C–C Activation

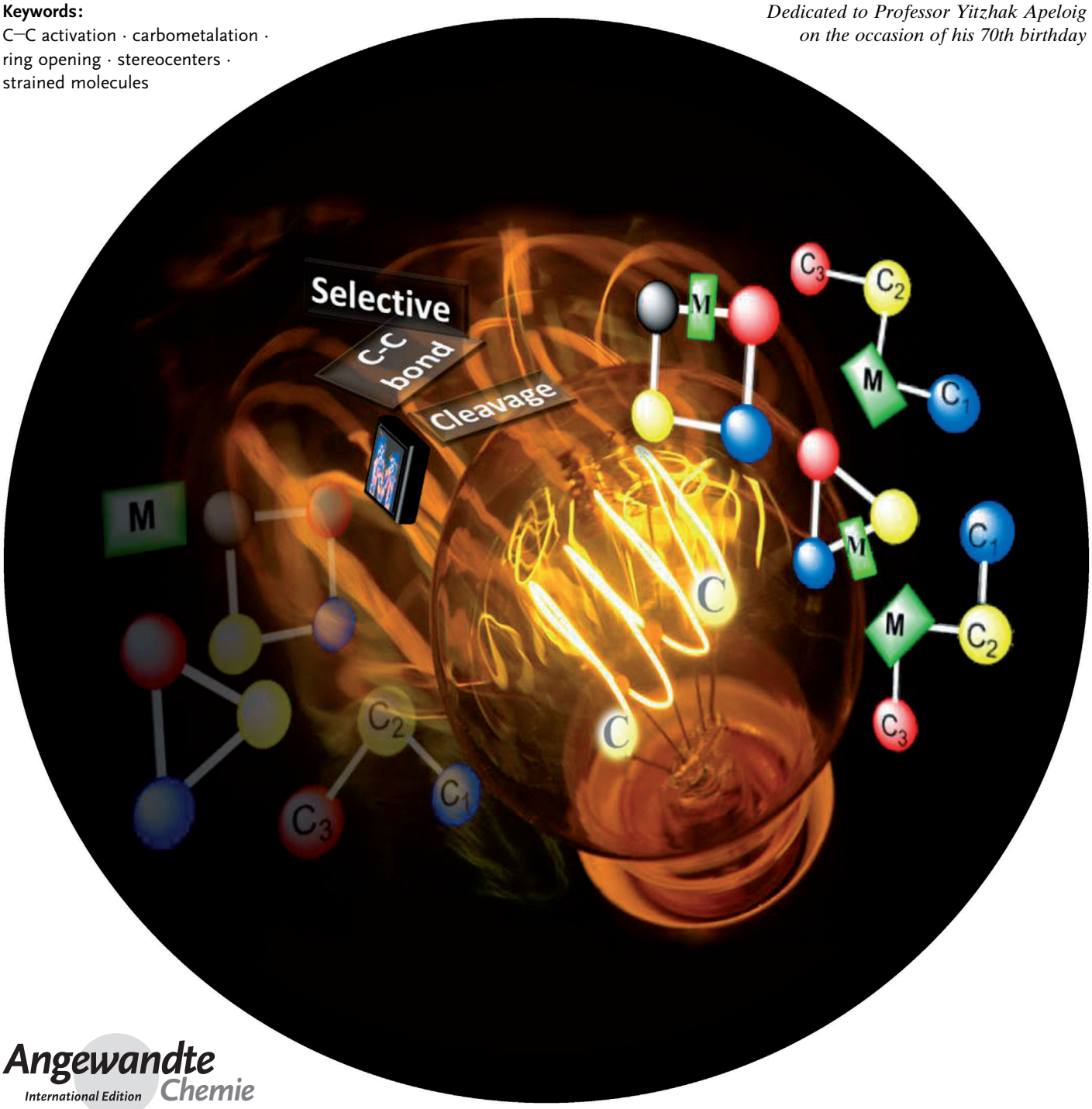
DOI: 10.1002/anie.201405067

Selective Carbon–Carbon Bond Cleavage for the Stereoselective Synthesis of Acyclic Systems

Ilan Marek, Ahmad Masarwa, Pierre-Olivier Delaye, and Markus Leibeling*

Keywords:
C–C activation · carbometalation · ring opening · stereocenters · strained molecules

Dedicated to Professor Yitzhak Apeloig on the occasion of his 70th birthday



Angewandte International Edition Chemie

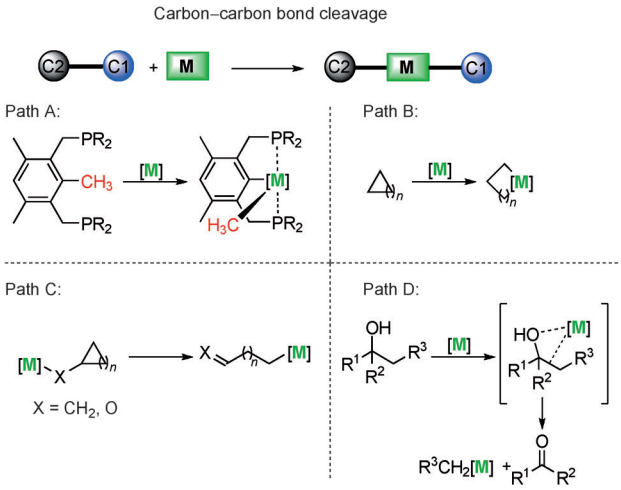
Most of the efforts of organic chemists have been directed to the development of creative strategies to build carbon–carbon and carbon–heteroatom bonds in a predictable and efficient manner. In this Review, we show an alternative approach where challenging molecular skeletons could be prepared through selective cleavage of carbon–carbon bonds. We demonstrate that it has the potential to be a general principle in organic synthesis for the regio-, diastereo-, and even enantioselective preparation of adducts despite the fact that C–C single bonds are among the least reactive functional groups. The development of such strategies may have an impact on synthesis design and can ultimately lead to new selective and efficient processes for the utilization of simple hydrocarbons.

From the Contents

1. Introduction

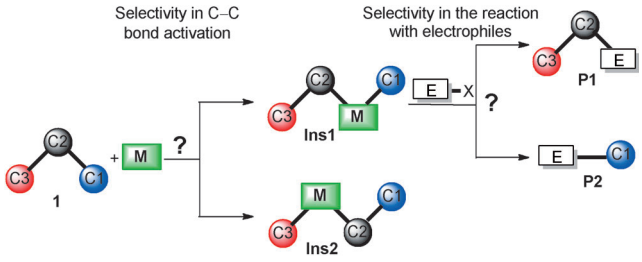
Since the 19th century, the efforts of organic chemists have mostly been directed towards building carbon–carbon and carbon–heteroatom bonds in a predictable and efficient manner while controlling all required stereogenic centers.[1] Despite this intense activity, there are still plenty of molecular frameworks that are extremely challenging to synthesize, and new and efficient approaches are constantly needed.[2] Although the approach of creating new bonds has clearly dominated the field of organic chemistry, carbon–carbon bond cleavage is now seen as an alternative for the construction of interesting molecular skeletons.[3] However, C–C bond cleavage may compete with C–H bond activation, which is nowadays a very important field of activity.[4] Indeed, the more successful development of C–H as compared to C–C bond activation is to a large part due to a number of effects: 1) C–C single bonds are chemically blocked by C–H bonds and are therefore less sterically accessible; 2) C–H bonds are present in larger abundance than C–C bonds; and 3) C–C bonds show less favorable orbital directionality than C–H bonds for interaction with a transition-metal complex.[5] A significant thermodynamic effect that favors C–H bond activation over C–C bond activation is the generally greater strength of M–H bonds by 20–25 kcal mol^{-1} with respect to M–C bonds in solution.

Over the years, several approaches have been developed for carbon–carbon bond cleavage (Scheme 1). A new perspective was offered by the introduction of pincer-type ligands (i.e. PCP ligands) for C–C bond activation. This conceptually important method enables a metal center to come close to the "hidden" C–C bond through intramolecular chelation (Scheme 1, path A).[6] This system is very effective mainly for hydrogenation and silylation reactions of unactivated C–C bonds.[7] Alternatively, metal-promoted C–C bond activation of strained alkanes has been known for several decades. In particular, strained cyclopropane derivatives, in which the relief of ring-strain energy (27.5 kcal mol^{-1}) facilitates C–C bond activation, have been recognized as a useful and powerful source of acyclic C_3 building blocks (Scheme 1, path B).[8] A third possibility is β-carbon fragmentation, which is mechanistically different, since it requires the initial positioning of a metal in the β-position to the broken C–C bond (Scheme 1, path C).[9–11] Such processes are also driven by strain release (and therefore proceed efficiently when $n = 1,2$). Finally, the β-carbon elimination of tertiary alcohols is also a useful and straightforward method that has found application in synthesis (Scheme 1, path D).[9–11] Reactions of more activated systems, such as donor–acceptor cyclopropanes,[12a,b] or ring fragmentation driven by an elimination reaction[12c] are not covered in this Review, as they have recently been treated in detail.[12]



Scheme 1. General scheme for C–C bond cleavage.

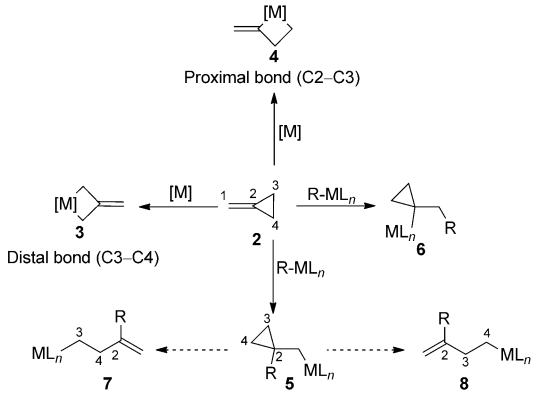
[*] Prof. Dr. I. Marek, Dr. A. Masarwa, Dr. P.-O. Delaye, Dr. M. Leibeling
Schulich Faculty of Chemistry and the Lise Meitner–Minerva Center for Computational Quantum Chemistry
Technion—Israel Institute of Technology
Technion City, Haifa 32000 (Israel)
E-mail: chilanm@tx.technion.ac.il



Scheme 2. Issues of selectivity.

When more than one C–C bond can be activated, the issue of selectivity arises. For example, in the formal C–C activation reaction of **1**, treatment with a transition-metal catalyst [M] could lead to two different types of activation: insertion of [M] into the C2–C3 bond to give **Ins2** or insertion of [M] into the C1–C2 bond to provide **Ins1** (Scheme 2). Assuming that it is possible to control the selectivity of the C–C activation (i.e. the unique formation of **Ins1**), the reactivity of C2–[M] versus C1–[M] has to be differentiated: The addition of the first electrophile could lead to the formation of **P1** or **P2**. Such selectivity issues are relevant for all modes of C–C bond cleavage (Scheme 1, paths A–C).

The issues of selectivity in carbon–carbon bond cleavage are best illustrated by the well-known reactivity of strained molecules,[9] such as methylenecyclopropane **2**. The reaction of **2** with transition metals is a perfect example, as it may lead to the formation of a variety of products: The insertion of [M] into the distal (C3–C4) bond provides **3**; the insertion of [M] into the proximal (C2–C3) bond gives **4**; and the addition of



Scheme 3. Possibilities in the C–C bond activation of methylenecyclopropane.

