**, (*R*)-**8**, and (*R*)-**9** of ≥99% *ee* by either reduction with $LiAlH_4$ or Cu-catalyzed cross-coupling in 64–80% yields (Scheme 3). (*R*)-2-Methyl-1-butanol (**3**) of ≥99% *ee* was also obtained by reduction of (*R*)-**2b** with $LiAlH_4$ (1.5 equiv) in 82% yield. (*S*)-**7** of ≥99% *ee* was prepared from (*R*)-**2b** in 62% yield by Cu-catalyzed cross-coupling and subsequent hydrolysis.

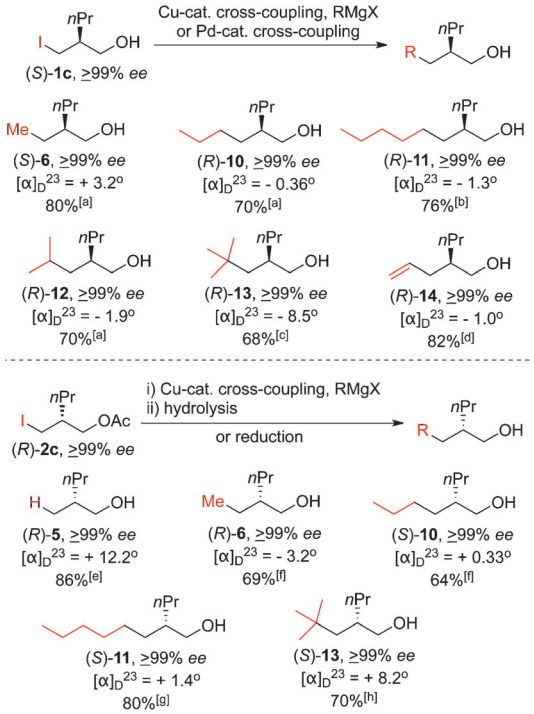
The preparation of (*S*)-**6** and (*R*)-**10** were performed by cross-coupling reactions of (*S*)-**1c** with methylmagnesium chloride (3.3 equiv) and *n*-propylmagnesium chloride (3.3 equiv) in the presence of 5 mol% of $CuCl_2$ and



Scheme 3. Synthesis of chiral tertiary alkyl-containing 1-alcohols from (*S*)-**1b** and (*R*)-**2b**. [a] $LiAlH_4$ (1.5 equiv). [b] $CuCl_2$ (5 mol%), PhC≡CMe (15 mol%), RMgCl (3.3 equiv). [c] i) $CuCl_2$ (5 mol%), PhC≡CMe (15 mol%), RMgCl (2.0 equiv). ii) KOH.

15 mol% of 1-phenylpropyne in 80% and 70% yields (Scheme 4). Furthermore, secondary and tertiary Grignard reagents can also be used under similar reaction conditions providing (*R*)-**12** and (*R*)-**13** in 70% and 68% yields, respectively. Acetylation of (*S*)-**1c** with Ac_2O followed by treatment with 3 mol% Li_2CuCl_4, *N*-methylpyrrolidone (NMP, 4 equiv) and *n*-pentylmagnesium bromide (2 equiv), and subsequent hydrolysis with KOH, provided (*R*)-**11** of ≥99% *ee* in 76% yield over three steps. In essentially the same way, (*S*)-**11** of ≥99% *ee* was also obtained in 80% yield over two steps from (*R*)-**2c**. The preparation of (*R*)-**14** of ≥99% *ee* was carried out by TBS protection of (*S*)-**1c**, [Pd(DPEphos)Cl_2]-catalyzed Negishi coupling, and TBAF desilylation in 82% yield over three steps. Reduction of (*R*)-**2c** with $LiAlH_4$ (1.5 equiv) gave (*R*)-**5** in 86% yield. The preparation of (*R*)-**6**, (*S*)-**10**, and (*S*)-**13** was performed by similar Cu-catalyzed cross-coupling and subsequent hydrolysis from (*R*)-**2c** in 69%, 64%, and 70% yields, respectively. It should be noted that the enantiomeric purity of alcohols **3**, **4**, and **5** can be readily determined by ^{1}H NMR spectroscopic analysis of their corresponding Mosher esters.[16] However, in those cases where the two alkyl branches at the chiral carbon atom are very similar to each other, as in the cases of **6**, **7**, **9**, **10**, **11**, and **13**, the chemical shifts of the diastereomeric Mosher esters were not sufficiently separated to allow quantitative determination of the enantiomeric purity by ^{1}H NMR spectroscopy. The enantiomeric purities of these compounds were therefore determined by chiral GC (see the Supporting Information).

In this study, we have developed a highly enantioselective and widely applicable route to various chiral 2-alkyl-1-alkanols, especially those of feeble chirality,[17] by ZACA and

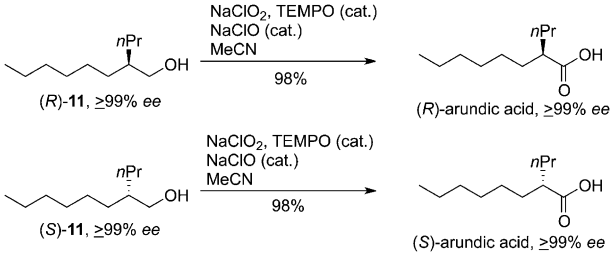


Scheme 4. Synthesis of chiral tertiary alkyl-containing 1-alcohols from (*S*)-**1c** and (*R*)-**2c**. [a] $CuCl_2$ (5 mol%), PhC≡CMe (15 mol%), RMgCl (3.3 equiv). [b] 1) Ac_2O; 2) Li_2CuCl_4 (3 mol%), NMP (4 equiv), *n*PentMgBr (2 equiv); 3) KOH/MeOH. [c] 1) Ac_2O; 2) $CuCl_2$ (5 mol%), PhC≡CMe (15 mol%), RMgCl (3 equiv); 3) KOH/MeOH. [d] 1) TBSCl; 2) i) *t*BuLi; ii) $ZnBr_2$; iii) CH_2=CHBr, [Pd(DPEphos)Cl_2]; 3) TBAF. [e] $LiAlH_4$ (1.5 equiv). [f] i) Li_2CuCl_4 (5 mol%), RMgCl (3 equiv); ii) KOH/MeOH. [g] i) Li_2CuCl_4 (3 mol%), NMP (4 equiv), *n*PentMgBr (2 equiv); ii) KOH/MeOH. [h] i) $CuCl_2$ (5 mol%), PhC≡CMe (15 mol%), RMgCl (3 equiv)ii) KOH/MeOH.

Pd- or Cu-catalyzed cross-coupling. Either enantiomer of such alcohols can be obtained in high enantioselectivity from the (*R*)- or (*S*)-enantiomer of **1**. With recent advances in Pd-, Ni-, and Cu-catalyzed cross-coupling of alkyl halides with a wide variety of alkyl (primary, secondary, and tertiary), cyclic alkyl, vinyl, and aryl Grignard reagents; organozinc species; or organoboron compounds;[18,19] we are inclined to believe that this study will provide a widely applicable, convenient, and efficient procedure for the synthesis of a very broad range of enantiomerically pure (≥99% *ee*) chiral tertiary alkyl-containing alcohols. It should also be noted that chiral 2-alkyl-1-alkanols can be readily transformed into their corresponding optically active aldehydes, carboxylic acids, and other classes of compounds.

(*R*)-Arundic acid is currently undergoing Phase II development for the treatment of acute ischemic stroke, as well as clinical development in other neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease.[20] Thus, arundic acid has been a highly coveted synthetic target in recent years, and a number of syntheses of this compound have been reported.[21] However, these methods have limitations and drawbacks, including the use of highly expensive chiral auxiliaries, modest enantiomeric purities, and low yields.

To demonstrate synthetic utility of the new protocol reported herein, both (*R*)- and (*S*)-arundic acids were prepared. (*R*)- and (*S*)-**11** of ≥99% *ee*, prepared by ZACA, lipase-catalyzed purification, and Cu-catalyzed cross-coupling tandem reactions (Scheme 4), were transformed into the corresponding (*R*)- and (*S*)-arundic acids in 98% yield by oxidation with $NaClO_2$ in the presence of catalytic amounts of NaClO and 2,2,6,6-tetramethylpiperidin-1-yloxyl (TEMPO).[21i] Thus, a highly enantioselective and efficient synthesis of (*R*)- and (*S*)-arundic acids was achieved in 25% and 28% over five steps, respectively, from allyl alcohol (Scheme 5).



Scheme 5. Synthesis of (*R*)- and (*S*)-arundic acids.

Conclusions

In summary, the present study has provided a widely applicable and highly enantioselective route to various chiral 2-alkyl-1-alkanols, especially those of feeble chirality, by a sequence of ZACA, lipase-catalyzed acetylation, and Pd- or Cu-catalyzed cross-coupling. Either enantiomer of the desired alcohols can be readily obtained in very high optical purity (≥99% *ee*) from the (*R*)- or (*S*)-enantiomer of **1** by using Pd- or Cu-catalyzed cross-coupling to introduce various primary, secondary, and tertiary carbon groups with retention of all carbon skeletal features of (*S*)-**1** or (*R*)-**2**. Oxidation of chiral 2-alkyl-1-alkanols provides the corresponding acids with high enantiomeric purity. The synthetic utility of the present method has been demonstrated in highly enantioselective syntheses of (*R*)-2-methyl-1-butanol (**3**) and (*R*)- and (*S*)-arundic acids. Further studies along these lines are currently ongoing.

Experimental Section

All reactions were run in a dry Ar atmosphere. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm Merck silica gel plates (60F-254) or by GC analysis of reaction aliquots. Chiral GC analysis was performed on an HP 7890 A gas chromatograph using a CP-Chirasil-Dex CB capillary column (25 m × 0.25 mm, 0.39 μm film). Flash chromatographic separations were carried out on 230–400 mesh silica gel. ^1H and ^{13}C NMR spectra were recorded on Varian-Inova-300 or Bruker-ARX-400 instruments. Optical rotations were measured on an Autopol III automatic polarimeter. $ZnBr_2$ was flame-dried in vacuo. THF was dried by distillation under Ar from sodium/benzophenone. CH_2Cl_2 was dried by distillation under Ar from CaH_2. (+)- and [(−)-$(NMI)_2ZrCl_2$][14a] were prepared as reported in the literature. Other commercially available solvents and reagents were of reagent grade and used without further purification, unless otherwise indicated.

*Representative Procedure for ZACA Reaction and Lipase-Catalyzed Acetylation. Synthesis of (S)-2-(Iodomethyl)pentan-1-ol (**1c**)*

To a solution of allyl alcohol (0.68 mL, 10 mmol) in CH_2Cl_2 (5 mL) was added dropwise nPr$_3$Al (2.9 mL, 15 mmol) at −78 °C under argon, and the resultant solution was stirred at 23 °C for 1 h. To a solution of iBu$_3$Al (2.5 mL, 10 mmol) in CH_2Cl_2 (10 mL) was added dropwise H_2O (0.18 mL, 10 mmol) at −78 °C under argon, and the mixture was slowly warmed to 23 °C and stirred for 1 h to give a clear solution of IBAO in CH_2Cl_2. To another solution of [(+)-(NMI)$_2$ZrCl$_2$] (334 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) at 0 °C were added consecutively nPr$_3$Al (2.9 mL, 15 mmol), the IBAO solution prepared above, and the pretreated solution of allyl alcohol. The resultant solution was warmed to 23 °C and stirred overnight. The solvents were evaporated in vacuo. The residue was dissolved in Et_2O (50 mL), and I_2 (15.3 g, 60 mmol) was introduced in three portions at 0 °C. The resultant mixture was stirred for 2 h at 23 °C, heated at reflux for additional 8 h, quenched with ice water, extracted with ether, washed with aqueous $Na_2S_2O_3$, dried over anhydrous $MgSO_4$, filtered, concentrated, and purified by column chromatography (silica gel, 20 % ethyl acetate in hexanes) to afford (*S*)-2-(iodomethyl)-pentan-1-ol (**1c**, 1.4 g, 59 % yield, 82 % *ee*).

To a solution of (*S*)-**1c** (228 mg, 1.0 mmol, 82 % *ee*) was added THF/H_2O (6 mL/6 μL), Amano AK lipase (40 mg), and vinyl acetate (0.9 mL, 10 mmol), and the mixture was stirred for 12 h at 23 °C. The resultant mixture was diluted with ether, filtered, concentrated, and purified by column chromatography (silica gel, 20 % ethyl acetate in hexanes) to afford (*S*)-**1c** (132 mg, 58 %). The optical purity was determined by Mosher ester analysis, ≥99 % *ee*. $[\alpha]_D^{23} = -3.9°$ (c = 1.4, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, J = 6.6 Hz, 3H), 1.2–1.4 (m, 6H), 3.30 (dd, J = 9.6, 5.1 Hz, 1H), 3.43 (dd, J = 10.2, 4.2 Hz, 1H), 3.4–3.5 (m, 1H), 3.6–3.7 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.7, 14.0, 19.6, 32.9, 40.8, 64.9 ppm. HRMS (EI) calcd for $C_6H_{13}IO$ $[M]^+$: 228.0011; found: 228.0015.

*Representative Procedure for Cu-Catalyzed Cross-Coupling. Synthesis of (S)-2-Ethylpentan-1-ol (**6**)*

To a solution of (*S*)-**1c** (92 mg, 0.4 mmol, ≥99 % *ee*), $CuCl_2$ (2.8 mg, 0.02 mmol), and 1-phenylpropyne (7.9 μL, 0.06 mmol) in THF (2 mL) was slowly added methylmagnesium chloride (3 M in THF, 0.44 mL, 1.32 mmol) at 0 °C, and the resultant solution was stirred for 2 h at 0 °C. The reaction was then quenched with aqueous NH_4Cl, extracted with Et_2O, dried over anhydrous $MgSO_4$, concentrated, and purified by column chromatography (silica gel, 20 % ethyl acetate in hexanes) to give (*S*)-2-ethylpentan-1-ol (*S*)-**6** (37 mg, 80 %). The optical purity was determined by chiral GC analysis, ≥99 % *ee*. $[\alpha]_D^{23} = +3.2°$ (c = 1.2, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85–0.95 (m, 6H), 1.15 (m, 1H), 1.22–1.45 (m, 7H), 3.55 ppm (dd, J = 5.4, 5.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.1, 14.5, 20.0, 23.3, 32.7, 41.7, 65.2 ppm. The optical purity of 99.3 % *ee* was determined by chiral GC analysis, CP-Chirasil-Dex CB capillary column (25 m × 0.25 mm, 0.39 μM film). Test conditions: carrier gas 8 psi H_2, oven program (60 °C for 8 min, then 2 °C min^{-1} to 90 °C for 20 min, then 20 °C min^{-1} to 190 °C for 2 min), detector FID 200 °C. Retention times (min): t_R 25.18 (minor); t_S 25.25 (major).

Synthesis of (R)-2-Propyloctanoic Acid. (R)-Arundic Acid

To a solution of (*R*)-**11** (86 mg, 0.5 mmol) and TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy free radical, 5.5 mg, 0.035 mmol) in CH_3CN (2.5 mL) and 0.67 M sodium phosphate buffer (pH 6.7, 1.9 mL) were added consecutively a solution of $NaClO_2$ (90 mg, 1.0 mmol) in H_2O (0.5 mL) and a solution of dilute NaOCl, prepared by diluting 5.25 % NaOCl (13 μL) with H_2O (0.25 mL). The mixture was stirred at 35 °C for 7 h and was cooled to 0 °C. 1 M HCl (3.0 mL) was added. The mixture was extracted with EtOAc and dried over anhydrous $MgSO_4$. After removing the volatiles in vacuo, the title product (89 mg, 98 %) was recovered as a colorless oil. $[\alpha]_D^{23} = -6.4°$ (c = 2.2, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.8–0.9 (m, 6H), 1.2–1.5 (m, 12H), 1.5–1.6 (m, 2H), 2.3–2.4 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 14.0, 20.5, 22.6, 27.3, 29.2, 31.7, 32.2, 34.3, 45.4, 183.5 ppm. The optical purity of 99.5 % *ee* was determined by chiral GC analysis of the corresponding alcohol by reduction with $LiAlH_4$. CP-Chirasil-Dex CB capillary column (25 m × 0.25 mm, 0.39 μM film). Test conditions: carrier gas 8 psi H_2, oven program (60 °C for 8 min, then 2 °C min^{-1} to 90 °C for 20 min, then 20 °C min^{-1} to 190 °C for 2 min), detector FID 200 °C. Retention times (min): t_R 47.1 (major); t_S 47.2 (minor).

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[1] I. Ojima et al. in *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), Wiley, **2010**, pp. 1–998.
[2] For examples of catalytic asymmetric hydrogenation of alkenes, see: a) R. Noyori in *Asymmetric Catalysis in Organic Synthesis* (Ed.: R. Noyori), Wiley, New York, **1994**, pp. 16–94; b) R. Noyori, *Angew. Chem.* **2002**, *114*, 2108–2123; *Angew. Chem. Int. Ed.* **2002**, *41*, 2008–2022; c) A. Lightfoot, P. Schnider, A. Pfaltz, *Angew. Chem.* **1998**, *110*, 3047–3050; *Angew. Chem. Int. Ed.* **1998**, *37*, 2897–2899; d) S. Bell, B. Wüstenberg, S. Kaiser, F. Menges, T. Netscher, *Science* **2006**, *311*, 642–644.
[3] a) T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976; b) K. B. Sharpless, *Angew. Chem.* **2002**, *114*, 2126–2135; *Angew. Chem. Int. Ed.* **2002**, *41*, 2024–2032.
[4] For examples of catalytic asymmetric carboalumination of alkenes, see: a) D. Kondakov, E. Negishi, *J. Am. Chem. Soc.* **1995**, *117*, 10771–10772; b) D. Kondakov, E. Negishi, *J. Am. Chem. Soc.* **1996**, *118*, 1577–1578; c) S. Huo, J. Shi, E. Negishi, *Angew. Chem.* **2002**, *114*, 2245–2247; *Angew. Chem. Int. Ed.* **2002**, *41*, 2141–2143; d) E. Negishi, Z. Tan, B. Liang, T. Novak, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5782–5787; e) T. Novak, Z. Tan, B. Liang, E. Negishi, *J. Am. Chem. Soc.* **2005**, *127*, 2838–2839; f) B. Liang, T. Novak, Z. Tan, E. Negishi, *J. Am. Chem. Soc.* **2006**, *128*, 2770–2771; g) E. Negishi, *Arkivoc.* **2011**, *viii*, 34–53; h) E. Negishi, *Angew. Chem.* **2011**, *123*, 6870–6897; *Angew. Chem. Int. Ed.* **2011**, *50*, 6738–6764.
[5] a) S. Huo, E. Negishi, *Org. Lett.* **2001**, *3*, 3253–3256; b) Z. Huang, Z. Tan, T. Novak, G. Zhu, E. Negishi, *Adv. Synth. Catal.* **2007**, *349*, 539–545; c) M. Magnin-Lachaux, Z. Tan, B. Liang, E. Negishi, *Org. Lett.* **2004**, *6*, 1425–1427; d) G. Zhu, B. Liang, E. Negishi, *Org. Lett.* **2008**, *10*, 1099–1101; e) Z. Tan, E. Negishi, *Angew. Chem.* **2004**, *116*, 2971–2974; *Angew. Chem. Int. Ed.* **2004**, *43*, 2911–2914; f) E. Pitsinos, N. Athinaios, Z. Xu, G. Wang, E. Negishi, *Chem. Commun.* **2010**, *46*, 2200–2202; g) G. Zhu, E. Negishi, *Org. Lett.* **2007**, *9*, 2771–2774.
[6] a) E. Negishi, *Bull. Chem. Soc. Jpn.* **2007**, *80*, 233–257; b) B. Liang, E. Negishi, *Org. Lett.* **2008**, *10*, 193–195; c) G. Zhu, E. Negishi, *Chem. Eur. J.* **2008**, *14*, 311–318.
[7] C.-S. Chen, Y. Fujimoto, G. Girdaukas, C. J. Sih, *J. Am. Chem. Soc.* **1982**, *104*, 7294–7299.
[8] (*S*)-2-Methyl-1-butanol of ≥98 % *ee* is commercially available from TCI ($66.30/25 mL or $285/mol).
[9] For examples of synthesis of (*R*)-2-methyl-1-butanol from methyl (*S*)-3-hydroxy-2-methylpropionate, see: a) K. Mori, H. Takikawa, *Liebigs Ann. Chem.* **1991**, 497–500; b) E. M. Santangelo, P. H. G. Zarbin, Q. B. Cass, J. T. B. Ferreira, A. G. Correa, *Synth. Commun.* **2001**, *31*, 3685–3698; c) A. Tai, E. Syouno, K. Tanaka, M. Fujita, T. Sugimura, Y. Higashiura, M. Kakizaki, H. Hara, T. Naito, *Bull. Chem. Soc. Jpn.* **2002**, *75*, 111–121; d) M. G. Organ, Y. V. Bilokin, S. Bratovanov, *J. Org. Chem.* **2002**, *67*, 5176–5183; e) T. Tachihara, S. Ishizaki, Y. Kurobayashi, H. Tamura, Y. Ikemoto, A. Onuma, K. Yoshikawa, T. Yanai, T. Kitahara, *Helv. Chim. Acta* **2003**, *86*, 274–279; f) E. M. Santangelo, A. G. Correa, P. H. G. Zarbin, *Tetrahedron Lett.* **2006**, *47*, 5135–5137; g) I. Danila, F. Riob, F. Piron, J. Puigmar-

tí-Luis, J. D. Wallis, M. Linares, H. Ågren, D. Beljonne, D. B. Amabilino, N. Avarvari, *J. Am. Chem. Soc.* **2011**, *133*, 8344–8353.
[10] Methyl (*S*)-(+)-3-hydroxy-2-methylpropionate of 99% *ee* is commercially available from Aldrich ($485/25 g or $2292/mol).
[11] a) H. C. Brown, T. Imai, M. C. Desai, B. Singaram, *J. Am. Chem. Soc.* **1985**, *107*, 4980–4983; b) H. C. Brown, R. G. Naik, R. K. Bakshi, C. Pyun, B. Singaram, *J. Org. Chem.* **1985**, *50*, 5586–5592.
[12] G. D. McAllister, R. J. K. Taylor, *Tetrahedron Lett.* **2004**, *45*, 2551–2554.
[13] J. K. Kochi, M. Tamura, *J. Am. Chem. Soc.* **1971**, *93*, 1485–1487.
[14] a) G. Erker, M. Aulbach, M. Knickmeier, D. Wingbermühle, C. Krüger, M. Nolte, S. Werner, *J. Am. Chem. Soc.* **1993**, *115*, 4590–4601; b) Available from Aldrich Chemical Co., Milwaukee, WI.
[15] J. Terao, H. Todo, S. A. Begum, H. Kuniyasu, N. Kambe, *Angew. Chem.* **2007**, *119*, 2132–2135; *Angew. Chem. Int. Ed.* **2007**, *46*, 2086–2089.
[16] J. A. Dale, H. S. Mosher, *J. Am. Chem. Soc.* **1973**, *95*, 512–519.
[17] a) K. Mislow, P. Bickart, *Isr. J. Chem.* **1976/77**, *15*, 1–6; b) K. Mislow in *Fuzzy Logic in Chemistry* (Ed.: D. H. Rouvray), Academic Press, **1997**, pp. 65–90; c) K. Mislow, *Collect. Czech Chem. Commun.* **2003**, *68*, 849–864.
[18] For reviews of metal-catalyzed cross-coupling reactions of alkyl halides, see: a) T.-Y. Luh, M. Leung, K.-T. Wong, *Chem. Rev.* **2000**, *100*, 3187–3204; b) A. C. Frisch, M. Beller, *Angew. Chem.* **2005**, *117*, 680–695; *Angew. Chem. Int. Ed.* **2005**, *44*, 674–688; c) A. Rudolph, M. Lautens, *Angew. Chem.* **2009**, *121*, 2694–2708; *Angew. Chem. Int. Ed.* **2009**, *48*, 2656–2670; d) R. Jana, T. P. Pathak, M. S. Sigman, *Chem. Rev.* **2011**, *111*, 1417–1492; e) N. Kambe, T. Iwasaki, J. Terao, *Chem. Soc. Rev.* **2011**, *40*, 4937–4947.
[19] For selected examples of metal-catalyzed cross-coupling reactions of alkyl halides, see: a) J. Terao, H. Watanabe, A. Ikumi, H. Kuniyasu, N. Kambe, *J. Am. Chem. Soc.* **2002**, *124*, 4222–4223; b) N. Hadei, E. A. B. Kantchev, C. J. O'Brien, M. G. Organ, *J. Org. Chem.* **2005**, *70*, 8503–8507; c) X. L. Hu, *Chem. Sci.* **2011**, *2*, 1867–1886; d) C.-T. Yang, Z.-Q. Zhang, Y.-C. Liu, L. Liu, *Angew. Chem.* **2011**, *123*, 3990–3993; *Angew. Chem. Int. Ed.* **2011**, *50*, 3904–3907.
[20] a) N. Tateishi, T. Mori, Y. Kagamiishi, S. Satoh, N. Katsube, E. Morikawa, T. Morimoto, T. Matsui, T. Asano, *J. Cereb. Blood Flow Metab.* **2002**, *22*, 723–734; b) L. A. Sorbera, J. Castaner, *Drugs Future* **2004**, *29*, 441–448.
[21] For examples of the synthesis of (*R*)- or (*S*)-arundic acid, see: a) T. Hasegawa, H. Yamamoto, *Bull. Chem. Soc. Jpn.* **2000**, *73*, 423–428; b) T. Hasegawa, H. Yamamoto, *Synthesis* **2003**, *8*, 1181–1186; c) T. Hasegawa, Y. Kawanaka, E. Kasamatsu, Y. Iguchi, Y. Yonekawa, M. Okamoto, C. Ohta, S. Hashimoto, S. Ohuchida, *Org. Process Res. Dev.* **2003**, *7*, 168–171; d) B. Pelotier, T. Holmes, O. Piva, *Tetrahedron: Asymmetry* **2005**, *16*, 1513–1520; e) J. M. Garcia, J. M. Odriozola, A. Lecumberri, J. Razkin, A. Gonzalez, *Tetrahedron* **2008**, *64*, 10664–10669; f) R. A. Fernandes, A. Dhall, A. B. Ingle, *Tetrahedron Lett.* **2009**, *50*, 5903–5905; g) T. Hasegawa, Y. Kawanaka, E. Kasamatsu, C. Ohta, K. Nakabayashi, M. Okamoto, M. Hamano, K. Takahashi, S. Ohuchida, Y. Hamada, *Org. Process Res. Dev.* **2005**, *9*, 774–781; h) D. Goswami, A. Chattopadhyay, *Lett. Org. Chem.* **2006**, *3*, 922–925; i) A. Gualandi, E. Emer, M. G. Capdevila, P. G. Cozzi, *Angew. Chem.* **2011**, *123*, 7988–7992; *Angew. Chem. Int. Ed.* **2011**, *50*, 7842–7846.

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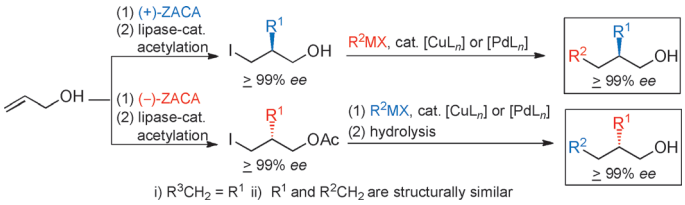
FULL PAPER

Asymmetric Synthesis

*Shiqing Xu, Ching-Tien Lee, Guangwei Wang, Ei-ichi Negishi**

Widely Applicable Synthesis of Enantiomerically Pure Tertiary Alkyl-Containing 1-Alkanols by Zirconium-Catalyzed Asymmetric Carboalumination of Alkenes and Palladium- or Copper-Catalyzed Cross-Coupling



Look, mom, one hand! 2-Alkyl-1-alkanols of feeble chirality have been synthesized by a sequence of zirconium-catalyzed asymmetric carboalumination of alkenes (ZACA), lipase-catalyzed acetylation, and Pd- or Cu-catalyzed cross-coupling in high enantiomeric purity of $\geq 99\,\%$ *ee*. The synthetic utility of this method has been demonstrated in highly enantioselective and efficient syntheses of (*R*)-2-methyl-1-butanol, (*R*)- and (*S*)-arundic acids.