Review

Catalytic enantioselective synthesis of chiral organic compounds
of ultra-high purity of >99% eeBy Ei-ichi NEGISHI^{*1,†} and Shiqing XU^{*1}

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Abstract: Shortly after the discovery of Zr-catalyzed carboalumination of alkynes in 1978, we sought expansion of the scope of this reaction so as to develop its alkene version for catalytic asymmetric C–C bond formation, namely the ZACA (Zr-catalyzed asymmetric carboalumination of alkenes). However, this seemingly easy task proved to be quite challenging. The ZACA reaction was finally discovered in 1995 by suppressing three competitive side reactions, *i.e.*, (i) cyclic carbometalation, (ii) β -H transfer hydrometalation, and (iii) alkene polymerization. The ZACA reaction has been used to significantly modernize and improve syntheses of various natural products including deoxypolypropionates and isoprenoids. This review focuses on our recent progress on the development of ZACA–lipase-catalyzed acetylation–transition metal-catalyzed cross-coupling processes for highly efficient and enantioselective syntheses of a wide range of chiral organic compounds with ultra-high enantiomeric purities.

Keywords: ZACA reaction, asymmetric catalysis, carboalumination, lipase-catalyzed acetylation, cross-coupling, chiral isotopomers

Despite major advances in organic synthesis predominantly over the past hundred years or so, *asymmetric synthesis of chiral organic compounds including the great majority of bioactive compounds, such as amino acids and their oligomers and polymers, i.e., peptides, has remained as one of the “last bastions” to be conquered.*

As alarmed by the unfortunate incident of a tranquilizer, Thalidomide,¹⁾ any bioactive organic compounds of biological and medicinal concerns must be prepared in the “YESES” manners, satisfying all of the following requirements including (i) high Yields, (ii) high Efficiency to be reflected most significantly in the number of synthetic steps, (iii) high Selectivity leading to high purity as high as required, (iv) Economy mandating highly catalytic processes, and (v) last but not least, unfailing Safety, which is often closely linked with Selectivity.

As is well known, discovery of the existence of enantiomeric isomers of organic compounds as well as their isolation as enantiomerically pure isomers with the use of tweezers under microscope were performed for the preparation of enantiomerically pure D-(–)- and L-(+)-tartaric acids as early as the mid-nineteenth century by L. Pasteur.^{2),3)}

Approximately half a century later, the first Nobel Prize in Chemistry was awarded to J. H. van’t Hoff in 1901.⁴⁾ Among his various contributions pertaining to the relationships between configurations of C atoms and various physical and chemical properties including chirality, optical activity, and so on, he predicted that α,ω -di-, tri-, or tetrasubstituted cumulenes, *i.e.*, $R^1R^2C=C=C\cdots C=C\cdots CR^3R^4$, can be chiral and optically active in cases where the number of cumulating C=C, *i.e.* n , is odd and 3 or higher.^{5),6)}

The second Nobel Prize in Chemistry in 1902 recognized E. Fischer’s astounding achievements in the syntheses of various complex organic compounds including a number of mono- and oligosaccharides.^{7),8)} As monumental as his *diastereoselective* syntheses were, additionally and more critically needed were *enantioselective* syntheses of a wide

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Proposed mechanism

Scheme 1. Zr-catalyzed carboalumination of alkynes (ZMA).

range of chiral organic compounds, as complementary, supplementary, and hopefully superior routes to the desired chiral organic compounds. This, however, proved to be a highly challenging goal.

Historically, yet another fundamentally significant advance in the asymmetric synthesis of chiral organic compounds was made about half a century later, when K. Ziegler^{9),10)} of Germany and G. Natta¹¹⁾ of Italy developed their isotactic polymerization of ethylene, propylene, and other alkenes, which led to their Nobel Prizes won in 1963. As both scientifically and industrially significant as these developments have been, these alkene polymerization reactions dealt only with “tacticity”, *i.e.*, relative stereochemistry rather than absolute stereochemistry.

Major revolutionary discoveries and developments along the latter line have been made mostly since the 1970s. Concurrently, a group of industrial researchers at Monsanto, led by W. S. Knowles,^{12),13)} and R. Noyori in Japan^{14),15)} reported highly catalytic and selective hydrogenation of alkenes, especially allyllically heterofunctional alkenes. Some promisingly leads reported by H. Kagan in France¹⁶⁾ are also noteworthy. K. B. Sharpless^{17),18)} with one of his associates T. Katsuki reported asymmetric epoxidation of allylic alcohols in 1980.¹⁷⁾ It should be clearly noted, however, that none of these enantioselective reactions directly involves C–C bond formation.