RML$_n$ to the exomethylene double bond leads to either regioisomer **5** or **6** (Scheme 3).[10] If **5** is formed, the cyclopropylmethyl–metal intermediate may undergo a subsequent ring-opening reaction to give either **7** or **8**, depending on the selectivity of C–C bond cleavage through mechanistic path C described in Scheme 1.[10] The advantage of such versatile reactivity is at the same time a constraint associated with these systems, as many products can be formed. Thus, it becomes clear that in systems in which the release of strain causes C–C bond cleavage, selectivity needs to be controlled.[11]

In this Review, we first consider the carbon–carbon bond cleavage of alkylidenecyclopropane derivatives, which usually

Ilan Marek received his PhD in 1988 from the University Pierre et Marie Curie, Paris (France). He obtained a research position at the CNRS in France in 1990 and moved in 1997 to the Technion—Israel Institute of Technology, where he has held the Sir Michael and Lady Sobell Academic Chair since 2005. His most recent awards include the Janssen Award for Creativity in Organic Synthesis (2012), the Israel Chemical Society Award for Excellence (2012), and his appointment as a Moore Distinguished Scholar by the California Institute of Technology in 2013.

Pierre-Olivier Delaye received his MS degree (biochemistry and organic chemistry) and his PhD in organometallic chemistry under the supervision of Prof. J. Szymoniak (2010) from the University of Reims Champagne-Ardenne (France). After a postdoctoral stay in the research group of Prof. I. Marek at the Technion—Israel Institute of Technology, he recently joined the University of Tours (France), where he is currently working on heterocyclic chemistry as a Teaching and Research Temporary Attaché (ATER) in the research group of Prof. J. Thibonnet and Prof. M. Abarbri.

Ahmad Masarwa studied chemistry at the Technion—Israel Institute of Technology. He completed his PhD studies on the selective metal-mediated carbon–carbon bond activation of strained compounds under the supervision of Prof. Ilan Marek in 2013. His work was recently selected for the IUPAC–Solvay International Award for Young Chemists. He is now carrying out postdoctoral studies in the research group of Prof. Richmond Sarpong at UC Berkeley (USA).

Markus Leibeling received his first degree in 2009 under the supervision of Prof. Daniel B. Werz at the University of Göttingen and completed his PhD funded by a Lichtenberg Fellowship of the CaSuS graduate school in 2013 on domino carbopalladation reactions on dialkynyl-substituted carbohydrates and arenes. After a short stay at the Technical University of Braunschweig, Markus began postdoctoral studies in the research group of Prof. Ilan Marek at the Technion—Israel Institute of Technology in December 2013 as a Feodor Lynen Fellow of the Humboldt Foundation.

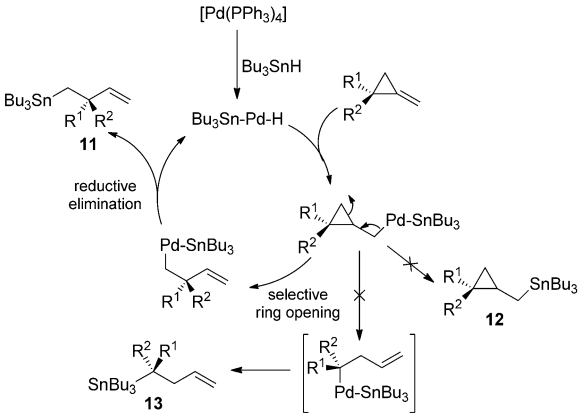
undergo fragmentation through β-carbon cleavage (Scheme 1, path C). The carbon–carbon bond cleavage of cyclopropanes and cyclobutanes either through direct C–C bond activation (Scheme 1, path B) or through β-carbon cleavage (Scheme 1, path C) is then discussed. Finally, a few examples of the β-carbon elimination of tertiary alcohols are discussed (Scheme 1, path D).

2. Carbon–Carbon Bond Cleavage of Alkylidenecyclopropanes

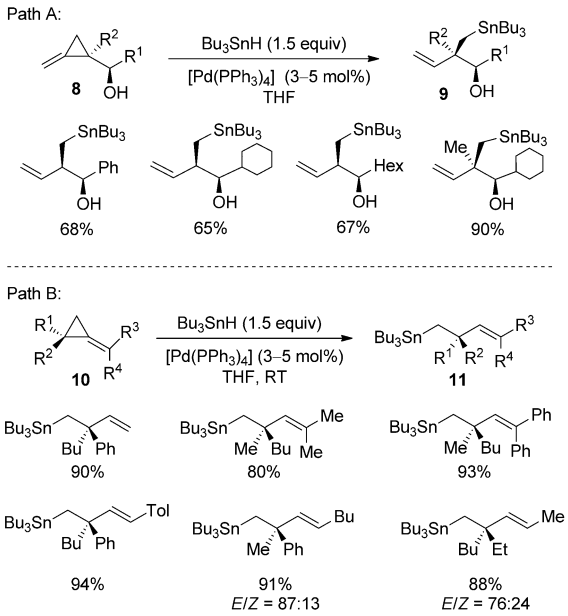
Predictable control of the reactivity of methylenecyclopropanes (MCPs) and alkylidenecyclopropanes (ACPs) is synthetically important for the formation of a unique product. However, this control is not usually possible by adjusting reaction conditions; instead, it is generally inherent to the structure of the substrate. Promising results were obtained when (methylenecyclopropyl)carbinols **8** were treated with a slight excess of tributyltin hydride in THF in the presence of a catalytic amount of $[Pd(PPh_3)_4]$ (3–5 mol%).[13] The corresponding ring-opened homoallylstannanes **9** were obtained in good to excellent yield as a single diastereoisomer (Scheme 4, path A). The relative configuration of homoallylstannanes **9** corresponds to that of the parent compounds **8**, thus establishing that there is no loss of the stereochemical information initially present in **8** throughout the course of the reaction. The same reaction could also be successfully applied to alkylidenecyclopropane derivatives **10**: Products **11** of selective ring opening were obtained in all cases (Scheme 4, path B).[14]

The formation of the final adducts could be rationalized by the following mechanism: Oxidative addition of a zerovalent palladium catalyst into the tin–hydrogen bond of tributyltin hydride first generates a stannylpalladium hydride species, which hydropalladates the exocyclic double bond of MCPs to afford the (cyclopropylmethyl)palladium stannane. Importantly, the ring opening of this intermediate is faster than reductive elimination, since no cyclopropylstannanes **12** were observed; furthermore, highly regioselective C–C cleavage occurs, since the primary homoallylstannane **11** rather than tertiary **13** was obtained (Scheme 5).[14]

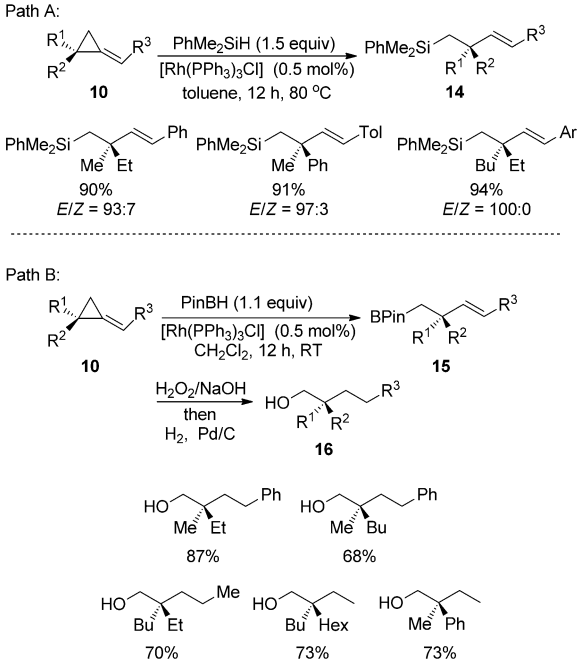
The rhodium-catalyzed hydrosilylation (Scheme 6, path A)[15] and hydroboration (Scheme 6, path B) of ACPs **10**[14] also proceeds smoothly, through selective C–C bond cleavage, to give a single isomer of the acyclic organosilanes **14** and boronate esters **15**, respectively, in good to excellent yields (Scheme 6) by a mechanism similar to that for the palladium-catalyzed hydrostannation. The reaction is stereoselective, as the *E*/*Z* ratio of homoallylsilanes **14** corresponds to the *E*/*Z* ratio of the initial alkylidenecyclopropanes **10**.[14]



Scheme 5. Proposed mechanism for the hydrostannylation of ACPs.

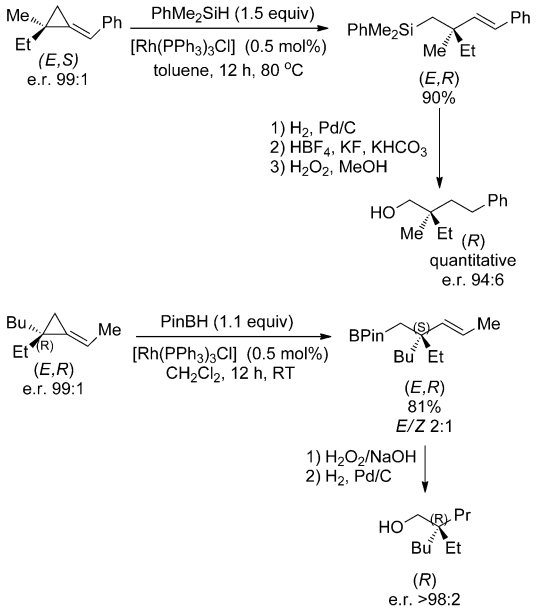


Scheme 4. Hydrostannylation of alkylidenecyclopropanes.



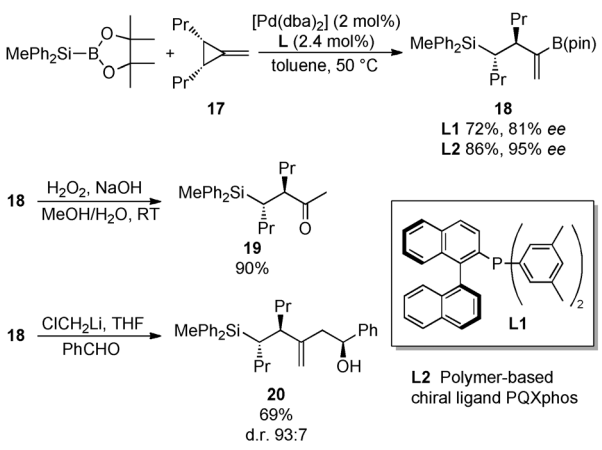
Scheme 6. Rhodium-catalyzed hydrosilylation and hydroboration of ACPs. PinBH = pinacolborane, Tol = *p*-tolyl.

As the ring cleavage always leads to the primary alkyl silane and boronate ester, the integrity of the quaternary stereogenic center remains unaffected by the process.[16,17] Therefore, when enantiomerically pure alkylidenecyclopropanes (*E*)-**10**[18] were subjected to the rhodium-catalyzed hydrosilylation and hydroboration reactions, the *E* homoallylsilane **14** and homoallylborane **15** were obtained with the same enantiomeric ratio, as determined after reduction of the double bond and an oxidation reaction (Scheme 7).[14,18,19]



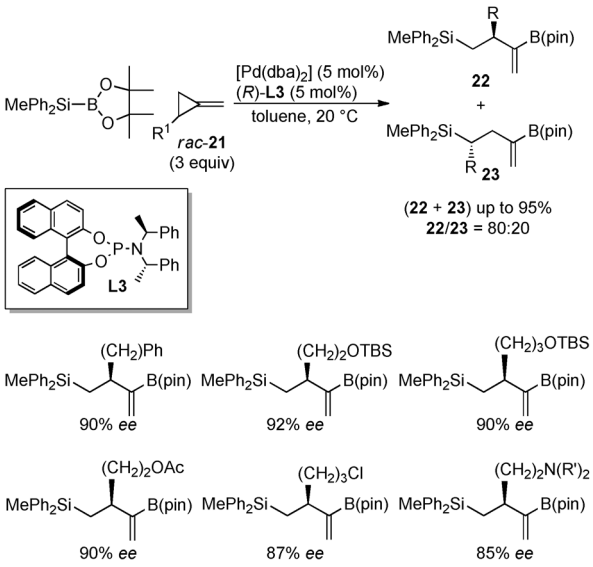
Scheme 7. Formation of enantiomerically enriched all-carbon quaternary stereogenic centers.

The asymmetric palladium-catalyzed silaborative C–C bond cleavage[20] of *meso*-methylenecyclopropane **17** led to the regioselective introduction of a silyl and a boryl group[21] at the cleaved C–C bond in good yield with reasonable enantioselectivity (Scheme 8).[22] The enantiomerically enriched silaboration product **18** is a versatile intermediate, as it could readily be transformed either into a β-silyl ketone **19** through oxidation or into a homoallylic alcohol **20** through a diastereoselective homologation–allylboration sequence.[23] When a polymer-based chiral ligand with a single-handed-helical backbone[24] was used instead of 2-diarylphosphanyl-1,1′-binaphthyl ligands, better yields and enantioselectivity were observed.[25]



Scheme 8. Desymmetrization of *meso* methylenecyclopropanes through selective C–C bond cleavage. dba = dibenzylideneacetone.

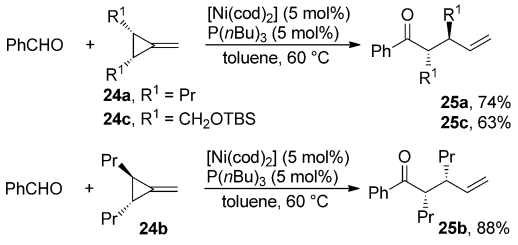
On the basis of this approach, the kinetic resolution of 1-alkyl 2-methylenecyclopropanes **21** through palladium-catalyzed silaborative C–C cleavage was investigated in detail. Enantiomerically enriched alkenyl boronic acid derivatives **22** were obtained in good yields with good enantioselectivity.[26] However, isomer **23** was always formed in roughly 20 % yield as a result of C–C bond cleavage of the proximal more substituted bond of **21** (Scheme 9).



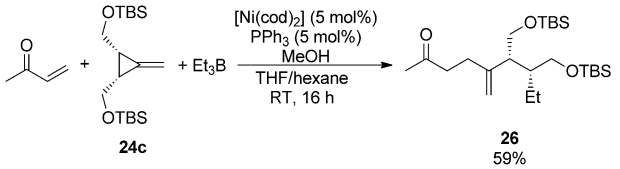
Scheme 9. Kinetic resolution of 1-alkyl 2-methylenecyclopropanes.

The nickel-catalyzed intermolecular hydroacylation of MCPs proceeds by stereospecific cleavage of the cyclopropane ring to give γ,δ-unsaturated ketones **25**.[27] The diastereomeric *cis* and *trans* MCPs **24a**,**b** reacted with benzaldehyde in a highly stereospecific manner to give (*S**,*S**)- and (*S**,*R**)-**25a**,**b**, respectively, with high diastereomeric purities. The reaction of **24c** bearing silyloxy groups took place slowly at 80 °C to give **25c** in moderate 63 % yield (Scheme 10).

In certain instances, the aldehyde can be replaced with an α,β-unsaturated carbonyl compound as the reaction partner, and the unsaturated C–C bond participates in the coupling



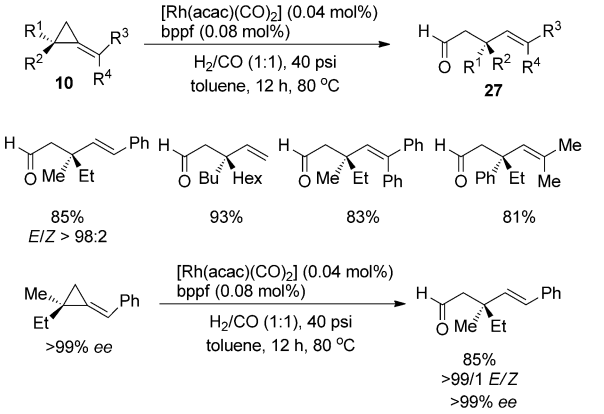
Scheme 10. Nickel-catalyzed intermolecular hydroacylation. cod = 1,5-cyclooctadiene, TBS = *tert*-butyldimethylsilyl.



Scheme 11. Nickel-catalyzed C–C bond cleavage of a methylenecyclopropane with an enone.

reaction prior to C–C cleavage (Scheme 11).[28] This alkylative coupling reaction of an enone with an MCP occurs by stereospecific C–C bond cleavage in the presence of triethylborane and a nickel catalyst to give a γ,δ-unsaturated ketone.

In a synthetically useful hydroformylation of MCPs and ACPs **10**, linear aldehydes **27** were obtained in good to excellent yields regardless of the substitution pattern of the starting material (Scheme 12).[29] In this reaction, the selective



Scheme 12. Hydroformylation of alkylidenecyclopropanes. acac = acetylacetonate, bppf = 1,1′-bis(diphenylphosphanyl)ferrocene.

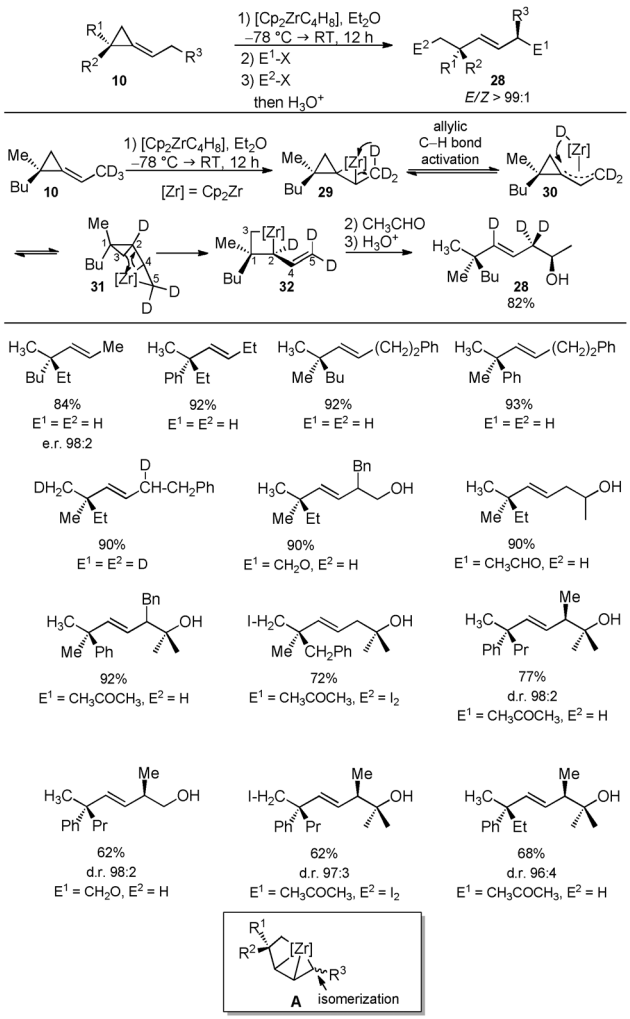
splitting of the C–C bond is faster than the insertion of CO/H_2 and reductive elimination, since no cyclopropylcarboxaldehydes were detected. In a further test of the utility of the hydroformylation reaction of alkylidenecyclopropanes in organic synthesis, readily obtained enantiomerically pure alkylidenecyclopropanes **10** were transformed into linear aldehydes **27** with an enantiomerically enriched quaternary stereogenic carbon center[17] (Scheme 12).[29]

When alkylidenecyclopropanes **10** are treated with the Negishi reagent $[C_4H_8ZrCp_2]$,[30] followed by the addition of two different electrophiles, an acyclic fragment **28** is obtained in good yields exclusively as the *E* isomer with the formation of two stereogenic centers, including an all-carbon quaternary stereocenter.[31] To gain better insight into the mechanism, the reaction was mapped out by deuterium-labeling experiments, which supported the hypothesis that after the reaction of $[C_4H_8ZrCp_2]$ with **10**, a new zirconacyclopropane **29** is formed. Then, through allylic C–D bond cleavage, the η^3-allyl intermediate **30** is generated, and after deuteride insertion, zirconacyclopropane **31** is obtained.[32] In an irreversible step, the zirconacyclopropane **31** is transformed into the allyl–alkyl zirconocene species **32** (which may be represented as its π-allylic zirconocene complex).[33] Therefore, of the two possible carbon–carbon bonds that could be activated (C1–C2 versus C2–C3 in **31**), only the C2–C3 bond is cleaved, thus leading to organozirconocene derivative **32** bismetalated in primary-alkyl and allyl positions. As the allylic C2–Zr fragment is more reactive than the alkyl C3–Zr fragment towards electrophiles,[34] the first electrophile reacts selectively with the allylzirconocene moiety at the C5 position. The second electrophile reacts with the remaining C3–Zr fragment to give functionalized **28**. Since enantiomerically enriched alkylidenecyclopropanes can be prepared readily,[16] and as the chiral quaternary center bears no risk of racemization in the process, the optical purity of the final product can be assumed to be identical. Indeed, when enantiomerically enriched **10** ($R^1 = Bu$, $R^2 = Et$, $R^3 = H$; e.r. 98:2) was treated with the Negishi reagent and H^+ as the electrophile, the same enantiomeric ratio of 98:2 was obtained. Regardless of the *E*/*Z* ratio of the starting ACPs **10**, only the *E* isomer of the opened adduct **28** was formed (*E*/*Z* > 98:2).[35]

To illustrate the broad applicability of this reaction, it was extended to the use of aldehydes and ketones as first electrophiles without a significant change in the yield of the overall transformation. The remaining primary organozirconocene species can now be trapped by a second electrophile, such as I_2, to give bifunctionalized adducts. Several examples illustrating this combined allylic C–H and selective C–C bond cleavage[31,36] coupled with dual reactivity are described in Scheme 13. This strategy holds potential for 1,4-induction in acyclic systems through the transfer of stereochemical information from remote positions. To generate such remote diastereoselectivity, alkylidenecyclopropane **10** ($R^1 = Ph$, $R^2 = Pr$, $R^3 = Me$) was treated under the same conditions with the Negishi reagent, and the reaction mixture was heated to 60 °C in THF for a few hours. After the addition of the first electrophile and subsequent hydrolysis, the open adduct was isolated with a diastereomeric ratio of 98:2 in good yield.[31] Interestingly, when the reaction mixture was not heated, the adduct was obtained with a modest 3:1 diastereomeric ratio, which may be attributed to the presence of conformational isomers of the substituted allylzirconocene fragment before reaction with the aldehyde; upon heating to 60 °C, the most thermodynamically stable *E* isomer is formed quantitatively (intermediate **A**, Scheme 13).[33] This sequence can be extended to the formation of a variety of other acyclic adducts with excellent diastereomeric ratios.

3. Carbon–Carbon Bond Activation of Cyclopropanes

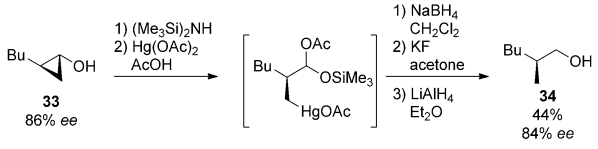
The utility of cyclopropanes in organic synthesis arises from the unique characteristics of the three-membered ring, which may undergo a variety of ring-opening reactions. Relief of ring strain provides a potent thermodynamic driving force for these processes. The ring opening of such systems has been the subject of many reviews, and its application in synthesis is extensive.[37] No attempt is made in this Review to describe all



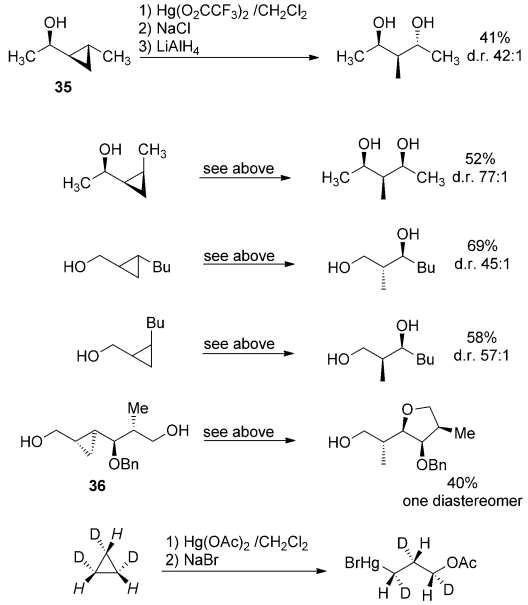
Scheme 13. Combination of allylic C–H and selective C–C activation. Bn = benzyl.

ring-opening reactions of cyclopropanes, but rather we focus on C–C bond activation of these three-membered rings for the construction of stereogenic centers in acyclic systems. On this basis, the ring opening of siloxycyclopropane derivatives gave β-acetoxymercury ketones,[38,39] and the enantiomerically enriched cyclopropanol[40] **33** was readily transformed into the acyclic alcohol **34** with almost the same *ee* value (Scheme 14).[41]

The stereospecific oxymercuration of cyclopropanes[41] in combination with the oxygen-directed cyclopropanation of acyclic alcohols[42,43] enabled the stereoselective preparation of polypropionate fragments. These original studies on conformationally flexible cyclopropylcarbinols showed a complete inversion of configuration at the cyclopropyl ring when



Scheme 14. Acetoxymercuration of cyclopropanols.



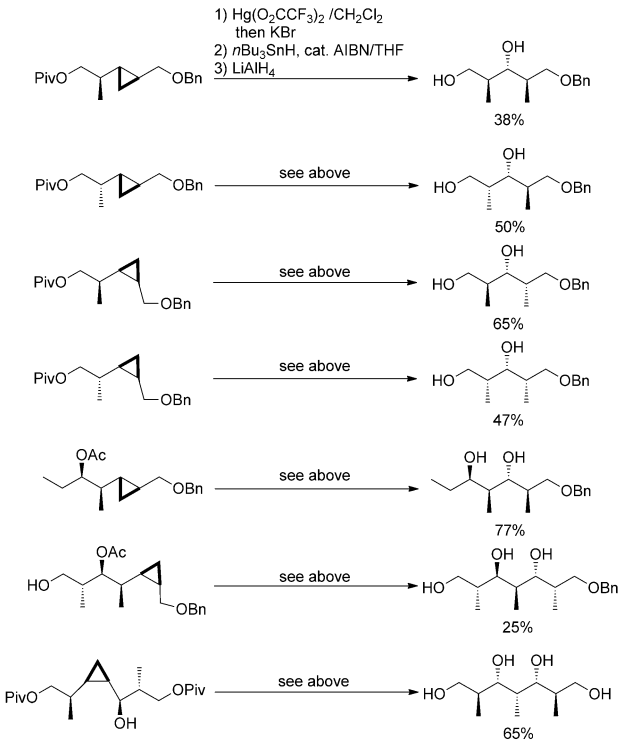
Scheme 15. Acetoxymercuration of cyclopropylcarbinol derivatives.

35 was treated with mercuric trifluoroacetate (Scheme 15).[44] The results demonstrate that stereospecific ring opening occurs with C–C activation of the distal bond of the cyclopropane ring relative to the hydroxy group.[45,46]

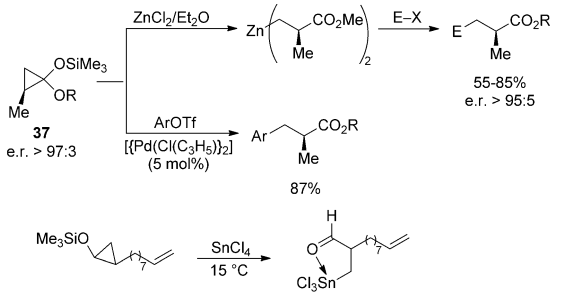
When alcohols containing an array of two or three adjacent cyclopropane rings were treated under the same conditions, electrophilic opening of the cyclopropane arrays occurred via a stabilized, free carbocation, and two diastereomers were obtained.[47] In contrast, excellent regio- and stereoselectivities were observed in the mercury-mediated intramolecular ring opening of **36** (Scheme 15) to form enantiomerically pure, highly substituted tetrahydrofurans.[47] The beauty of such an approach is that the cyclopropane can be considered as an equivalent of a methylhydroxy group, whose configuration is controlled by the initial stereogenic centers of the three-membered ring. Thus, stereotriads, stereotetrads, and stereopentads could be obtained from appropriately substituted cyclopropane derivatives (Scheme 16).[48,49]

The chiral homoenolate of methyl isobutyrate could be prepared by the selective ring opening of siloxycyclopropane **37** with half an equivalent of freshly prepared $ZnCl_2$ in Et_2O at room temperature. Interestingly, the chirality was fully retained even after aging of the homoenolate for several days (Scheme 17).[50] This C–C bond activation could also be performed catalytically if **37** was added to an aryl triflate in the presence of 5–10 mol% of a palladium catalyst.[51] However, the treatment of substituted **37** with $TiCl_4$ led to the formation of isomers of the ring-opened products.[52]

This reaction was used for a tandem transformation of the ethoxycarbonyl-substituted α,β-unsaturated ketone **38** by treatment with bis(iodozincio)methane in the presence of trimethylsilyl chloride to give **39**. The product **39** can then further react diastereoselectively, via an intermediate siloxyallyl metal species, with tosylimines to furnish secondary amines **40** in excellent yield as a single diastereoisomer

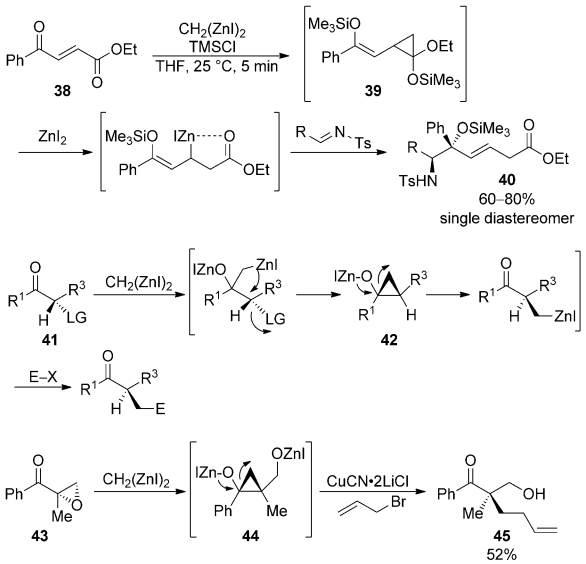


Scheme 16. Preparation of polyketide fragments. AIBN = azobisisobutyronitrile, Piv = pivaloyl.



Scheme 17. Selective C–C bond cleavage of siloxycyclopropanes. Tf = trifluoromethanesulfonyl.

(Scheme 18).[53] According to this principle of sequential nucleophilic reactions, the addition of bis(iodozincio)methane to ketone **41**, which possesses a leaving group at the α-position, afforded the zinc alkoxide of cyclopropanol **42**.[54,55] When the resulting mixture was treated with electrophiles, enantiomerically pure α-tertiary ketones were obtained with the same enantiomeric purity as that of the starting material **41** (Scheme 18). Although this method was very efficient for the construction of tertiary stereocenters at the α-position of ketones, the establishment of an all-carbon quaternary stereocenter was much more difficult, since the intramolecular S_N2 reaction does not proceed effectively. As an epoxide is a better leaving group, treatment of the α-methyl α,β-epoxyketone **43** with bis(iodozincio)methane led to the formation of the zinc alkoxide **44**. Then, when the mixture

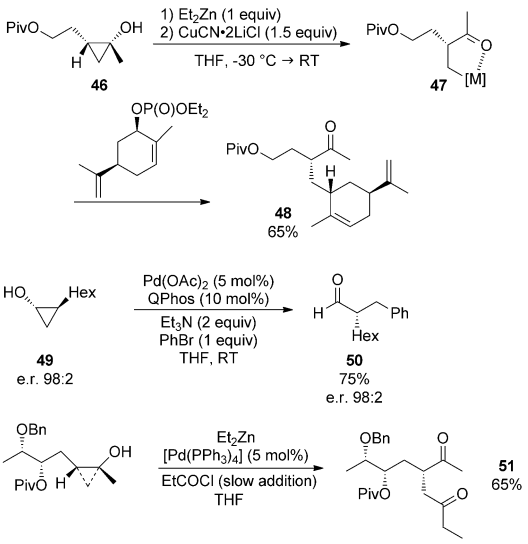


Scheme 18. Selective formation of zinc alkoxides of cyclopropanols through tandem reactions. TMS = trimethylsilyl, Ts = *p*-toluenesulfonyl.

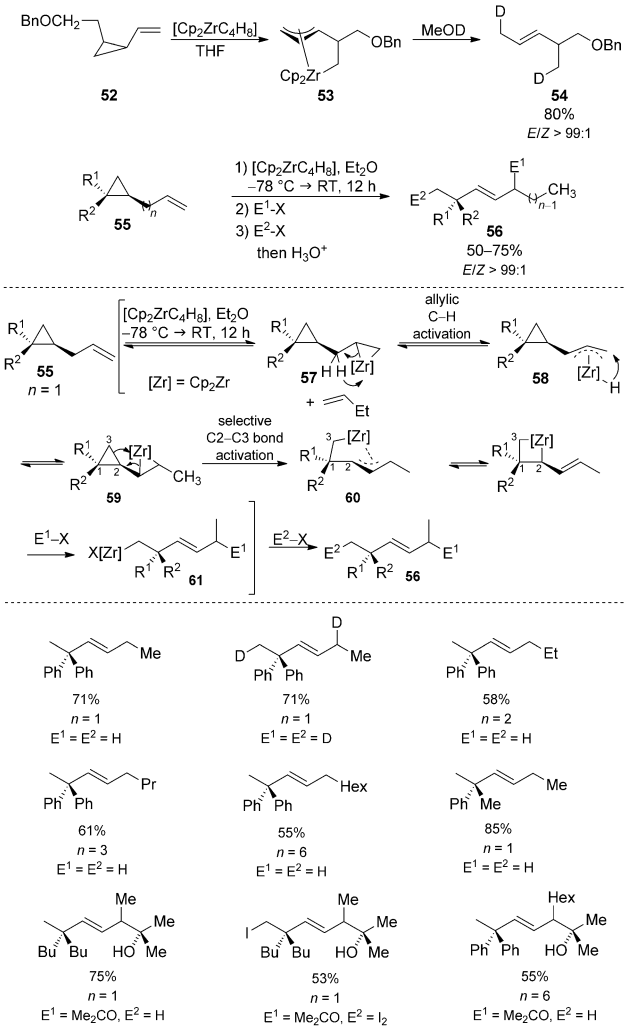
was treated with CuCN·2 LiCl and allyl bromide, ketone **45** with an all-carbon quaternary stereocenter was formed with the same *ee* value as that of the starting epoxyketone compound (Scheme 18).[54] Similarly, the iridium catalyst $[\{Cp^*IrCl_2\}_2]$ transformed selectively substituted cyclopropanols into α-alkyl ketones.[56]

Clearly, the direct treatment of cyclopropanol **46**, readily accessible through the Kulinkovitch cyclopropanation reaction,[40] with diethylzinc and a copper salt should also result in the formation of the zinc (or copper) homoenolate **47** through the selective ring-opening of the metal cyclopropanolate. In situ trapping leads to functionalized adducts **48** (Scheme 19).[57] A cyclopropanol could also be directly treated with a palladium catalyst in the presence of an aryl halide to afford the β-arylated aldehyde **50** in 75 % yield and with the same enantiomeric ratio as that of the starting cyclopropanol **49** through a direct homoenolate arylation reaction (Scheme 19).[58] When this palladium catalysis is combined with Et_2Zn, an acylation reaction to give functionalized 1,4-diketones **51** is possible (Scheme 19).[59]

Doubly activated cyclopropanes, such as 1,1-cyclopropane diester derivatives, have also been studied extensively owing to their ability to react with different nucleophiles. However, as the mechanism is more closely related to C–C bond fragmentation through conjugate addition than C–C bond cleavage, it is not described in this Review.[12a,b,60–62] Interestingly, when vinylcyclopropane **52** was treated with the zirconacyclopropane $[Cp_2ZrC_4H_8]$,[30] selective carbon–carbon bond cleavage led to the η^3 π-allylic complex **53**, which reacted selectively with 2 equivalents of MeOD to give the dideutero adduct **54** (Scheme 20).[33,63] This selective C–C bond cleavage has recently been merged with allylic C–H bond activation for the transformation of ω-enecyclopropane species **55** into functionalized products **56** through the use of a single organometallic species.[31] This "zirconium walk" chemistry had already been developed for the transformation



Scheme 19. Selective ring opening of cyclopropanol derivatives.



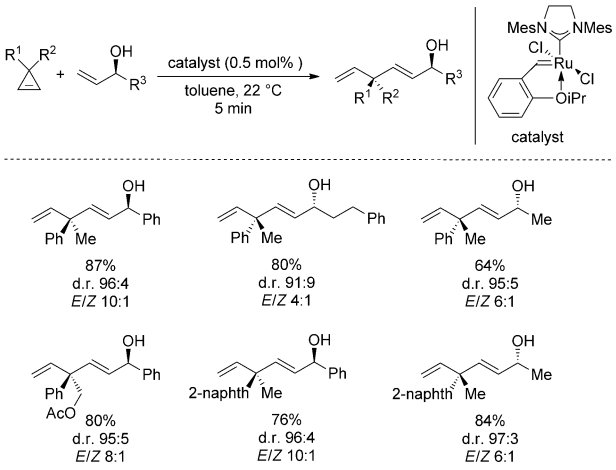
Scheme 20. Zirconocene-mediated selective C–C bond cleavage.

of simple ω-unsaturated fatty alcohols[32] and ω-nonconjugated enol ether derivatives[35,64,65] and alkylidenecyclopropanes[31] into allyl-, dienyl-, and cyclobutylzirconocene derivatives, respectively.[31,32] The transformation could be rationalized by the following mechanism: $[C_4H_8ZrCp_2]$ reacts first with the remote double bond of **55** to give the corresponding zirconacyclopropane **57**. Then, by allylic C–H bond activation, the η^3-allyl intermediate **58** is generated as a transient species. This intermediate undergoes hydride insertion to give a new zirconacyclopropane **59** with a carbon–zirconium bond at the β-position to the three-membered ring (Scheme 20).[31] When **59** is formed, irreversible C2–C3 bond cleavage occurs to give the primary acyclic organometallic species **60**. The next challenge is the differentiation of the two carbon–metal bonds in **60** for reaction with two different electrophiles. As the allyl zirconocene moiety (C2–Zr) is significantly more reactive than the alkyl zirconocene moiety (C3–Zr), the first electrophile reacts selectively through an S_E2' reaction to give **61**, which then goes on to react with a second electrophile to form **56** (Scheme 20) as a single *E* isomer in excellent yield. This tandem allylic C–H activation/selective C–C bond cleavage was not limited to ω-enecyclopropanes with a one-carbon-atom tether, as longer-chain compounds **55** ($n = 2$–6) also underwent this transformation through an initial migration of the zirconocene along the alkyl chain with the formation of products **56** in good yields.

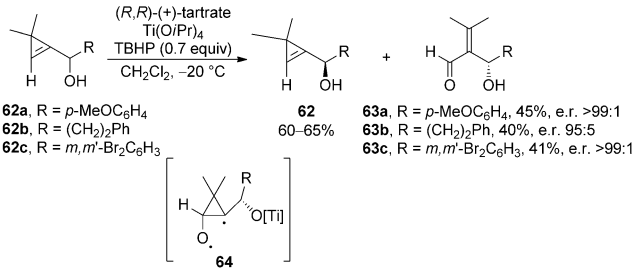
4. Carbon–Carbon Bond Activation of Cyclopropene Derivatives

Although mechanistically different from classical C–C bond activation (conceptually different from the four suggested approaches in Scheme 1), ring-opening metathesis can be used for the cleavage of double bonds.[66] For example, ruthenium-catalyzed diastereoselective ring-opening/cross-metathesis (DROCM) reactions of cyclopropenes with enantiomerically enriched allylic alcohols enable the rapid formation of nonconjugated dienes possessing remote 1,4-stereocenters with very high diastereoselectivity (Scheme 21).[67] The stereoselectivity of these ruthenium-catalyzed DROCM reactions is rationalized by uncommon hydrogen bonding between the hydrogen atom of the hydroxy group and the chloride ligand of the Ru catalyst.

The strained double bond of cyclopropenes can also undergo an oxidation reaction to give open-chain adducts.[68] Thus, when the Sharpless kinetic resolution[69] was performed on cyclopropenyl alcohols **62**, enals **63** corresponding to the Baylis–Hillman adducts[70] were obtained in excellent chemical yield, along with the unreacted enantiomerically enriched cyclopropenyl alcohol **62**,[16] with outstanding enantiomeric ratios (Scheme 22).[71] Interestingly, the mechanistic hypothesis for this oxidation reaction suggests a biradical intermediate **64**.



Scheme 21. Ruthenium-catalyzed diastereoselective ring-opening/cross-metathesis (DROCM) reactions. Mes = mesityl (2,4,6-trimethylphenyl).

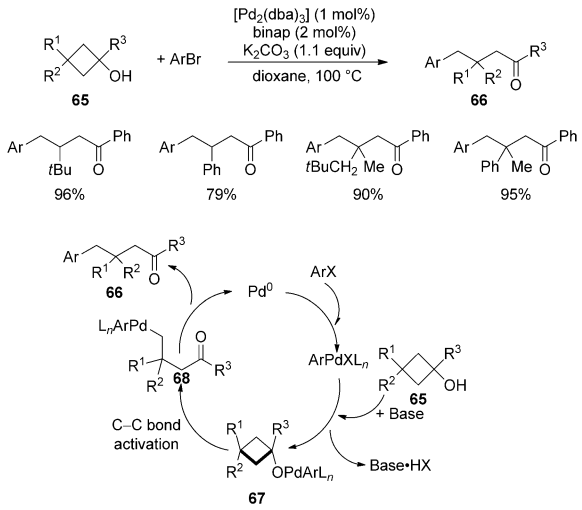


Scheme 22. Regioselective C–C bond cleavage in the oxidation of cyclopropenylcarbinols. TBHP = *tert*-butyl hydroperoxide.

5. Carbon–Carbon Bond Cleavage of Cyclobutane Derivatives

As discussed previously, the release of ring strain (27.5 kcal mol^{-1})[72] in the C–C activation of cyclopropanes can lead to the selective formation of acyclic compounds possessing stereogenic centers. As the strain energy of cyclobutanes (26.7 kcal mol^{-1}) is similar to that of cyclopropanes, carbon–carbon activation in four-membered rings has recently been a topic of major investigations. However, DFT calculations have shown that the total C–C bond strain of cyclopropanes is about 10 kcal mol^{-1} higher than that of cyclobutanes. This difference is thought to be due to the higher C–H bond energies in cyclobutanes (8.0 kcal mol^{-1}).[73,74]

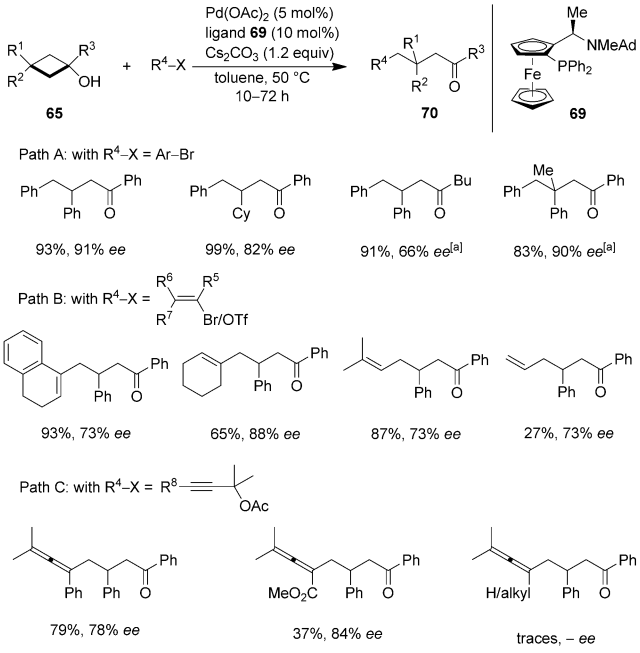
One of the pioneering examples of the C–C bond cleavage of cyclobutanols through β-carbon cleavage was reported by Uemura and co-workers, who developed an aerobic palladium-catalyzed ring-opening reaction.[75] This original transformation was applied to the formation of γ-arylated ketones **66** from cyclobutanols **65** in high chemical yields (Scheme 23).[76] From a simple mechanistic point of view, an oxidative addition reaction of the palladium catalyst into the aryl halide bond forms the aryl palladium species, which subsequently undergoes a base-promoted substitution to provide the palladium(II) alcoholate **67**. A regio- and



Scheme 23. Palladium-catalyzed arylation of *tert*-cyclobutanols **65** and plausible catalytic cycle for the arylation. binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl.

therefore diastereoselective β-carbon cleavage gives rise to the alkyl palladium intermediate **68**. Since the reductive elimination is favored over β-hydride elimination, product **66** is formed in the last bond-forming step with regeneration of the palladium(0) catalyst.

Although this early example with binap as the chiral ligand led to no asymmetric induction, the following more elaborate, optimized catalytic system with ferrocenyl ligands of type **69** led to selective cleavage of one of the enantiotopic carbon–carbon bonds of the cyclobutane (Scheme 24).[77] The highest enantioselectivity was observed for chiral ferrocenyl



Scheme 24. Palladium-catalyzed asymmetric arylation, vinylation, and allenylation of *tert*-cyclobutanols. Ad = adamantyl, Cy = cyclohexyl.

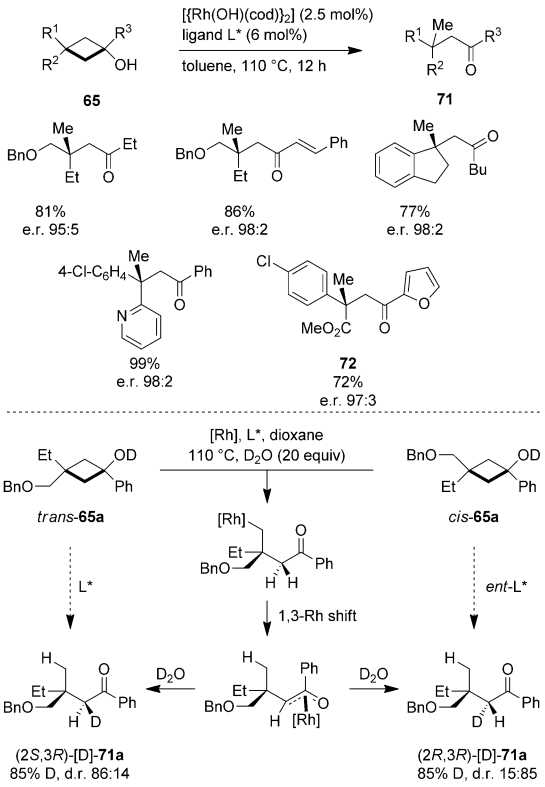
N,P ligands with bulky substituents at the amine functionality (such as adamantyl in **69**). The nature of the cyclobutanol substrate is of importance: Use of the *cis* isomer leads to **70** with an increased enantiomeric ratio. Variation of the substitution at C3 revealed only slightly inferior selectivities for 3-alkyl-substituted cyclobutanols in comparison to aryl substitution. The use of 1-alkyl-substituted starting materials provided lower selectivities. Several aryl bromides and aryl chlorides were suitable substrates and were transformed into the desired products **70** in high yield with good enantioselectivity. It was also shown that quaternary substitution at C3 was completely tolerated during the reaction: High yields and selectivities were observed for the formation of the all-carbon quaternary stereogenic center (Scheme 24, path A). Asymmetric vinylation gave similar good results. Thus, different vinyl halides and triflates could be used with equal success (Scheme 24, path B). Finally, the approach was extended to an allenylation procedure with propargylic acetates (Scheme 24, path C). The reaction proceeded in good yield with good selectivity for aryl- and methoxycarbonyl-substituted alkynes but failed for terminal as well as alkyl-substituted alkynes.

This asymmetric selective C–C bond cleavage of cyclobutanols was also extended to rhodium catalysis[78] with the chiral and highly sterically encumbered (*R*)-DTBM-segphos ligand. The scope of the reaction is broad and is largely independent of the nature of R^3 in **65** (R^3 = aryl, heteroaryl, alkyl as well as alkenyl; Scheme 25).[79,80] In the specific case of the 3-aryl-substituted cyclobutanol substrate leading to **72**, the reaction needed to be performed with the bulkier (*R*)-DTBM-MeOBiphep ligand to avoid the formation of an indanol through a different downstream mechanism.

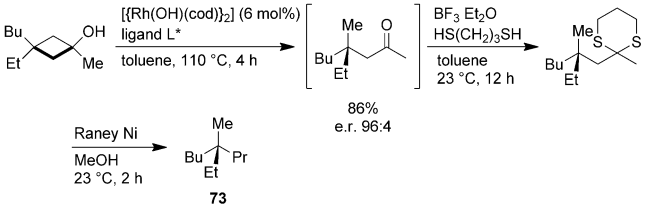
Deuterium-labeling experiments of *trans*-**65** (R^1 = CH_2OBn, R^2 = Et, R^3 = Ph) revealed that the protonation occurs at the rhodium enolate, which is formed by a 1,3-rhodium shift. The subsequent deuteration gave a diastereomeric ratio of 86:14 in favor of the 2*S*,3*R* isomer, whereas similar treatment of *cis*-**65** (R^1 = Et, R^2 = CH_2OBn, R^3 = Ph) with the opposite enantiomer of the chiral ligand led to the 2*R*,3*R* adduct with d.r. 15:85. The origin of the selectivity in the C–C cleavage step was recently confirmed by DFT calculations (for the formation of cyclic products).[81] This strategy has been applied to the enantioselective synthesis of 4-ethyl-4-methyloctane (**73**), the simplest unbranched saturated hydrocarbon with a quaternary stereogenic center (Scheme 26).

The reactive intermediates in the selective C–C cleavage of cyclobutanols can be viewed as δ-oxoalkyl anion equivalents. In combination with organometallic catalysts, they serve as excellent nucleophiles in reactions with isocyanates. Interestingly, the reaction with a rhodium catalyst proceeded through a sequence of C–C cleavage steps rather than a simple O-carbamoylation reaction, as usually observed with classical organometallic species (Scheme 27).[82] An oxetanol was also selectively converted into the ring-opened amide with complete retention of the configuration of the starting material.[82]

The rhodium-catalyzed addition of boronic esters to cyclobutanones, followed by carbon–carbon bond cleavage

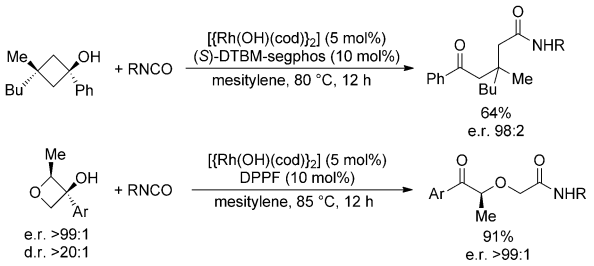


Scheme 25. Rhodium-catalyzed asymmetric C–C bond cleavage of cyclobutanols **65** and proposed mechanism.



Scheme 26. Preparation of enantiomerically enriched 4-ethyl-4-methyloctane (**73**).

to give acyclic adducts, has also been investigated, but to date no diastereo- or enantioselective approaches have been reported.[83] The same holds for the iridium-catalyzed



Scheme 27. Rhodium-catalyzed ring opening favors C- over O-carbamoylation.

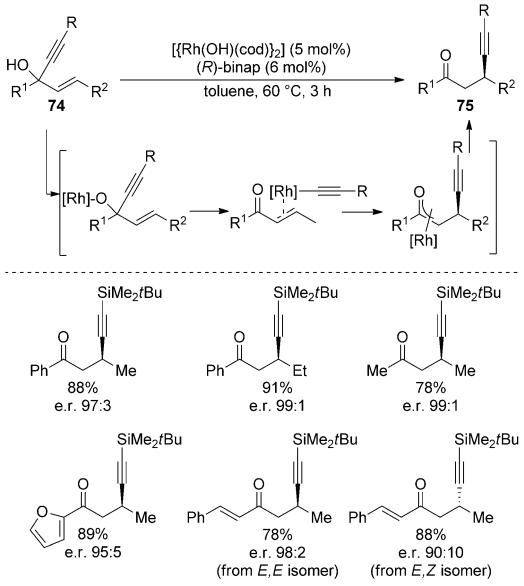
carbon–carbon bond cleavage of cyclobutanone *O*-benzoyloximes.[84]

6. Carbon–Carbon Bond Cleavage of Unstrained Derivatives

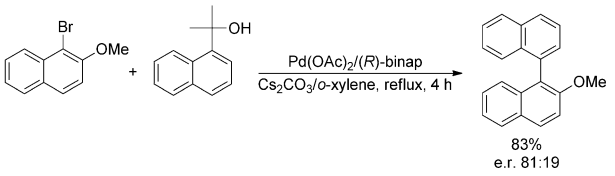
Although the cleavage of carbon–carbon bonds has mainly been observed for systems in which the release of ring strain is the driving force for the reaction, the activation of a few unstrained structures for the preparation of acyclic systems with stereogenic centers by C–C cleavage has been reported. The C–C cleavage of tertiary alcohols is a typical example. The treatment of racemic enynols **74** with a rhodium/(*R*)-binap catalyst in toluene at 60 °C gave β-alkynyl ketones **75** in excellent yields and enantiomeric ratios. The direct rhodium-catalyzed asymmetric alkynylation of conjugated enones proceeds in extremely low yield (6%); the dimerization of the terminal alkyne is the main competing reaction (70%). With the carbon–carbon bond-cleavage procedure, no free alkynes are present in the reaction mixture, and the dimerization cannot occur. Furthermore, the enone generated in situ by carbon–carbon bond cleavage is located close to the rhodium center, thus facilitating the reaction with the alkynyl rhodium species (Scheme 28).[85]

In a similar process, certain α,α-disubstituted aryl methanols efficiently react with aryl bromides to give biaryl compounds through palladium-catalyzed cleavage of the $C(sp^2)$–$C(sp^3)$ bond (Scheme 29).[86]

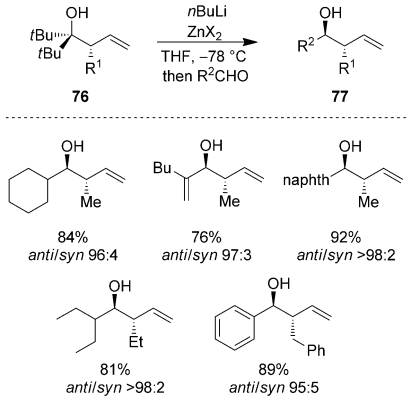
Several other systems undergo the cleavage of carbon–carbon bonds to give reactive intermediates. For example, allyl zinc reagents can be formed by the fragmentation of 1,1-bis(*tert*-butyl) homoallylic alcohols **76**. In the presence of a strong base, substrates **76** were transformed into an allyl zinc intermediate, which was subsequently trapped with an



Scheme 28. Rhodium-catalyzed asymmetric C–C cleavage of alkynyl–alkenyl carbinols.



Scheme 29. Palladium-catalyzed arylative C–C cleavage of α,α-disubstituted aryl methanols.

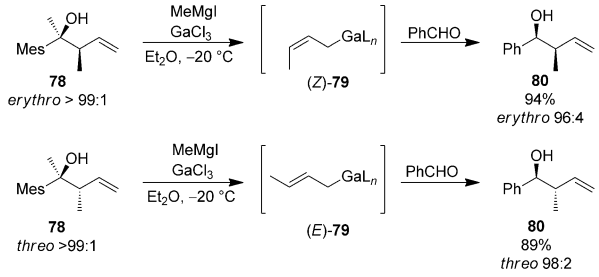


Scheme 30. Diastereoselective formation of homoallylic alcohols via masked allyl zinc reagents.

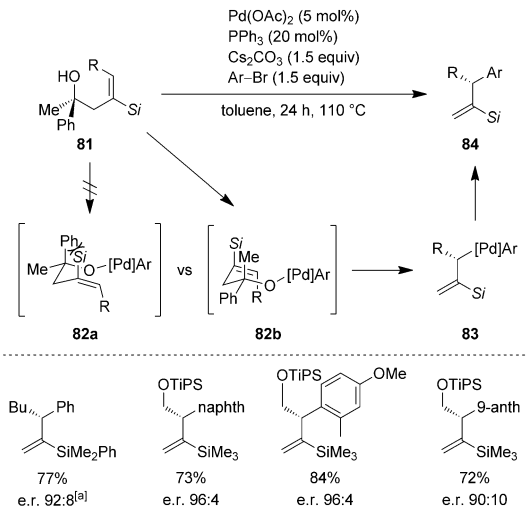
appropriately substituted aldehyde to give stereodefined homoallylic alcohols **77** (Scheme 30).[87]

This approach could be extended to a variety of retroallylation reactions by the use of other transition metals, such as palladium,[88] rhodium,[89] and copper species.[90] Another variation makes use of gallium intermediates **79** to form differently substituted homoallylic alcohols **80**.[91] Interestingly, the diastereomeric nature of the respective *erythro* and *threo* starting materials **78** is retained in the product. Depending on the relative configuration of the starting material, either the *E* or *Z* crotylgallium derivative is formed, thus leading to the *anti* or *syn* homoallylic alcohol **80**, respectively, with high diastereoselectivity (Scheme 31).

This retroallylation strategy was nicely applied to the palladium-catalyzed asymmetric allylation of aryl halides. When **81** was treated with a palladium catalyst and an aryl bromide, an oxidative addition occurred, followed by



Scheme 31. Gallium-mediated allyl transfer from bulky homoallylic alcohols.



Scheme 32. Palladium-catalyzed transfer of chirality from homoallylic alcohols **81.** [a] Substrate **81** with an enantiomeric ratio of 97:3 was used. In all other cases, the enantiomeric ratio of **81** was above 99.5:0.5. 9-anth = 9-anthracenyl, TiPS = triisopropylsilyl.

a halide–alkoxide exchange to give **83** (Scheme 32). From the two possible intermediates **82a**,**b**, **82b** presents less steric interactions and gives, after carbon–carbon bond cleavage, complex **83**. Subsequent reductive elimination forms the corresponding allylated aryl species **84**. The allyl transfer proceeds via the six-membered chairlike transition state **82b**, in which the configuration of the starting material is transferred to the product. Enantiomerically enriched allylic alcohols **81** induced chirality transfer to provide ready access to optically enriched **84** (in all cases, the enantiomeric ratio of **81** was above 99.5:0.5, except for the substrate with R = Bu and Ar = Ph, when it was 97:3).[92]

7. Outlook

The efforts of organic chemists are usually directed towards the development of creative strategies for the construction of carbon–carbon and carbon–heteroatom bonds in a predictable and efficient manner. In this Review, we have shown an alternative approach: The synthesis of challenging acyclic molecular skeletons is also possible through regio-, diastereo-, or enantioselective carbon–carbon bond activation, even though C–C single bonds are among the least reactive functional groups. The development of such strategies may have a profound impact on how synthetic routes are designed, as it may lead to the invention of new selective and efficient processes for the utilization of simple hydrocarbons. There is no doubt that the power of C–C bond cleavage in stereoselective synthesis will continue to flourish and lead to elegant new transformations.

This research was supported by the Israel Science Foundation, which is administrated by the Israel Academy of Sciences and Humanities (140/12), and by the European Research Council under the Seventh Framework Program of the European Community (ERC grant agreement no. 338912). M.L. thanks the Alexander von Humboldt Foundation for a Feodor Lynen Research Fellowship for experienced researchers. I.M. holds the Sir Michael and Lady Sobell Academic Chair.

Received: May 7, 2014
Published online: September 29, 2014

[1] E. M. Carreira, L. Kvaerno, *Classics in Stereoselective Synthesis*, Wiley-VCH, Weinheim, **2009**.
[2] a) P. A. Wender, B. L. Miller, *Nature* **2009**, *460*, 197; b) N. Z. Burns, P. S. Baran, R. W. Hoffmann, *Angew. Chem.* **2009**, *121*, 2896; *Angew. Chem. Int. Ed.* **2009**, *48*, 2854; c) P. S. Baran, T. J. Maimone, J. M. Richter, *Nature* **2007**, *446*, 404; d) B. M. Trost, *Science* **1991**, *254*, 1471.
[3] For reviews on C–C cleavage, see: a) K. Ruhland, *Eur. J. Org. Chem.* **2012**, 2683; b) C. Aïssa, *Synthesis* **2011**, 3389; c) M. Murakami, T. Matsuda, *Chem. Commun.* **2011**, *47*, 1100; d) H. Yorimitsu, K. Oshima, *Bull. Chem. Soc. Jpn.* **2009**, *82*, 778; e) Y. J. Park, J.-W. Park, C.-H. Junn, *Acc. Chem. Res.* **2008**, *41*, 222; f) M. Murakami, M. Makino, S. Ashida, T. Matsuda, *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1315; g) J. A. Tunge, E. C. Burger, *Eur. J. Org. Chem.* **2005**, 1715; h) C.-H. Jun, *Chem. Soc. Rev.* **2004**, *33*, 610; i) C. Perthuisot, B. L. Edelbach, D. L. Zubris, N. Simhai, C. N. Iverson, C. Müller, T. Satoh, W. D. Jones, *J. Mol. Catal. A* **2002**, *189*, 157; j) M. Murakami, Y. Ito, *Top. Organomet. Chem.* **1999**, *3*, 97; k) J. L. Beauchamps, *Chem. Rev.* **1990**, *90*, 629.
[4] For reviews on C–H activation, see: a) L. Ackermann, *Acc. Chem. Res.* **2013**, *46*, 281; b) K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res.* **2012**, *45*, 788; c) L. Ackermann, *Modern Arylation Methods*, Wiley-VCH, Weinheim, **2009**; d) R. G. Bergman, *Science* **1984**, *223*, 902.
[5] B. Rybtchinski, D. Milstein, *Angew. Chem.* **1999**, *111*, 918; *Angew. Chem. Int. Ed.* **1999**, *38*, 870.
[6] M. Gozin, A. Weisman, Y. Ben-David, D. Milstein, *Nature* **1993**, *364*, 699.
[7] M. Gozin, M. Aizenberg, S.-Y. Liou, A. Weisman, Y. Ben-David, D. Milstein, *Nature* **1994**, *370*, 42.
[8] A. Maercker, J. D. Roberts, *J. Am. Chem. Soc.* **1966**, *88*, 1742.
[9] a) C. A. Carson, M. A. Kerr, *Chem. Soc. Rev.* **2009**, *38*, 3051; b) M. Rubin, M. Rubina, V. Gevorgyan, *Chem. Rev.* **2007**, *107*, 3117; c) M. Yu, B. L. Pagenkopf, *Tetrahedron* **2005**, *61*, 321; d) M. Rubina, V. Gevorgyan, *Tetrahedron* **2004**, *60*, 3129; e) O. G. Kulinkovich, *Chem. Rev.* **2003**, *103*, 2597.
[10] For reviews, see: a) G. Audran, H. Pelissier, *Adv. Synth. Catal.* **2010**, *352*, 575; b) M. Rubin, M. Rubina, V. Gevorgyan, *Chem. Rev.* **2007**, *107*, 3117; c) A. Brandi, S. Cicchi, F. M. Cordero, A. Goti, *Chem. Rev.* **2003**, *103*, 1213; d) I. Nakamura, Y. Yamamoto, *Adv. Synth. Catal.* **2002**, *344*, 111; e) A. de Meijere, S. I. Kozhushkov, A. F. Khlebnikov, *Top. Curr. Chem.* **2000**, *207*, 89; f) A. Goti, F. M. Cordero, A. Brandi, *Top. Curr. Chem.* **1996**, *178*, 1; g) M. Lautens, W. Klute, W. Tam, *Chem. Rev.* **1996**, *96*, 49; h) P. Binger, U. Schuchardt, *Chem. Ber.* **1981**, *114*, 3313.
[11] I. Marek, S. Simaan, A. Masarwa, *Angew. Chem.* **2007**, *119*, 7508; *Angew. Chem. Int. Ed.* **2007**, *46*, 7364.
[12] For a recent review on the ring cleavage of donor–acceptor cyclopropanes, see: a) T. F. Schneider, J. Kaschel, D. B. Wertz, *Angew. Chem.* **2014**, *126*, 5608; *Angew. Chem. Int. Ed.* **2014**, *53*, 5504; b) H.-U. Reissig, R. Zimmer, *Chem. Rev.* **2003**, *103*, 1151; for C–C fragmentation, see: M. A. Drahl, M. Manpadi, L. J. Williams, *Angew. Chem.* **2013**, *125*, 11430; *Angew. Chem. Int. Ed.* **2013**, *52*, 11222.
[13] M. Lautens, C. Meyer, A. Lorenz, *J. Am. Chem. Soc.* **1996**, *118*, 10676.

[14] S. Simaan, A. F. G. Goldberg, S. Rosset, I. Marek, *Chem. Eur. J.* **2010**, *16*, 774.
[15] A. G. Bessmertnykh, K. A. Blinov, Y. K. Grishin, N. A. Donskaya, E. V. Tveritinova, N. M. Yur'eva, I. P. Beletskaya, *J. Org. Chem.* **1997**, *62*, 6069.
[16] a) S. Simaan, I. Marek, *Chem. Commun.* **2009**, 292; b) A. Masarwa, A. Stanger, I. Marek, *Angew. Chem.* **2007**, *119*, 8185; *Angew. Chem. Int. Ed.* **2007**, *46*, 8039; c) S. Simaan, A. Masarwa, P. Bertus, I. Marek, *Angew. Chem.* **2006**, *118*, 4067; *Angew. Chem. Int. Ed.* **2006**, *45*, 3963; d) S. Simaan, I. Marek, *Org. Lett.* **2007**, *9*, 2569.
[17] For reviews on the formation of all-carbon quaternary stereocenters, see: a) A. Y. Hong, B. M. Stoltz, *Eur. J. Org. Chem.* **2013**, 2745; b) J. P. Das, I. Marek, *Chem. Commun.* **2011**, *47*, 459; c) C. Hawner, A. Alexakis, *Chem. Commun.* **2010**, *46*, 7295; d) M. Bella, T. Casperi, *Synthesis* **2009**, 1583; e) P. G. Cozzi, R. Hilgraf, N. Zimmermann, *Eur. J. Org. Chem.* **2007**, 5969; f) I. Marek, G. Sklute, *Chem. Commun.* **2007**, *43*, 1683; g) B. M. Trost, C. Jiang, *Synthesis* **2006**, 369; h) J. Christoffers, A. Baro, *Adv. Synth. Catal.* **2005**, *347*, 1473; i) I. Denissova, L. Barriault, *Tetrahedron* **2003**, *59*, 10105; j) J. Christoffers, A. Mann, *Angew. Chem.* **2001**, *113*, 4725; *Angew. Chem. Int. Ed.* **2001**, *40*, 4591; k) E. J. Corey, A. Guzman-Perez, *Angew. Chem.* **1998**, *110*, 2092; *Angew. Chem. Int. Ed.* **1998**, *37*, 388; l) I. Marek, Y. Minko, M. Pasco, T. Mejuch, N. Gilboa, H. Chechik, J. D. Das, *J. Am. Chem. Soc.* **2014**, *136*, 2682.
[18] S. Simaan, A. Masarwa, E. Zohar, A. Stanger, P. Bertus, I. Marek, *Chem. Eur. J.* **2009**, *15*, 8449.
[19] The *E* and *Z* isomers of ACPs **10** have opposite absolute configurations. The *E*/*Z* ratio of (*E*)-**10** is 93:7, and the absolute configuration of (*E*)-**10** is *S*, whereas (*Z*)-**10** is *R*-configured. Each geometric isomer was formed with an enantiomeric ratio of >99:1. Accordingly, in the rhodium-catalyzed hydrosilylation reaction of enantiomerically pure **10** [(*E*,*S*)-**10**/(*Z*,*R*)-**10** = 93:7], *E* and *Z* homoallylsilanes **14** were formed with the same *E*/*Z* ratio as that of the starting material [(*E*,*R*)-**14**/(*Z*,*S*)-**14** = 93:7]. After chromatographic separation of the two isomers, they were each subjected to hydrogenation of the double bond, followed by oxidation. The corresponding saturated alcohols containing a quaternary center were obtained in quantitative yield with an enantiomeric ratio similar to that of the starting material (Scheme 7).
[20] M. Suginome, T. Matsuda, Y. Ito, *J. Am. Chem. Soc.* **2000**, *122*, 11015.
[21] M. Oestreich, E. Hartmann, M. Mewald, *Chem. Rev.* **2013**, *113*, 402.
[22] T. Ohmura, H. Taniguchi, Y. Kondo, M. Suginome, *J. Am. Chem. Soc.* **2007**, *129*, 3518.
[23] a) M. Pasco, N. Gilboa, T. Mejuch, I. Marek, *Organometallics* **2013**, *32*, 942; b) I. Marek, *Tetrahedron* **2002**, *58*, 9463; c) D. S. Matteson, R. W. H. Mah, *J. Am. Chem. Soc.* **1963**, *85*, 2599.
[24] a) T. Yamamoto, Y. Akai, Y. Nagata, M. Suginome, *Angew. Chem.* **2011**, *123*, 9006; *Angew. Chem. Int. Ed.* **2011**, *50*, 8844; b) T. Yamamoto, T. Yamada, Y. Nagata, M. Suginome, *J. Am. Chem. Soc.* **2010**, *132*, 7899; c) T. Yamamoto, M. Suginome, *Angew. Chem.* **2009**, *121*, 547; *Angew. Chem. Int. Ed.* **2009**, *48*, 539.
[25] Y. Akai, T. Yamamoto, Y. Nagata, T. Ohmura, M. Suginome, *J. Am. Chem. Soc.* **2012**, *134*, 11092.
[26] T. Ohmura, H. Taniguchi, M. Suginome, *Org. Lett.* **2009**, *11*, 2880.
[27] H. Taniguchi, T. Ohmira, M. Suginome, *J. Am. Chem. Soc.* **2009**, *131*, 11298.
[28] K. Ogata, D. Shimada, S. Furuya, S.-I. Fukuzawa, *Org. Lett.* **2013**, *15*, 1182.
[29] S. Simaan, I. Marek, *J. Am. Chem. Soc.* **2010**, *132*, 4066.
[30] a) E. Negishi, T. Takahashi, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 755; b) E. Negishi, T. Takahashi, *Acc. Chem. Res.* **1994**, *27*, 124.
[31] A. Masarwa, D. Didier, T. Zabrodski, M. Schinkel, L. Ackermann, I. Marek, *Nature* **2014**, *505*, 199.
[32] a) N. Chinkov, A. Levin, I. Marek, *Angew. Chem.* **2006**, *118*, 479; *Angew. Chem. Int. Ed.* **2006**, *45*, 465; b) N. Chinkov, A. Levin, I. Marek, *Synlett* **2006**, 501; c) N. Chinkov, S. Majumdar, I. Marek, *J. Am. Chem. Soc.* **2003**, *125*, 13258.
[33] a) S. Harada, H. Kiyono, R. Nishio, T. Taguchi, Y. Hanzawa, *J. Org. Chem.* **1997**, *62*, 3994; b) P. W. Dimmock, R. Whitby, *J. Chem. Soc. Chem. Commun.* **1994**, 2323.
[34] a) L. T. Kliman, S. N. Mlynarski, S. N. Ferris, J. P. Morken, *Angew. Chem.* **2012**, *124*, 536; *Angew. Chem. Int. Ed.* **2012**, *51*, 521; b) I. Marek, *Tetrahedron* **2002**, *58*, 9463; c) D. Brasseur, I. Marek, J.-F. Normant, *Tetrahedron* **1996**, *52*, 7235; d) I. Marek, J.-F. Normant, *Chem. Rev.* **1996**, *96*, 3241.
[35] For the isomerization of double bonds with zirconocene reagents, see: a) F. Shahera, I. Zouev, I. Marek, *Tetrahedron* **2004**, *60*, 1329; b) N. Chinkov, H. Chechik, S. Majumdar, I. Marek, *Synthesis* **2002**, 2473; c) S. Farhat, I. Marek, *Angew. Chem.* **2002**, *114*, 1468; *Angew. Chem. Int. Ed.* **2002**, *41*, 1410; d) A. Liard, H. Chechik, S. Farhat, N. Molender-Vais, C. Averbuj, I. Marek, *J. Organomet. Chem.* **2001**, *624*, 26; e) A. Liard, I. Marek, *J. Org. Chem.* **2000**, *65*, 7218.
[36] For examples of dual C–H and C–C activation, see: a) M. A. Bowring, R. G. Bergman, T. D. Tilley, *J. Am. Chem. Soc.* **2013**, *135*, 13121; b) S. Kundu, J. Choi, D. Y. Wang, Y. Choliy, T. J. Emge, K. Krogh-Jespersen, A. S. Goldman, *J. Am. Chem. Soc.* **2013**, *135*, 5127; c) C. Aïssa, D, Crepin, D. J. Tetlow, K. Y. T. Ho, *Org. Lett.* **2013**, *15*, 1322; d) N. Ishida, Y. Shimamoto, T. Yano, M. Murakami, *J. Am. Chem. Soc.* **2013**, *135*, 19103; e) C. Mukai, Y. Ohta, Y. Oura, Y. Kawaguchi, F. Inagaki, *J. Am. Chem. Soc.* **2012**, *134*, 19580; f) D. Crepin, C. Tugny, J. H. Murray, C. Aïssa, *Chem. Commun.* **2011**, *47*, 10957; g) J. Choi, D. Y. Wang, S. Kundu, Y. Choliy, T. J. Emge, K. Krogh-Jespersen, A. S. Goldman, *Science* **2011**, *332*, 1545; h) D. Crepin, J. Dawick, C. Aïssa, *Angew. Chem.* **2010**, *122*, 630; *Angew. Chem. Int. Ed.* **2010**, *49*, 620; i) T. Seiser, G. Cathomen, N. Cramer, *Synlett* **2010**, 1699; j) C. Aïssa, A. Fürstner, *J. Am. Chem. Soc.* **2007**, *129*, 14836; k) M. Shi, L.-P. Liu, J. Tang, *J. Am. Chem. Soc.* **2006**, *128*, 7430; l) C.-H. Jun, C. W. Moon, D.-Y. Lee, *Chem. Eur. J.* **2002**, *8*, 2422; m) A. D. Aloise, M. E. Layton, M. D. Shair, *J. Am. Chem. Soc.* **2000**, *122*, 12610; n) J. O. Hoberg, P. W. Jennings, *J. Am. Chem. Soc.* **1990**, *112*, 5347.
[37] A. de Meijere, *Chem. Rev.* **2003**, *103*, 931 and references cited therein.
[38] I. Ryu, K, Matsumoto, M. Ando, S. Murai, N. Sonoda, *Tetrahedron Lett.* **1980**, *21*, 4283.
[39] B. Giese, H. Horler, *Tetrahedron Lett.* **1983**, *24*, 3221.
[40] O. G. Kulinkovich, *Chem. Rev.* **2003**, *103*, 2597.
[41] a) E. M. Bassan, C. A. Baxter, G. L. Beutner, K. M. Emerson, F. J. Fleitz, S. Johnson, S. Keen, M. M. Kim, J. T. Kuethe, W. R. Leonard, P. R. Mullens, D. J. Muzzio, C. Roberge, N. Yasuda, *Org. Process Res. Dev.* **2012**, *16*, 87; b) T. Imai, H. Mineta, S. Nishida, *J. Org. Chem.* **1990**, *55*, 4986.
[42] D. B. Collum, F. Mohamadi, J. S. Hallock, *J. Am. Chem. Soc.* **1983**, *105*, 6882.
[43] A. H. Hoveyda, D. A. Evans, G. C. Fu, *Chem. Rev.* **1993**, *93*, 1307.
[44] A. B. Charette, A. Beauchemin, *Org. React.* **2004**, *58*, 1.
[45] D. B. Collum, W. C. Still, F. Mohamadi, *J. Am. Chem. Soc.* **1986**, *108*, 2094.
[46] P. Kočovský, J. Šrogl, M. Pour, A. Gogoll, *J. Am. Chem. Soc.* **1994**, *116*, 186.
[47] a) A. G. Barrett, W. Tam, *J. Org. Chem.* **1997**, *62*, 4653; b) A. G. M. Barrett, W. Tam, *J. Org. Chem.* **1997**, *62*, 7673.

[48] a) M. Defosseux, N. Blanchard, C. Meyer, J. Cossy, *Tetrahedron* **2005**, *61*, 7632; b) M. Defosseux, N. Blanchard, C. Meyer, J. Cossy, *J. Org. Chem.* **2004**, *69*, 4626; c) J. Cossy, N. Blanchard, C. Meyer, *Org. Lett.* **2001**, *3*, 2567; d) J. Cossy, N. Blanchard, C. Meyer, *Eur. J. Org. Chem.* **2001**, 2841; e) J. Cossy, N. Blanchard, C. Hamel, C. Meyer, *J. Org. Chem.* **1999**, *64*, 2608; f) J. Cossy, N. Blanchard, C. Meyer, *Synthesis* **1999**, 1063; g) J. Cossy, N. Blanchard, C. Meyer, *Tetrahedron Lett.* **1999**, *40*, 8361.

[49] C. Meyer, N. Blanchard, M. Defosseux, J. Cossy, *Acc. Chem. Res.* **2003**, *36*, 766.

[50] E. Nakamura, K. Sekiya, I. Kuwajima, *Tetrahedron Lett.* **1987**, *28*, 337.

[51] a) S. Aoki, T. Fujimura, E. Nakamura, I. Kuwajima, *J. Am. Chem. Soc.* **1988**, *110*, 3296; b) D. Rosa, A. Orellana, *Org. Lett.* **2011**, *13*, 110; c) D. Rosa, O. Arellana, *Chem. