Review

Catalytic enantioselective synthesis of chiral organic compounds of ultra-high purity of >99% ee

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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 alkynes). 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 carbbometalation, (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

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 in 1901 recognized J. H. van’t Hoff’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 range of chiral organic compounds with ultra-high enantiomeric purities.

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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.

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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. Ziegler9),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 allylically heterofunctional alkenes. Some promisingly leads reported by H. Kagan in France16) are also noteworthy. K. B. Sharpless17),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) 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 alkyn carboalumination reaction catalyzed by Cp₂ZrCl₂ (ZMA),19)–21) our search for a more highly coveted alkene-version of the reaction was resumed in the early 1980s. If only the alkyn 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 asymmetric carboalumination of alkenes). We believed that our notion of promoting carbometalation of alkenes with “super-acidic” bimetallic
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 hydrometallation 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.

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

| Year | Name of Natural Product | Reference |
|------|-------------------------|-----------|
| 2005 | bis-Deoxylophotoxin      | 25        |
| 2006 | 1-N-Acetyllysine thioester of seco-Proansamitoci | 26 |
|      | Carbazomadurin B         | 27        |
|      | 1,22-Dihydroxynitranes   | 28        |
|      | (+)-Epoleptaene          | 29        |
|      | Aurisides A and B        | 30        |
|      | (35)-Oxidosqualene (analog) | 31   |
|      | Dolabelide C (C1–C15 fragment) | 32 |
| 2007 | Amphinomilide X and Y (C12–C21 fragment) | 33 |
|      | Dechloroansamitocin P-3  | 34        |
|      | Iromycins                | 35        |
|      | Nakiterplosin            | 36        |
|      | Coenzyme Q10             | 37        |
|      | (–)-Reidispergolide A    | 38        |
|      | Iridal’s core structure  | 39        |
|      | (±)-Phomactin B2         | 40        |
|      | Amphinomilide H and G    | 41        |
| 2008 | Calliptoside Aglycone    | 42        |
|      | Baflomycin A1 (C1–C17 and C18–C25 fragments) | 43 |
|      | Nafurediniflumycin 3a, and (–)-baflomycin A1 (key intermediates) | 44 |
|      | (–)-Reidispergolide A    | 45        |
| 2009 | Amphinomilides B1, B4, G1, H1, and H2 | 46 |
|      | Phomactins               | 47        |
|      | Verticipyrone            | 48        |
|      | (+)-Myrhanol A           | 49        |
|      | Plaunotol                | 50        |
|      | Marinomycin A (monomeric counterpart) | 51 |
| 2010 | Carbazomadurin A         | 52        |
|      | Melogynin A              | 53        |
|      | Maytansinoids            | 54        |
|      | Ansamitocins P-2 to P-4  | 54        |

Continued on next page.
| Year      | Name of Natural Product                          | Reference |
|-----------|--------------------------------------------------|-----------|
| 2011–2015 | Mycolactones A and B                            | 55        |
|           | Leiodermatolide (macrocyclic core)              | 56        |
|           | N-acetyl-S-farnesyl-L-cysteine                   | 57        |
|           | FTPA triazole I                                  | 58        |
|           | (+)-Concanamycin F                               | 59        |
|           | Bafillomycin A1                                  | 60        |
|           | Palmerolide (C16–C24 fragment)                  | 61        |
|           | Carbazomadurin A                                | 62        |
|           | (S)-(+-)-Carbazomadurin B                       | 63        |
|           | Leiodolide A (C22–C31 fragment)                 |           |
|           | Celastrol                                        | 64        |
|           | Enokipodin B                                    | 65        |
|           | 24-Fluorinated Bafillomycin (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        |

![Structural formulas](image1.png)

![Structural formulas](image2.png)

![Structural formulas](image3.png)
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 (EBI)ZrCl₂79) and its partially hydrogenated derivatives80) were less effective. The most effective among those tested is Erker’s (NMI)₂ZrCl₂.81) 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-
tion and higher alkylalumination.\textsuperscript{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).\textsuperscript{82,83}

\textbf{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 \(20 \times 10^3\) to \(\geq 10^4\) 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.\textsuperscript{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 deoxypropionate and related compounds containing two or more

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\textbf{Scheme 4.} Zr-catalyzed asymmetric carboalumination of alkenes (\textbf{ZACA}).
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 vinyl-lation 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 Bu$_2$AlH (DIBAL-H) in a 1:2 molar ratio as a catalyst system, and (iii) DMF as a solvent. The ZACA reaction of 1-ctene 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 stereo-controlled sp$^2$–sp$^3$ cross-coupling reactions89) allowed convergent assembly of smaller building blocks to build-up long polydeoxypropionate chains with

| 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        |

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

Table 2. Statistical enantiomeric amplification in iterative enantioselective process

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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 deoxypolypropionates 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 available from TCI >98% ee, $88/25mL

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

| Additive (equiv) | Solvent | Temp. (°C) | Catalyst (%) | Yield (%) |
|-----------------|---------|------------|--------------|-----------|
| ZnBr₂ (1)       | THF     | 60         | Pd(PPh₃)₅ (5)| 14        |
| ZnBr₂ (1)       | DMF     | 120        | Cl₂Pd(DPEphos) (5) + Bu₂AlH (10) | 36 |
| ZnBr₂ (3)       | DMF     | 120        | Cl₂Pd(DPEphos) (5) + Bu₂AlH (10) | 63 |
| Zn(OTf)₂ (1)    | DMF     | 70         | Cl₂Pd(DPEphos) (3) + Bu₂AlH (6) | 71 |

Scheme 7. “One-pot” ZACA–Pd-catalyzed vinylation tandem process.
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 \(E\) (enantioselective 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 \(ee_o\) is 70% and \(E = 50\); \(\leq 85\%\) if \(ee_o\) is 80% and \(E = 30\); \(\leq 95\%\) if \(ee_o\) is 90% and \(E = 20\).\(^90\)\(^,\)\(^91\) It is clear that neither the ZACA reaction alone nor the lipase-catalyzed acetylation alone can be expected to provide 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,
preferably 80–90% ee but minimally ≥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 $\pi$-bonds or heterofunctional groups, have been efficiently synthesized in ≥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 ≥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 ≥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

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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

| Initial ee$_0$ (%) | $E$ | Max. yield (%) | Initial ee$_0$ (%) | $E$ | Max. yield (%) |
|-------------------|----|---------------|-------------------|----|---------------|
| 0 (racemic)       | 100| ≤2            | 70                | 100| ≤85           |
|                   | 90 | 0             |                   | 50 | −80           |
| 20                | 100| ≤35           | 20                | 20 | −25           |
|                   | 80 | −20           |                   | 10 | 0             |
|                   | 60 | 0             |                   | 0  |               |
| 50                | 100| ≤70           | 80                | 100| ≤90           |
|                   | 50 | −55           |                   | 30 | −85           |
|                   | 40 | −25           |                   | 20 | −70           |
|                   | 30 | 0             |                   | 10 | 0             |
| 60                | 100| ≤80           | 90                | 100| ≤95           |
|                   | 50 | −65           |                   | 20 | <95           |
|                   | 30 | −25           |                   | 10 | 80            |
|                   | 20 | 0             |                   | 5  | 0             |

* $E$ (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.

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\[ E = 33 \implies \text{proximal heteroatoms (halogen, oxygen, etc.)} \]

\[ E = 42 \implies \text{proximal } \pi \text{-bonds (aromatic groups, double bonds, etc.)} \]

\[ E < 5 \implies \text{alkyl-substituted (low } E \text{ factor)} \]
catalytic amounts of NaClO and 2,2,6,6-tetramethylpiperidin-1-yloxyl (TEMPO). Thus, a highly enantioselective (>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 >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 calystatin A, by PdCl2(DPEphos)-catalyzed Negishi coupling reactions where the second Negishi coupling proceeding 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 calystatin A, by PdCl2(DPEphos)-catalyzed Negishi coupling reactions where the second Negishi coupling proceeding with a clean stereoinversion (Scheme 12).87)

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 >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 (MNPNP), which had been used in determining the absolute configuration of chiral secondary alcohols.98),99) Presumably the naphthyl ring of MNP esters would exert greater anisotropic shielding effects than α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) phenyl group. Indeed, the two terminal methyl groups of the diastereomeric MNP ester showed no separation (Scheme 14). The MNP ester analysis was also successfully applied to chiral discrimination of other δ- and ε-chiral primary

| R     | Initial Yield (%) | Initial ee (%) | Enzyme | Solvent, Temp. °C | Conversion (%) | Recovery (%) | Final ee (%) |
|-------|-------------------|----------------|--------|-------------------|---------------|-------------|--------------|
| Ph    | 85                | 89             | Amano PS | THF/H2O 23       | 22            | 68          | 93           |
|       |                   |                | Amano PS | THF/H2O 23       | 50            | 43          | 96           |
| PhCH2 | 85                | 76             | PPL     | THF/H2O 23       | 31            | 62          | 99           |
| Ph(CH2)2 | 85         | 78             | Amano PS | THF/H2O 23       | 30            | 64          | 99           |
| n-Hex | 76                | 75             | Amano PS | CH2Cl2 0         | 16            | 80          | 98           |
| n-Hex | 71                | 72             | Amano PS | CH2Cl2 0         | 38            | 60          | 98           |
alcohols, which demonstrated surprising long-range anisotropic differential shielding effects. It should be noted that the diastereotopic chemical shift differences of MNP esters were affected by NMR solvent and resonance frequency (MHz) of NMR. $d$-Acetonitrile, $d$-acetone, $d$-methanol and/or CDCl₃ 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 C₁₅ vitamin E side-chain 19 (Scheme 15).¹⁰⁰ The key α,ω-dioxy-
Scheme 12. ZACA–lipase-catalyzed acetylation–Pd-catalyzed cross-coupling process for the synthesis of (−)-callystatin A.

R\textsuperscript{1} = alkyl group, R\textsuperscript{2} = alkyl, alkenyl, alkynyl, or aryl group

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

Scheme 13. Synthesis of γ and more-remotely chiral 1-alkanols of ≥99% ee.
functional C₅ synthon 15 (≥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 C₅ iodide 16 were employed as the key steps for preparing the C₁₅ vitamin E side-chain 19, which was shown to be >99% ee by ¹H NMR analysis of its MαNP 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...
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" \(^{104}\).

Three deuterium-substituted \(\delta\)-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 \textit{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 \(\delta,\omega\)-dioxyfunctional 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 disappointing 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 \(\text{CH}_3\) vs. \(\text{CDH}_2\), \(\text{CH}_3\text{CH}_2\) vs. \(\text{CD}_3\text{CH}_2\), 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 \(\beta\)- and \(\gamma\)-chiral isotopomers, \(e.g.,\) \((S)-21\), were successfully determined by \(^1\text{H}\) 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 \(\gamma\)-chiral alkanol \((S)-21\), showed completely separate \(^1\text{H}\) NMR signals. The enantiomeric purities of more remotely chiral, \(e.g.,\) \(\delta\)- and \(\varepsilon\)-chiral, isotopomers have been determined by the MoNP 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.

Scheme 18. Synthesis of δ-chiral isotopomers.
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 carbometalation started, when Dr. D. E. Van Horn discovered the alkyn 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.

Scheme 19. Methyl resonances in the ^1H NMR spectra (CD3CN, 600 MHz) of Mosher ester derived from γ-chiral alkanol (S)-21.
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)\(^{82,105}\)                     | ![Structure](image1) | total                        |
| (2)   | vitamin K (2001 and 2007)\(^{92,105}\)                    | ![Structure](image2) | total                        |
| (3)   | phytol (2001)\(^{105}\)                                   | ![Structure](image3) | total                        |
| (4)   | scyphostatin (2004, 2010 and 2012)\(^{106-108}\)         | ![Structure](image4) | sidechain\(^{106,107}\) and total synthesis\(^{108}\) |
| (5)   | TMC–151A-F C11–C20 fragment (2004)\(^{83}\)              | ![Structure](image5) | C11–C20 fragment            |
| (6)   | siphonarional (2004)\(^{109}\)                            | ![Structure](image6) | total                        |
| (7)   | siphonarienone (2004)\(^{109}\)                           | ![Structure](image7) | total                        |
| (8)   | siphonarienolone (2004)\(^{109}\)                         | ![Structure](image8) | total                        |
| (9)   | (+)-sambutoxacin C9–C18 fragment (2004)\(^{109}\)       | ![Structure](image9) | C9–C18 fragment             |
| (10)  | 6,7-dehydrostipiamide (2004)\(^{110}\)                   | ![Structure](image10) | total                        |
| (11)  | ionomycin C1–C10 fragment (2005)\(^{86}\)                | ![Structure](image11) | C1–C10 fragment             |
| (12)  | borrelidin C3–C11 fragment (2005)\(^{86}\)               | ![Structure](image12) | C3–C11 fragment             |
| (13)  | preen gland wax of the graylag goose, *Anser anser* (2006)\(^{87}\) | ![Structure](image13) | total                        |
| (14)  | doliculide C1–C9 fragment (2006)\(^{87}\)               | ![Structure](image14) | C1–C9 fragment              |

*Continued on next page.*
Continued.

| Entry | Chiral Compounds of Biological and Medicinal Interest (Year) | Structure | Total or Fragment Synthesis |
|-------|-----------------------------------------------------------|-----------|-----------------------------|
| (15)  | (+)-stellattamide A (2007) | ![Structure](image1.png) | sidechain |
| (16)  | (+)-stellattamide B (2007) | ![Structure](image2.png) | C5–C11 sidechain |
| (17)  | (-)-spongidepsin (2007) | ![Structure](image3.png) | total |
| (18)  | (+)-discodermolide (2007) | ![Structure](image4.png) | C11–C17 fragment |
| (19)  | (-)-callystatin A (2007) | ![Structure](image5.png) | C1–C11 fragment |
|       | archazolides A and B (2007) | ![Structure](image6.png) | C7–C15 fragment |
| (20)  | A: R = Me | ![Structure](image7.png) | C9–C18 fragment (formal total) |
|       | B: R = H | ![Structure](image8.png) | |
| (21)  | nafuredin (2008) | ![Structure](image9.png) | |
| (22)  | milbemycin β3 (2008) | ![Structure](image10.png) | C1–C13 fragment |
| (23)  | baflomycin A1 (2008) | ![Structure](image11.png) | C1–C11 fragment |
| (24)  | fluvinacin A1 (2008) | ![Structure](image12.png) | total |

Continued on next page.
### References

1. Miller, M.T. (1991) Thalidomide embryopathy: A model for the study of congenital incomitant horizontal strabismus. Trans. Am. Ophthalmol. Soc. 81, 623–674.

2. Pasteur, L. (1848) Mémoire sur la relation qui peut exister entre la forme cristalline et la composition chimique, et sur la cause de la polarisation rotatoire (Memoir on the relationship which can exist between crystalline form and chemical composition, and on the cause of rotary polarization). C. R. Acad. Sci. (Paris) 26, 535–538.

3. Pasteur, L. (1848) Sur les relations qui peuvent exister entre la forme cristalline, la composition chimique et le sens de la polarisation rotatoire (On the relations that can exist between crystalline form, and chemical composition, and the sense of rotary polarization). Ann. Chim. Phys. 24, 442–459.

4. Van’t Hoff, J.H. (1874) Sur les formules de structure dans l’espace. Arch. Neerl. Sci. 9, 445–454.

5. Van’t Hoff, J.H. (1877) Die Lagerung der Atome im Raume. Friedrich Vieweg und Sohn, Braunschweig.

6. Yosida, T., Williams, R.M. and Negishi, E. (1974) A stereoselective synthesis of trans-1,4-dialky-1,2,3-butatrienes via hydroboration. J. Am. Chem. Soc. 96, 3688–3690.

7. Fischer, E. (1891) Ueber die configuration des traubenzuckers und seiner isomeren. Ber. Dtsch. Chem. Ges. 24, 2683–2687.

8. Fischer, E. and Thierfelder, H. (1894) Verhalten der verschiedenen zucker gegen reine hefen. Ber. Dtsch. Chem. Ges. 27, 2031–2037.

9. Ziegler, K., Holzkamp, E., Breil, H. and Martin, H. (1955) Das Mülheimer normaldruck-polyäthylenverfahren. Angew. Chem. 67, 541–547.

10. Natta, G. (1956) Stereoökziszeiche katalysen und isotaktische polymere. Angew. Chem. 68, 393–403.

11. Vineyard, B.D., Knowles, W.S., Sabacky, M.J., Bachman, G.L. and Weinkauf, D.J. (1977) Asymmetric hydrogenation. Rhodium(I)-catalyzed asymmetric hydrogenation of \( R, S \)-acylamino-acrylic acids. J. Am. Chem. Soc. 99, 7932–7934.

12. Miyashita, A., Yasuda, A., Takaya, H., Toriumi, K., Ito, T., Souchi, T. and Noyori, R. (1980) Synthesis of \( R, S \)-arundic acids (2012).

13. Noyori, R. (2002) Asymmetric catalysis: science and opportunities (Nobel Lecture). Angew. Chem. Int. Ed. 41, 1998–2007.

14. Dang, T.P. and Kagan, H.B. (1971) The asymmetric...
synthesis of hydrotropic acid and amino-acids by homogeneous catalytic hydrogenation. J. Chem. Soc. D 10, 481.
17) Katsuki, T. and Sharpless, K.B. (1980) The first practical method for asymmetric epoxidation. J. Am. Chem. Soc. 102, 5974–5976.
18) Sharpless, K.B. (2002) Searching for new reactivity (Nobel Lecture). Angew. Chem. Int. Ed. 41, 2024–2032.
19) Van Horn, D.E. and Negishi, E. (1978) Controlled carbometallation. The reaction of acetylenes with organoalane-zirconocene dichloride complexes as a route to stereo- and regio-defined trisubstituted olefins. J. Am. Chem. Soc. 100, 2252–2254.
20) Negishi, E., Oksikado, N., King, A.O., Van Horn, D.E. and Spiegel, B.I. (1978) Double and multiple catalysis in the cross-coupling reaction and its application to the stereo- and regioselective synthesis of trisubstituted olefins. J. Am. Chem. Soc. 100, 2254–2256.
21) Negishi, E., Van Horn, D.E. and Yoshida, T. (1985) Carbometallation reaction of alkyynes with organoalane-zirconocene derivatives as a route to stereo- and regio-defined trisubstituted alkenes. J. Am. Chem. Soc. 107, 6639–6647.
22) Negishi, E. (2007) Transition metal-catalyzed organometallic reactions that have revolutionized organic synthesis. Bull. Chem. Soc. Jpn. 80, 233–257.
23) Negishi, E. and Owczarczyk, Z. (1991) Highly selective synthesis of vitamin A and its derivatives. Critical comparison of some known palladium-catalyzed alkynyl-alkenyl coupling reactions. Tetrahedron Lett. 32, 6683–6686.
24) Zeng, F. and Negishi, E. (2001) A novel, selective, and efficient route to carotenoids and related natural products via Zr-catalyzed carboalumination and Pd- and Zn-catalyzed cross coupling. Org. Lett. 3, 719–720.
25) Cases, M., Gonzalez-Lopez de Turiso, F., Hadjisostorion, M.S. and Pattenden, G. (2005) Synthetic studies towards furanocembranoid diterpenes. A total synthesis of bis-deoxyxophotoxzin. Org. Biomol. Chem. 3, 2786–2804.
26) Frenzel, T., Bruenjes, M., Quitschalle, M. and Kirschning, A. (2006) Synthesis of the N-acetylcysteamine thioester of seco-proasmanitocin. Org. Lett. 8, 135–138.
27) Knoell, J. and Knoepler, H.-J. (2006) First total synthesis and assignment of the absolute configuration of the neuronal cell protecting alkaloid carbazomadurin B. Synlett 4, 651–653.
28) Wilson, M.S., Woo, J.C.S. and Dake, G.R. (2006) A synthetic approach toward nitilol: construction of two 1,22-dihydroxynitilol derivatives. J. Org. Chem. 71, 4237–4245.
29) Tan, Z. and Negishi, E. (2006) Selective synthesis of epotalactene featuring efficient construction of methyl [Z]-2-iodo-2-butenoate and (2R,3S,4S)-2-trimethylsilyl-2,3-epoxy-4-methyl-γ-butyrolactone. Org. Lett. 8, 2783–2785.
30) Suenaga, K., Hoshino, H., Yoshii, T., Mori, K., Sone, H., Bessho, Y., Sakakura, A., Hayakawa, I., Yamada, K. and Kigoshi, H. (2006) Enantioselective synthesis of aurisides A and B, cytotoxic macrocyclic glycosides of marine origin. Tetrahedron 62, 7687–7698.
31) Winne, J.M., Guang, B., D’Herde, J. and De Clercq, P.J. (2006) Application of the B-alkyl Suzuki–Miyaura cross-coupling reaction to the stereo-selective synthesis of analogues of (3S)-oxidosqualene. Org. Lett. 8, 4815–4818.
32) Vincent, A. and Prunet, J. (2006) Enantioselective synthesis of the C1–C15 fragment of dolabellane C. Synlett 14, 2269–2271.
33) Rodriguez-Escrich, C., Olivella, A., Urpi, F. and Vilarrasa, J. (2007) Toward a total synthesis of amphidinolide X and Y. The tetrahydrofuran-containing fragment C12–C21. Org. Lett. 9, 989–992.
34) Meyer, A., Bruenjes, M., Tať, F., Frenzel, T., Sasse, F. and Kirschning, A. (2007) Chemoenzymatic approaches toward dolchloaransamitocin P-3. Org. Lett. 9, 1489–1492.
35) Shojaii, H., Li-Boehler, Z. and Von Zeeschitz, P. (2007) Iromycins: A new family of pyridone metabolites from streptomyces sp. II. Convergent total synthesis. J. Org. Chem. 72, 5091–5097.
36) Ito, T., Ito, M., Arimoto, H., Takamura, H. and Uemura, D. (2007) Studies toward the total synthesis of nakiterpiosin: construction of the CDE ring system by a transannular Diels–Alder strategy. Tetrahedron Lett. 48, 5465–5469.
37) Lipshutz, B.H., Butler, T., Lower, A. and Servesko, J. (2007) Enhancing regiocontrol in carboaluminations of terminal alkynes. Application to the one-pot Synthesis of coenzyme Q10. Org. Lett. 9, 3737–3740.
38) Paterson, I., Ashton, K., Britton, R., Cecere, G., Chouraqui, G., Florence, G.J. and Stafford, J. (2007) Total synthesis of (−)-reidispogonilide A, an actin-targeting marine macrolide. Angew. Chem. Int. Ed. 46, 6167–6171.
39) Corbi, A., Gauron, G., Castro, L.M., Dakir, M. and Arseniyadis, S. (2007) A domino-based approach toward stereodefined heavily functionalized cyclohexanes: synthesis of iridal core structure. Org. Lett. 9, 4745–4748.
40) Huang, J., Wu, C. and Wulff, W.D. (2007) Total synthesis of (±)-phomactin B2 via an intramolecular cyclohexadiene annulation of a chromium carbene complex. J. Am. Chem. Soc. 129, 13366–13367.
41) Fuerstner, A., Bouchez, L.C., Funel, J.-A., Liepins, V., Poree, F.-H., Gilmour, R., Beaufils, F., Laurich, D. and Tamiya, M. (2007) Total syntheses of amphidinolide H and G. Angew. Chem. Int. Ed. 46, 9265–9270.
42) Marshall, J.A. and Eilam, P.M. (2008) A formal synthesis of the callipeltoside aglycone. Org. Lett. 10, 93–96.
43) Yadav, J.S., Reddy, K.B. and Sabitha, G. (2008) Stereocovertgent synthesis of C1-C17 and C18-C25 fragments of bafilomycin A1. Tetrahedron 64,
44) Zhu, G. and Negishi, E. (2008) 1,4-Pentenyne as a five-carbon synthon for efficient and selective syntheses of natural products containing 2,4-dimethyl-1-penten-1,5-yldiene and related moieties by means of Zr-catalyzed carbaoamination of alkynes and alkenes. Chemistry 14, 311–318.

45) Paterson, I., Ashton, K., Britton, R., Cecere, G., Chouraqui, G., Florence, G.J., Knust, H. and Stafford, J. (2008) Total synthesis of (−)-reidipongiolide A, an actin-targeting macroide isolated from the marine sponge *Reisdespongia coccrata*. Chem. Asian J. 3, 367–387.

46) Fuerstner, A., Bouchez, L.C., Morency, L., Funel, J.-A., Liepins, V., Poree, F.-H., Gilmour, R., Laurich, D., Beaufils, F. and Tamiya, M. (2009) Total syntheses of amphiidinolides B1, B4, G1, H1 and structure revision of amphiidinolide H2. Chemistry 15, 3983–4010.

47) Blackburn, T.J., Helliwell, M., Kilner, M.J., Lee, A.T.L. and Thomas, E.J. (2009) Further studies upon deprotection. Chemistry 15, 1971–1982.

48) Lipshutz, B.H. and Amorelli, B. (2009) Carboalumination of a highly fluorinated ba-chiral ketone. Tetrahedron Lett. 50, 3550–3554.

49) Domingo, V., Silva, L., Dieguez, H.R., Arteaga, J.F., Quilez del Moral, J.F. and Barrero, A.F. (2009) Enantioselective total synthesis of the C22–C31 fragment of leiodolide A. Tetrahedron Lett. 50, 2144–2146.

50) Lipshutz, B.H. and Amorelli, B. (2009) Carboalumination/Ni-catalyzed couplings. A short synthesis of verticipyrone. Tetrahedron Lett. 50, 2144–2146.

51) Domingo, V., Silva, L., Dieguez, H.R., Arteaga, J.F., Quilez del Moral, J.F. and Barrero, A.F. (2009) Enantioselective total synthesis of the potent anti-inflammatory (+)-myrrhanol A. J. Org. Chem. 74, 6151–6156.

52) Hirata, Y., Yukawa, T., Kashihara, N., Nakao, Y. and Hyama, T. (2009) Nickel-catalyzed carbocyanation of alkynes with allyl cyanides. J. Am. Chem. Soc. 131, 10964–10973.

53) Aman, S., Bareille, L., Belostoa, V. and Cossy, J. (2009) Synthesis of the monomeric counterpart of marinomycin A. J. Org. Chem. 74, 7665–7674.

54) Hieda, Y., Choshi, T., Fukuoka, H. and Hibi, S. (2010) A novel total synthesis of the bioactive poly-substituted carbazole alkylid carbazomadurin A. Tetrahedron Lett. 51, 3593–3596.

55) Fotsop, D.F., Roussi, F., Leverrier, A., Breteche, A. and Gueritte, F. (2010) Biomimetic total synthesis of meiogynin A, an inhibitor of Bcl-xL and Bak interaction. J. Org. Chem. 75, 7412–7415.

56) Harmrolfs, K., Brunjes, M., Draeger, G., Floss, H.G., Sasse, F., Taft, F. and Kirschning, A. (2010) Cyclization of synthetic *scco*-proansamitocin to ansamitocin macroactams by actinomysnema pretiosum as biocatalyst. ChemBioChem 11, 2517–2520.

57) Wang, G., Yin, N. and Negishi, E. (2011) Highly selective total synthesis of fully hydroxy-protected mycolactones A & B and their stereoisomerization upon deprotection. Chemistry 17, 4118–4130.

58) Bergman, J.A., Hahne, K., Song, J., Hrycyna, C.A. and Gibbs, R.A. (2011) Lipid and sulfur substituted prenylcysteine analogs as human Icmt inhibitors. Bioorg. Med. Chem. Lett. 21, 5616–5619.

59) Paterson, I., Steadman, T., McLeod, M.D. and Trieselmann, T. (2011) Stereocontrolled total synthesis of (+)-concanamycin F: the strategic use of boron-mediated aldol reactions of chiral ketones. Tetrahedron 67, 10119–10128.

60) Kleinbeck, F., Fettes, G.J., Fader, L.D. and Carreira, E.M. (2012) Total synthesis of bafibomycin A. Chemistry 18, 3598–3610.

61) Lisboa, M.P., Jeong-Im, J.H., Jones, D.M. and Dudley, G.B. (2012) Toward a new palmerolide assembly strategy: synthesis of C16–C24. Synlett 23, 1493–1496.

62) Hieda, Y., Choshi, T., Fujioka, H. and Hibi, S. (2013) Total synthesis of the neuronal cell-protecting carbazole alkylid carbazomadurin A and (S)(+)-carbazomadurin B. Eur. J. Org. Chem. 2013, 7391–7401.

63) Zhang, X., Liu, J., Sun, X. and Yu, Y. (2013) An efficient cis-reduction of alkyne to alkene in the presence of a vinyl iodide: stereoselective synthesis of the C22–C31 fragment of leiodolide A. Tetrahedron 69, 1553–1558.

64) Kaiser, T.M., Huang, J. and Yang, J. (2013) Regiochemistry discoveries in the use of isoxazole as a handle for the rapid construction of an all-carbon macrocyclic precursor in the synthetic studies of celestrol. J. Org. Chem. 78, 6297–6302.

65) McGrath, K.P. and Hoveyda, A.H. (2014) A multi-component Ni-, Zr-, and Cu-catalyzed strategy for enantioselective synthesis of alkynyl-substituted quaternary carbons. Angew. Chem. Int. Ed. 53, 1910–1914.

66) Shibata, H., Tsuchikawa, H., Matsumori, N., Murata, M. and Usui, T. (2014) Design and synthesis of 24-fluorinated bafibomycin analogue as an NMR probe with potent inhibitory activity to vascular-type ATPase. Chem. Lett. 43, 474–476.

67) Das, S. and Goswami, R.K. (2013) Stereoselective total synthesis of teiomycins A and B and revision of the NMR spectroscopic data of teiomycin B. J. Org. Chem. 78, 7274–7280.

68) Clark, J.S., Yang, C. and Osnowsk, A.P. (2013) Synthesis of the C18–C34 Fragment of Amphidinolides C, C2, and C3. Org. Lett. 15, 1464–1467.

69) Saltnan, A. and Theodorakis, E.A. (2013) Synthesis of a highly functionalized core of verrillin. Org. Lett. 15, 2410–2413.

70) Domingo, V., Lorenzo, L., Quilez del Moral, J.F. and Barrero, A.F. (2013) First synthesis of (−)-myrrhanol C, an anti-prostate cancer lead. Org. Biomol. Chem. 11, 559–562.
82) Huo, S., Shi, J. and Negishi, E. (2002) A new protocol for the enantioselective synthesis of methyl substituted alkanols and their derivatives through a hydroalumination/zirconium-catalyzed alkylalumination tandem process. Angew. Chem. Int. Ed. 41, 2141–2143.

83) Negishi, E., Tan, Z., Liang, B. and Novak, T. (2004) A new, efficient, and general route to reduced polypropionates via Zr-catalyzed asymmetric C–C bond formation. Proc. Natl. Acad. Sci. U.S.A. 101, 5782–5787.

84) For review articles, see: Hanessian, S., Giroux, S. and Mascetti, V. (2006) The iterative synthesis of acyclic deoxypropionate units and their implication in polyketide-derived natural products. Synthesis 7, 1057–1076.

85) ter Horst, B., Feringa, B.L. and Minnaard, A.J. (2010) Iterative strategies for the synthesis of deoxypropionates. Chem. Commun. 46, 2535–2547.

86) Novak, T., Tan, Z., Liang, B. and Negishi, E. (2005) All-catalytic, efficient, and asymmetric synthesis of α,ω-diheterofunctional reduced polypropionates via “one-pot” Zr-catalyzed asymmetric carboalumination–Pd-catalyzed cross-coupling tandem process. J. Am. Chem. Soc. 127, 2838–2839.

87) Liang, B., Novak, T., Tan, Z. and Negishi, E. (2006) Catalytic, efficient, and syn-selective construction of deoxypropionates and other chiral compounds via Zr-catalyzed asymmetric carboalumination of allyl alcohol. J. Am. Chem. Soc. 128, 2770–2771.

88) Xu, S., Oda, A., Bobinski, T., Li, H., Matsueda, Y. and Negishi, E. (2015) Highly efficient, convergent, and enantioselective synthesis of phthioceracic acid. Angew. Chem. Int. Ed. 54, 9319–9322.

89) Yang, C.-T., Zhang, Z.-Q., Liang, J., Lin, J.-H., Lu, X.-Y., Chen, H.-H. and Liu, L. (2012) Copper-catalyzed cross-coupling of nonactivated secondary alkyl halides and tosylates with secondary alkyl Grignard reagents. J. Am. Chem. Soc. 134, 11124–11127.

90) Chen, C.S., Fujimoto, Y., Girdaukas, G. and Sih, C.J. (1982) Quantitative analyses of biochemical kinetic resolutions of enantiomers. J. Am. Chem. Soc. 104, 7294–7299.

91) Chen, C.S. and Sih, C.J. (1989) General aspects and optimization of enantioselective biocatalysis in organic solvents: The use of lipases. Angew. Chem. Int. Ed. Engl. 28, 695–707.

92) Huang, Z., Tan, Z., Novak, T., Zhu, G. and Negishi, E. (2007) Zirconium-catalyzed carboalumination of alkene: ZACA-lipase catalyzed acetylation synergy. Adv. Synth. Catal. 349, 539–545.

93) Xu, S., Lee, C.-T., Wang, G. and Negishi, E. (2013) Widely applicable synthesis of enantioselectively pure tertiary alkyl-containing 1-alkanols by zirconium-catalyzed asymmetric carboalumination of alkene and palladium- copper-catalyzed cross-coupling. Chem. Asian J. 8, 1829–1835.

94) Tateishi, N., Mori, T., Kagamiishi, Y., Satoh, S., Katsube, N., Morikawa, E., Morimoto, T., Matsui, T. and Asano, T. (2002) Astrocytic activation and delayed infantar expansion after permanent focal ischemia in rats. Part II: Suppression of astrocytic activation by a novel agent R(-)-2-propyloctanoic acid (ONO-2536) leads to mitigation of delayed infarct expansion and early improvement of neurologic deficits. J. Cereb. Blood Flow Metab. 22, 723–734.

95) Sorbera, L.A. and Castaner, J. (2004) Arundic acid–Astrocyte-modulating agent treatment of stroke
treatment of neurodegeneration. Drugs Future 29, 441–448.

96) Xu, S., Oda, A., Kamada, H. and Negishi, E. (2014) Highly enantioselective synthesis of γ-, δ-, and ε-chiral 1-alkanols via Zr-catalyzed asymmetric carboalumination of alkenes (ZACA)–Cu- or Pd-catalyzed cross-coupling. Proc. Natl. Acad. Sci. U.S.A. 111, 8368–8373.

97) Dale, J.A. and Mosher, H.S. (1973) Nuclear magnetic resonance enantiomeric regents. Configurational correlations via nuclear magnetic resonance chemical shifts of diastereomeric mandelate, O-methylmandelate, and alpha-methoxy-alpha-trifluoromethylphenylacetate (MTPA) esters. J. Am. Chem. Soc. 95, 512–519.

98) Harada, N., Watanabe, M., Kuwahara, S., Sugio, A., Kasai, Y. and Ichikawa, A. (2000) 2-Methoxy-2-(1-naphthyl)propionic acid, a powerful chiral auxiliary for enantioresolution of alcohols and determination of their absolute configurations by the 1H NMR anisotropy method. Tetrahedron Asymmetry 11, 1249–1253.

99) Kasai, Y., Sugio, A., Sekiguchi, S., Kuwahara, S., Matsumoto, T., Watanabe, M., Ichikawa, A. and Harada, N. (2007) Conformational analysis of MoN esters, powerful chiral resolution and 1H NMR anisotropy tools-aromatic geometry and solvent effects on Δδ values. Eur. J. Org. Chem. 1811–1826.

100) Matsue, A., Xu, S. and Negishi, E. (2015) A novel highly enantio- and diastereoselective synthesis of vitamin E side-chain. Tetrahedron Lett. 56, 3346–3348.

101) Mislow, K. and Bickart, P. (1976) An epistemological note on chirality. Isr. J. Chem. 15, 1–6.

102) Mislow, K. (1997) Fuzzy restrictions and inherent uncertainties in chirality studies. In Fuzzy Logic in Chemistry (ed. Rouvray, D.H.). Academic press, San Diego, pp. 65–90.

103) Mislow, K. (2003) Absolute asymmetric synthesis: a commentary. Collect. Czech. Chem. Commun. 68, 849–864.

104) Xu, S., Oda, A. and Negishi, E. (2014) Enantioselective synthesis of chiral isopomers of 1-alkanols by a ZACA–Cu-catalyzed cross-coupling protocol. Chemistry 20, 16060–16064.

105) Huo, S. and Negishi, E. (2001) A convenient and asymmetric protocol for the synthesis of natural products containing chiral alkyl chains via Zr-catalyzed asymmetric carboalumination of alkenes. Syntheses of phytol and vitamins E and K. Org. Lett. 3, 3253–3256.

106) Tan, Z. and Negishi, E. (2004) An efficient and general method for the synthesis of α,ω-difunctional reduced polypropionates by Zr-catalyzed asymmetric carboalumination: synthesis of the scyphostatin sidechain. Angew. Chem. Int. Ed. 43, 2911–2914.

107) Xu, S., Lee, C.-T., Rao, H. and Negishi, E. (2011) Highly (>98%) stereo- and regioselective tri-substituted alkene synthesis of wide applicability via 1-halo-1-alkyne hydroboration–tandem Negishi–Suzuki coupling or organoborate migratory insertion. Adv. Synth. Catal. 353, 2981–2987.

108) Pitsinos, E., Athinaios, N., Xu, Z., Wang, G. and Negishi, E. (2010) Total synthesis of (+)-scyphostatin featuring an enantioselective and highly efficient route to the side-chain via Zr-catalyzed asymmetric carboalumination of alkenes (ZACA). Chem. Commun. 46, 2200–2202.

109) Magnn-Lachaux, M., Tan, Z., Liang, B. and Negishi, E. (2004) Efficient and selective synthesis of siphonaretolone and related reduced polypropionates via Zr-catalyzed asymmetric carboalumination. Org. Lett. 6, 1425–1427.

110) Zeng, X., Zeng, F. and Negishi, E. (2004) Efficient and selective synthesis of 6,7-dehydrostipiamide via Zr-catalyzed asymmetric carboalumination and Pd-catalyzed cross-coupling of organozincs. Org. Lett. 6, 3245–3248.

111) Zhu, G. and Negishi, E. (2007) Fully reagent-controlled asymmetric synthesis of (−)-spongidepin via the Zr-catalyzed asymmetric carboalumination of alkenes (ZACA reaction). Org. Lett. 9, 2771–2774.

112) Huang, Z. and Negishi, E. (2007) Highly stereo- and regioselective synthesis of (Z)-trisubstituted alkenes via 1-bromo-1-alkyne hydroboration-migratory insertion–Zn-promoted iodinolysis and Pd-catalyzed organozinc cross-coupling. J. Am. Chem. Soc. 129, 14788–14792.

113) Liang, B. and Negishi, E. (2008) Highly efficient asymmetric synthesis of fluvirucine A4 via Zr-catalyzed asymmetric carboalumination of alkenes (ZACA)–lipase-catalyzed acetylation tandem process. Org. Lett. 10, 193–195.

114) Zhu, G., Liang, B. and Negishi, E. (2008) Efficient and selective synthesis of (S,R,R,S,R,S)-4,6,8,10,16,18-hexamethylocosane via Zr-catalyzed asymmetric carboalumination of alkenes (ZACA) reaction. Org. Lett. 10, 1099–1101.

115) Xu, Z. and Negishi, E. (2008) Efficient and stereoselective synthesis of yellow scale pheromone via alkyn haloboration, Zr-catalyzed asymmetric carboalumination of alkenes (ZACA reaction), and Pd-catalyzed tandem Negishi coupling. Org. Lett. 10, 4311–4314.

116) Ribe, S., Kondu, R.K., Beratan, D.N. and Wipf, P. (2000) Optical rotation computation, total synthesis, and stereochemistry assignment of the marine natural product pitiamide A. J. Am. Chem. Soc. 122, 4608–4617.

117) Wipf, P. and Hopkins, T.D. (2005) Total synthesis and structure validation of (+)-bistramide C. Chem. Commun. 27, 3421–3423.

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Profile

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Profile

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