Discovery and application of Zr-catalyzed methylalumination of alkynes (ZMA)

In 1978, we discovered **Zr**-catalyzed methylalumination of alkynes (ZMA)^{19)–21)} and tentatively proposed its mechanism as shown in Scheme 1. The synthetic scope and utility of the ZMA reaction may be most vividly appreciated by noting numerous examples of its application to natural product syntheses. About 150 natural product syntheses were listed in our previous review.²²⁾ Since then, its use in more than 60 natural product syntheses has been reported. Some representative examples are listed in Table 1 and Scheme 2.

Discovery of Zr-catalyzed asymmetric carboalumination of alkenes (ZACA)

Encouraged by the discovery and development of the alkyne carboalumination reaction catalyzed by Cp_2ZrCl_2 (ZMA),^{19)–21)} our search for a more highly coveted alkene-version of the reaction was resumed in the early 1980s. If only the alkyne carboalumination could be modified for discovering the corresponding alkene carboalumination reaction with suitable chiral zirconocene derivatives, we would most likely discover a catalytic and enantioselective C–C bond-forming reaction, namely the ZACA (**Zr**-catalyzed **a**symmetric **c**arboalumination of **a**lkenes). We believed that our notion of promoting carbometallation of alkenes with “super-acidic” bimetallic

Table 1. Some representative examples of natural products synthesized by using Zr-catalyzed carboalumination of alkynes

Year	Name of Natural Product	Reference
2005	bis-Deoxyphotoxin	25
2006	<i>N</i> -Acetylcysteamine thioester of <i>seco</i> -Proansamitoci	26
	Carbazomadurin B	27
	1,22-Dihydroxynitienes	28
	(+)-Epolactaene	29
	Aurisides A and B	30
	(3 <i>S</i>)-Oxidosqualene (analogs)	31
	Dolabelide C (C1–C15 fragment)	32
2007	Amphidinolide X and Y (C12–C21 fragment)	33
	Dechloroansamitocin P-3	34
	Iromycins	35
	Nakiterpiosin	36
	Coenzyme Q10	37
	(–)-Reidispongiolide A	38
	Iridal's core structure	39
	(±)-Phomactin B2	40
	Amphidinolide H and G	41
2008	Callipeltoside Aglycone	42
	Bafilomycin A1 (C1–C17 and C18–C25 fragments)	43
	Nafuredinmilbemycin β 3, and (–)-bafilomycin A1 (key intermediates)	44
	(–)-Reidispongiolide A	45
2009	Amphidinolides B1, B4, G1, H1, and H2	46
	Phomactins	47
	Verticipyrene	48
	(+)-Myrrhanol A	49
	Plaunotol	50
	Marinomycin A (monomeric counterpart)	51
2010	Carbazomadurin A	52
	Meiogynin A	53
	Maytansinoids	54
	Ansamitocins P-2 to P-4	54

Continued on next page.

reagents consisting of alkylalanes and 16-electron zirconocene derivatives^{21),72)} should provide us with desirable alkene carbometalation reactions. This, however, proved to be more challenging and time-consuming endeavor than anticipated. In the end, however, our basic assumptions proved to be reasonable, and what may be termed a “one-step Ziegler-Natta alkene polymerization reaction” was almost single-handedly discovered in 1995 by Dr. D. Y. Kondakov (Scheme 3).^{73)–75)}

All of the available data and observations are consistent with our notions and belief that the reaction involves Al-promoted carbozirconation of alkenes in accord with widely accepted mechanistic

insights in the area of the Ziegler-Natta alkene polymerization. The observed high enantioselectivity seems to strongly favor Al-promoted carbozirconation mechanism as opposed to Zr-promoted carboalumination mechanism. Why did the discovery of the alkene ZACA reaction take such a long time, *i.e.*, 17 years, after the discovery of the Zr-catalyzed carboalumination of alkynes? Arguably, carbometalation is fundamentally less facile than hydrometalation for various reasons which are not discussed here except to point out more stringent steric requirements stemming from shear bulk and more highly directional properties of C relative to H, just to mention a few.

Continued.

Year	Name of Natural Product	Reference
2011–2015	Mycolactones A and B	55
	Leiodermatolide (macrocyclic core)	56
	<i>N</i> -acetyl-S-farnesyl-L-cysteine	57
	FTPA triazole I	58
	(+)-Concanamycin F	59
	Bafilomycin A1	60
	Palmerolide (C16–C24 fragment)	61
	Carbazomadurin A	62
	(<i>S</i>)-(+)-Carbazomadurin B	62
	Leiodolide A (C22–C31 fragment)	63
	Celastrol	64
	Enokipodin B	65
	24-Fluorinated Bafilomycin (analog)	66
	Ieodomycins A and B	67
	Amphidinolides C, C2, and C3 (C-18–C-34 Fragment)	68
	Verrillin (functionalized core)	69
	(+)-Myrrhanol C	70
	Myceliothermophins C, D, and E	71

Scheme 2. Syntheses of vitamin A and β - and γ -carotenes by Zr-catalyzed carboalumination of alkynes (ZMA).^{23),24)}

Scheme 3. Zr-catalyzed asymmetric carboalumination of alkenes (ZACA).

We painfully learned that the reaction of 1-alkenes with alkylalanes in the presence of zirconocene derivatives could undergo a few other competitive side reactions in addition to the desired single-stage carbometalation shown in the green frame of Scheme 4, of which (i) H-transfer hydrometalation,⁷⁶⁾ (ii) the Kaminsky version of Ziegler-Natta polymerization,⁷⁷⁾ (iii) bimetallic cyclic carbometalation,⁷⁴⁾ and (iv) monometallic cyclic carbometalation⁷⁸⁾ are representative. For favorable results, all of the side reactions shown in the red frame of Scheme 4 must be effectively suppressed.

Having learned about these major pitfalls, the remaining major task was to find some satisfactory chiral zirconocene catalysts with sufficiently, but not excessively, bulky ligands to suppress unwanted side

reactions, while promoting the desired alkene carbometalation. In this respect, no systematic catalyst optimization involving catalyst design has as yet been made. Instead, a dozen to fifteen known chiral zirconocene complexes were initially screened. Widely used $(\text{EBI})\text{ZrCl}_2$ ⁷⁹⁾ and its partially hydrogenated derivatives⁸⁰⁾ were less effective. The most effective among those tested is Erker's $(\text{NMI})_2\text{ZrCl}_2$.⁸¹⁾ Although methylalumination is singularly important from the viewpoint of the synthesis of natural products, it is ironically the uniquely unfavorable case where the ee figures are around 75%, as compared with ethylalumination and higher alkylalumination which proceeds in 90–95% ee. An attractive alternative has been developed by taking advantage of high enantioselectivity observed in ethylalumina-

Scheme 4. Zr-catalyzed asymmetric carboalumination of alkenes (ZACA).

tion and higher alkylaluminum.^{82),83)} There are currently three Zr-catalyzed asymmetric carboalumination protocols that can be used for the synthesis of methyl-branched 1-alkanols (Scheme 5).^{82),83)}

Development and application of ZACA reaction

Despite some room for improvement, especially (i) improvement of the enantioselectivity of carboalumination and (ii) realization of higher turnover numbers through elevation of the current level of $20\text{--}10^3$ to $\geq 10^3\text{--}10^4$ or higher, the ZACA reaction promises to provide a widely applicable, efficient, and selective asymmetric method for the synthesis of a variety of chiral organic compounds. In view of the abundant presence of deoxypropionate-containing natural products with diverse fascinating biological

activities, intense efforts for the development of efficient and stereoselective methods for their synthesis have been made.^{84),85)} Since deoxypropionates are devoid of heterofunctional groups that could assist asymmetric C–C or C–H bond formation, most of the currently known and widely used methods for their constructions have to install temporary functional or chiral directing groups that are to be removed later. These methods construct deoxypropionate units in a linear-iterative fashion, and one iteration cycle typically requires 3–6 steps to introduce one methyl-branched chiral center.

Through several conceptual and methodological breakthroughs, some highly efficient, selective, and practical processes for the synthesis of deoxypropionates and related compounds containing two or more

Scheme 5. Three protocols for enantioselective synthesis of methyl-substituted 1-alkanols.

Table 2. Statistical enantiomeric amplification in iterative enantioselective process

ee in step or species I (%)	ee in step or species II (%)	Overall ee (%)
70	70	94.0
80	80	97.6
90	80	98.8
90	90	99.4
99	99	99.995

asymmetric carbon atoms have been developed in the authors' group through exploitation of the *statistical enantiomeric amplification principle* (Table 2). These breakthroughs include (i) realization that Me-branched chiral compounds can be synthesized by ZACA reaction via a few alternate and mutually complementary routes (Scheme 5), (ii) unexpected finding that *2,4-dimethyl-1-hydroxybutyl moieties can be readily purified by ordinary chromatography* (Scheme 6),⁸³ and (iii) subsequent Pd- or Cu-catalyzed cross-coupling proceeds with essentially full (>99%) retention of newly formed chiral centers (Scheme 7).⁸⁶

One-Pot ZACA–Pd-Catalyzed Vinylation Tandem Process for One-Step Iterative Homologation by a Propylene Unit. Initially, the authors' group used a three-step iterative homologation cycle for incorporation of one propylene unit,⁸³ which consisted of (i) ZACA-oxidation, (ii) iodination, and (iii) metalation–Pd-catalyzed vinylation. Since the initial

ZACA reaction product is an alkylalane, its direct use in the Pd-catalyzed vinylation was explored by skipping oxidation and iodination, which led to a highly efficient one-pot ZACA–Pd-catalyzed vinylation tandem process for one-step iterative homologation by a propylene unit.⁸⁶ The isoalkyldimethylalanes, generated by ZACA reaction, was directly used for Pd-catalyzed vinylation with (i) $Zn(OTf)_2$ as an additive, (ii) $Pd(DPEphos)Cl_2$ and tBu_2AlH (DIBAL-H) in a 1:2 molar ratio as a catalyst system, and (iii) DMF as a solvent. The ZACA reaction of 1-octene proceeded in 75% ee (Mosher ester analysis of 2-methyl-1-octanol after oxidation). After Pd-catalyzed vinylation at elevated temperature (even at 120 °C), the product **7** was formed in 75% ee. Thus, no detectable racemization took place under the conditions of the Pd-catalyzed vinylation.

The one-pot ZACA–Pd-catalyzed vinylation tandem process developed above has been used to the synthesis of α,ω -diheterofunctional deoxypolypropionates and related compounds containing two or more asymmetric carbon atoms,^{86,87} e.g., all-(*R*)-2,4,6,8-tetramethyldecanoic acid, a preen gland wax of graylag goose, Anser anser (Scheme 8).⁸⁷

Recently, we developed a highly concise, convergent, and enantioselective access to polydeoxypropionates.⁸⁸ ZACA–Pd-catalyzed vinylation was used to prepare smaller deoxypropionate fragments, and then two key sequential Cu-catalyzed stereocontrolled sp^3 – sp^3 cross-coupling reactions⁸⁹ allowed convergent assembly of smaller building blocks to build-up long polydeoxypropionate chains with

Scheme 6. Synthesis of all four possible stereoisomers of 2,4-dimethyl-1-hexanols (1).

Scheme 7. "One-pot" ZACA-Pd-catalyzed vinylation tandem process.

excellent stereoselectivity. We employed this strategy for the synthesis of phthioceranic acid, a key constituent of the cell-wall lipid of *Mycobacterium tuberculosis*, in just 8 longest linear steps with essentially full (>99%) stereocontrol (Scheme 9).

ZACA-lipase-catalyzed acetylation-Pd- or Cu-catalyzed cross-coupling processes

Having developed unprecedentedly efficient methods for the synthesis of deoxypolyprenates

with two or more stereogenic carbon centers as discussed above, it was acutely realized that, *only if ZACA products containing just one stereogenic carbon center can be readily and predictably purified, the ZACA-based asymmetric synthetic method would become much more widely applicable.* The senior author recently became fully aware of the following strengths and weaknesses of the previously known lipase-catalyzed (*S*)-selective acetylation: (i) Enantiomerically pure (*R*)-2-methyl-1-alkanols can be

Scheme 8. Allyl alcohol-based route to α,ω -diheterofunctional deoxypolypropionates.

Scheme 9. Highly efficient, convergent, and enantioselective synthesis of phthioceranic acid.

reliably obtained from their racemic mixtures, although the maximally attainable yield (or recovery) of (*R*)-alcohols of $\geq 98\%$ ee is limited to 50% or, more specifically $\leq 25\%$ if $E = 10$, $\leq 35\%$ if $E = 20$, and $\leq 45\%$ if $E = 100$, where E (enantiomeric ratio or selectivity factor) = $\ln[(1 - C)(1 - ee)] / \ln[(1 - C)(1 + ee)]$ and C and ee are the extent of conversion and the enantiomeric excess of the unreacted alcohol, respectively.^{90,91} As such, it is not an attractive method, especially if the starting 2-methyl-1-alkanols are very expensive; (ii) Much more striking and important is that the lipase-catalyzed acetylation method is practically incapable of providing the $\geq 99\%$ pure acetates of (*S*)-2-methyl-1-alkanols from their racemic mixtures in one cycle, since it can be predicted that the maximally attainable yields of $\geq 99\%$ pure acetates would be

$\leq 1-2\%$ ($E \leq 100$).^{90,91} Consequently, iterative purification processes, in which the purity of desired compound must be gradually elevated, will be required. This theoretical prediction also points to a significant advantage in being able to start with enantiomerically enriched (*S*)-2-methyl-1-alkanols as shown in Table 3. Some maximally attainable yields of $\geq 99\%$ pure acetates of (*S*)-2-methyl-1-alkanols can be predicted as follows: $\leq 80\%$ if the initial ee_0 is 70% and E is 50; $\leq 85\%$ if ee_0 is 80% and E is 30; $\leq 95\%$ if ee_0 is 90% and E is 20.^{90,91} It is clear that neither the ZACA reaction alone nor the lipase-catalyzed acetylation alone is capable of providing a satisfactory method for the synthesis of either *R* or *S* isomer of 2-methyl-1-alkanols of $\geq 99\%$ isomeric purity but that a combination of the two would be, provided that (i) the ZACA reaction is sufficiently enantioselective,

Table 3. Significance of high initial enantiomeric excess (ee_0) and selectivity factor (E) on the maximally attainable yields of (*S*)-2-alkyl-1-alkanols of $>98\%$ $ee^{(90,91)}$

Initial ee_0 (%)	$E^{[a]}$	Max. yield (%)	Initial ee_0 (%)	$E^{[a]}$	Max. yield (%)
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

$E = 33$	$\Rightarrow$	proximal heteroatoms (halogen, oxygen, etc.)
$E = 42$	$\Rightarrow$	proximal π -bonds (aromatic groups, double bonds, etc.)
$E = 22$
$E < 5$	$\Rightarrow$	alkyl-substituted (low E factor)

$$^a E \text{ (enantiomeric ratio or selectivity factor)} = \ln[(1 - C)(1 - ee)] / \ln[(1 - C)(1 + ee)]$$

C and ee are the extent of conversion and the enantiomeric excess of the unreacted alcohol, respectively

preferably 80–90% ee but minimally $\geq 70\%$ ee and (ii) the E values are sufficiently high, preferably ≥ 20 –30. The ZACA–lipase-catalyzed acetylation sequential process has indeed been successfully applied to the purification of either *R* or *S* isomers of 2-methyl-1-alkanols, as represented in Table 4.⁹²⁾ Thus, 2-alkyl-1-alkanols, even in some cases of lacking any proximal π -bonds or heterofunctional groups, have been efficiently synthesized in $\geq 98\%$ ee by ZACA–lipase-catalyzed acetylation sequential protocol.⁹²⁾

As discussed above, the efficiency of the lipase-catalyzed acetylation critically depends on the selectivity factor (E).^{90,91)} In more demanding (feebly chiral) cases, especially when two alkyl groups are very similar, it is difficult to purify to $>98\%$ ee even from enantiomerically enriched mixtures by lipase-catalyzed acetylation. To overcome this difficulty, the ZACA–lipase-catalyzed acetylation–Pd- or Cu-catalyzed cross-coupling sequential process was considered and developed for the synthesis of various feebly chiral 2-alkyl-1-alkanols of $>99\%$ ee as outlined in Scheme 10.⁹³⁾ By virtue of the high selectivity factor (E) associated with iodine, either (*S*)- or (*R*)-

enantiomer of 3-iodo-2-alkyl-1-alkanols (**3**), prepared by ZACA reaction of allyl alcohol, can be readily purified to the level of $\geq 99\%$ 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*)-**3** or (*R*)-**4** for introduction of various primary, secondary and tertiary carbon groups with retention of all carbon skeletal features.⁹³⁾

The ZACA–lipase-catalyzed acetylation–Pd- or Cu-catalyzed cross-coupling process has been applied to highly efficient and enantioselective synthesis of various chiral 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.^{94,95)} (*R*)- and (*S*)-**5** of $\geq 99\%$ ee , prepared via ZACA–lipase-catalyzed purification–Cu-catalyzed cross-coupling (Scheme 11), were transformed into the corresponding (*R*)- and (*S*)-arundic acids in 98% yield by oxidation with NaClO_2 in the presence of

Table 4. ZACA–lipase-catalyzed acetylation processes for the synthesis of 2-methyl-1-alkanols

R	Initial Yield (%)	Initial ee (%)	Enzyme	Solvent	Temp [°C]	Conversion (%)	Recovery (%)	Final ee (%)
Ph	85	89	Amano PS	THF/H ₂ O	23	22	68	93
			Amano PS	THF/H ₂ O	23	50	43	96
			PPL	THF/H ₂ O	23	31	62	99
PhCH ₂	85	76	PPL	THF/H ₂ O	23	48	51	77
			Amano PS	THF/H ₂ O	23	40	59	99
Ph(CH ₂) ₂	85	78	PPL	THF/H ₂ O	23	30	64	99
			Amano PS	THF/H ₂ O	23	38	56	99
<i>n</i> -Hex 	76	75	Amano PS	CH ₂ Cl ₂	0	16	80	98
<i>n</i> -Hex	71	72	Amano PS	CH ₂ Cl ₂	0	38	60	98

catalytic amounts of NaClO and 2,2,6,6-tetramethylpiperidin-1-yloxy (TEMPO). Thus, a highly enantioselective ($\geq 99\%$ ee) and efficient synthesis of (*R*)- and (*S*)-arundic acids was achieved in 25% and 28% over five steps, respectively, from allyl alcohol.⁹³⁾

(*S*)-2-Methyl-3-iodo-1-propanol **6** of $\geq 99\%$ ee, obtained by ZACA-iodolysis–lipase-catalyzed acetylation from allyl alcohol, was converted to 1,1-dibromo-alkene **7** in 74% yield over four steps.⁸⁷⁾ Compound **7** was further transformed to **8**, a potential intermediate for the synthesis of callistatin A, by PdCl₂(DPEphos)-catalyzed Negishi coupling reactions where the second Negishi coupling proceeded with a clean stereoinversion (Scheme 12).⁸⁷⁾

As satisfactory as the procedure shown in Scheme 10 is, its synthetic scope is limited to the preparation of 2-chirally-substituted 1-alkanols. In search for an alternative and more generally applicable procedure, we developed a new protocol for the synthesis of γ - and more-remotely chiral alcohols of high enantiomeric purity through simple paradigm shift, as summarized in Scheme 13.⁹⁶⁾

Having developed a widely applicable route to various γ - and more-remotely chiral alcohols by ZACA/oxidation–lipase-catalyzed acetylation–Cu- or Pd-catalyzed cross-coupling protocol, our attention was necessarily and increasingly drawn into the

methods of determination of enantiomeric purities of the final desired alcohols, which proved to be quite challenging. For most of alkanols where the stereogenic center generated was in the γ or δ position relative to the OH group, the enantiomeric purities of $\geq 99\%$ ee were successfully determined by chiral gas chromatography or NMR analysis of Mosher esters.⁹⁷⁾ However, initial attempts to determine the enantiomeric excess in more demanding cases, such as 4-alkyl-1-alcohols and 5-alkyl-1-alcohols, using chiral GC, HPLC and Mosher ester analysis were unsatisfactory.

A solution to the above-mentioned difficulty was found through the use of 2-methoxy-2-(1-naphthyl)-propionic acid (M α NP), which had been used in determining the absolute configuration of chiral secondary alcohols.^{98),99)} Presumably the naphthyl ring of M α NP esters would exert greater anisotropic shielding effects than α -methoxy- α -trifluoromethyl-phenylacetic acid (MTPA) phenyl group. Indeed, the two terminal methyl groups of the diastereomeric M α NP ester (*R,R*)- and (*R,S*)-**13**, derived from ε -chiral alcohol (*R*)-**11**, showed completely separate ¹H NMR signals, while the diastereomeric MTPA ester **12** showed no separation (Scheme 14). The M α NP ester analysis was also successfully applied to chiral discrimination of other δ - and ε -chiral primary

Scheme 10. Synthesis of feebly chiral 2-substituted 1-alkanols of $\geq 99\%$ ee.

Scheme 11. ZACA-lipase-catalyzed acetylation-Cu-catalyzed cross-coupling process for the synthesis of (R)- and (S)-arundic acids.

alcohols, which demonstrated surprising long-range anisotropic differential shielding effects. It should be noted that the diastereotopic chemical shift differences of $\text{M}\alpha\text{NP}$ esters were affected by NMR solvent and resonance frequency (MHz) of NMR. *d*-Acetonitrile, *d*-acetone, *d*-methanol and/or CDCl_3 have been shown to be suitable solvents. The higher

the resonance frequency, the better discrimination of chemical shifts obtained.

ZACA-lipase-catalyzed acetylation-Cu-catalyzed cross-coupling synergy has been applied to a highly enantioselective ($>99\%$ ee) and diastereoselective ($>98\%$ de) synthesis of chiral C_{15} vitamin E side-chain **19** (Scheme 15).¹⁰⁰ The key α,ω -dioxo-

Scheme 12. ZACA–lipase-catalyzed acetylation–Pd-catalyzed cross-coupling process for the synthesis of (–)-callystatin A.

Note: N.D. means "non-detectable".

Scheme 13. Synthesis of γ - and more-remotely chiral 1-alkanols of $\geq 99\%$ ee.

Scheme 14. Methyl resonances in the ^1H NMR spectra (CDCl_3 , 600 MHz) of MTPA ester and M α NP ester derived from ε -chiral alcohol (*R*)-11.

Scheme 15. The synthesis of C_{15} vitamin E side-chain 19.

functional C_5 synthon **15** ($\geq 99\%$ ee) was readily prepared by ZACA–lipase-catalyzed acetylation, which can be further functionalized at both ends. Two sequential Cu-catalyzed alkyl–alkyl cross-coupling reactions of the enantiomerically pure C_5 iodide **16** were employed as the key steps for preparing the

C_{15} vitamin E side-chain **19**, which was shown to be $>99\%$ ee by ^1H NMR analysis of its M α NP ester (Scheme 16).¹⁰⁰⁾

Chiral compounds arising from the replacement of hydrogen (H) with deuterium (D) are very important in the fields of organic chemistry and

Scheme 16. ^1H NMR spectra of diastereomeric MaNP esters of γ -chiral alcohol **19** (CDCl_3 , 600 MHz).

biochemistry. Some of these chiral compounds whose specific rotation values are practically non-measurable, due to very small differences between the isotopomeric groups, exhibit “cryptochirality”^{101)–103)} representing a class of compounds which have been very difficult to synthesize and distinguish. Our ZACA–lipase-catalyzed acetylation–Cu-catalyzed cross-coupling processes provide a general and efficient method for the highly enantioselective ($\geq 99\%$ ee) and catalytic synthesis of various 1-alkanols of isotopomeric “cryptochirality” (Scheme 17).¹⁰⁴⁾

Three deuterium-substituted δ -chiral isotopomers (*R*)-**22**, **23**, and **24** were prepared by ZACA/oxidation–lipase-catalyzed acetylation–Cu-catalyzed cross-coupling. ZACA reaction of TBS-protected 4-penten-1-ol followed by *in situ* oxidation with O_2 provided intermediate (*S*)-**25** of 85% ee in 67% yield. This crude (*S*)-**25** was readily purified to the level of $\geq 99\%$ ee by Amano PS lipase-catalyzed acetylation in 70% recovery.⁹⁶⁾ After conversion of (*S*)-**25** into iodide, Cu-catalyzed cross-coupling with three different deuterium-substituted Grignard reagents was then used for the synthesis of isotopomers (*R*)-**22**, **23**, and **24** (Scheme 18).¹⁰⁴⁾ To further demonstrate the high efficiency of ZACA–lipase-catalyzed acetylation tandem process for preparation of α,ω -dioxifunctional alcohols in high enantiomeric purity,

one control experiment of lipase-catalyzed acetylation of *rac*-**25** was performed. Under the optimal conditions, lipase-catalyzed acetylation of *rac*-**25** still only produced (*S*)-**25** of 87.8% ee in a disappointingly low recovery of 10%. Thus, it is practically impossible to synthesize (*S*)-**25** of $\geq 99\%$ ee through lipase-catalyzed acetylation of a racemic mixture of **25**.

As might be expected, none of these isotopomers synthesized above exhibited measurable optical rotation due to very small differences between the isotopomeric groups, such as CH_3 vs. CDH_2 , CH_3CH_2 vs. CD_3CH_2 , and $\text{CH}_3\text{CH}_2\text{CH}_2$ vs. $\text{CH}_3\text{CD}_2\text{CH}_2$. Enantiomeric purities ($\geq 99\%$ ee) of β - and γ -chiral isotopomers, *e.g.*, (*S*)-**21**, were successfully determined by ^1H NMR analysis of their Mosher esters.⁹⁷⁾ As shown in Scheme 19, the terminal methyl groups of the diastereomeric Mosher esters (*S,R*)- and (*S,S*)-**26**, derived from γ -chiral alkanol (*S*)-**21**, showed completely separate ^1H NMR signals. The enantiomeric purities of more remotely chiral, *e.g.*, δ - and ε -chiral, isotopomers have been determined by the MaNP ester analysis.

Conclusions

The ZACA reaction is a catalytic asymmetric C–C bond forming reaction of terminal alkenes of

The only difference between R¹ and CH₂R² is isotope (H/D) substitution

Scheme 17. Synthesis of various chiral isotopomers of 1-alkanols.

[a] i) (+)-(NMI)₂ZrCl₂ (1 mol%), ⁿPr₃Al (2 equiv), IBAO (1 equiv); ii) O₂

[b] cat. Amano lipase PS, vinyl acetate [c] CuCl₂ (5 mol%), PhC≡CMe (15 mol%), NMP (6 equiv), RMgX

Scheme 18. Synthesis of δ-chiral isotopomers.

Scheme 19. Methyl resonances in the ^1H NMR spectra (CD_3CN , 600 MHz) of Mosher ester derived from γ -chiral alkanol (*S*)-**21**.

one-point-binding without requiring any other functional groups, even though various functional groups may be present. Through conversion of terminal alkenes to chiral alkylalanes which allow for a wide range of *in situ* transformations, ZACA reaction provides a widely applicable, efficient and selective method for catalytic asymmetric C–C bond formation, which has already been used for the syntheses of various chiral natural products as summarized in Table 5. It should be noted that ZACA–lipase-catalyzed acetylation–transition metal-catalyzed cross-coupling processes provide a general and ultimately satisfactory access towards a variety of chiral organic compounds with ultra-high (>99%) purity levels, which have been otherwise very difficult to synthesize. One of the paradigms we rely heavily on is (i) to purify functionally rich and thus readily purifiable intermediates prepared by ZACA reaction to the level of >99% ee by lipase-catalyzed acetylation, and (ii) to further modify through the use of Pd- or Cu-catalyzed cross-coupling proceeding with essentially full (>99%) retention of all carbon skeletal features of intermediates.

Acknowledgements

Our investigation of the Zr-catalyzed carbometallation started, when Dr. D. E. Van Horn discovered the alkyne version of Zr-catalyzed carboalumination

in 1978. Our subsequent attempts for discovering its alkene version, *i.e.*, the alkene ZACA reaction, proved to be highly challenging and elusive, but investigations with this goal first led to the development of some interesting and useful chemistry of “ZrCp₂”, most extensively studied by Dr. T. Takahashi. Long-pending discovery of the highly coveted alkene version of ZACA reaction was almost single-handedly discovered by Dr. D. Y. Kondakov in 1995. Its intensive further development was spearheaded by a series of able workers represented by Dr. S. Huo, a tightly collaborating trio of Dr. Z. Tan, Dr. B. Liang, and Dr. T. Novak as well as by others including Dr. Z. Huang, Ms. M. Magnin-Lachaux, Dr. N. Yin, Dr. G. Zhu, Dr. Z. Xu and Dr. G. Wang. Our most recent and current activities are spearheaded by Dr. S. Xu and others, notably those from Teijin, Ltd., Japan, including Mr. A. Oda, Mr. H. Kamada, Mr. Y. Matsueda, and Mr. M. Komiyama, as well as Dr. H. Li and Dr. T. Bobinski, who have been rapidly expanding and elevating the scope and value of the ZACA-based asymmetric syntheses. Last but not least, we thank generous financial supports provided over many years predominately by NSF and NIH, Purdue University, in particular, H. C. Brown Distinguished Professorship Fund, Teijin, Ltd., Japan, and Japan Science and Technology Agency.

Table 5. Natural products and related compounds of biological and medicinal interest synthesized via ZACA reaction

Entry	Chiral Compounds of Biological and Medicinal Interest (Year)	Structure	Total or Fragment Synthesis
(1)	vitamin E (2001 and 2002) ^(82),105)		total
(2)	vitamin K (2001 and 2007) ^(92),105)		total
(3)	phytol (2001) ⁽¹⁰⁵⁾		total
(4)	scyphostatin (2004, 2010 and 2012) ^(106)–108)		sidechain ^(106),107) and total synthesis ⁽¹⁰⁸⁾
(5)	TMC-151A-F C11–C20 fragment (2004) ⁽⁸³⁾		C11–C20 fragment
(6)	siphonarienal (2004) ⁽¹⁰⁹⁾		total
(7)	siphonarienone (2004) ⁽¹⁰⁹⁾		total
(8)	siphonarienolone (2004) ⁽¹⁰⁹⁾		total
(9)	(+)-sambutoxin C9–C18 fragment (2004) ⁽¹⁰⁹⁾		C9–C18 fragment
(10)	6,7-dehydrostipiamide (2004) ⁽¹¹⁰⁾		total
(11)	ionomycin C1–C10 fragment (2005) ⁽⁸⁶⁾		C1–C10 fragment
(12)	borrelidin C3–C11 fragment (2005) ⁽⁸⁶⁾		C3–C11 fragment
(13)	preen gland wax of the graylag goose, <i>Anser anser</i> (2006) ⁽⁸⁷⁾		total
(14)	doliculide C1–C9 fragment (2006) ⁽⁸⁷⁾		C1–C9 fragment

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Entry	Chiral Compounds of Biological and Medicinal Interest (Year)	Structure	Total or Fragment Synthesis
(15)	(+)-stellattamide A (2007) ⁹²⁾		sidechain
(16)	(+)-stellattamide B (2007) ⁹²⁾		C5–C11 sidechain
(17)	(–)-spongidepsin (2007) ¹¹¹⁾		total
(18)	(+)-discodermolide (2007) ¹¹²⁾		C11–C17 fragment
(19)	(–)-callystatin A (2007) ¹¹²⁾		C1–C11 fragment
(20)	archazolides A and B (2007) ¹¹²⁾ A: R = Me B: R = H		C7–C15 fragment
(21)	nafuredin (2008) ⁴⁴⁾		C9–C18 fragment (formal total)
(22)	milbemycin β ₃ (2008) ⁴⁴⁾		C1–C13 fragment
(23)	bafilomycin A ₁ (2008) ⁴⁴⁾		C1–C11 fragment
(24)	fluvirucin A ₁ (2008) ¹¹³⁾		total

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Entry	Chiral Compounds of Biological and Medicinal Interest (Year)	Structure	Total or Fragment Synthesis
(25)	4,6,8,10,16,18-hexamethyldocosane (2008) ¹¹⁴⁾		total
(26)	yellow scale pheromone (2008) ¹¹⁵⁾		total
(27)	(<i>R</i>)- and (<i>S</i>)-arundic acids (2012) ⁹³⁾		total
(28)	phthioceranic acid (2015) ⁸⁸⁾		total
(29)	(7 <i>S</i> ,10 <i>R</i>)-pitiamide A (2000) ¹¹⁶⁾		total
(30)	(7 <i>R</i> ,10 <i>R</i>)-pitiamide A (2000) ¹¹⁶⁾		total
(31)	(+)-bistramide C (2005) ¹¹⁷⁾		total

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Profile

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Profile

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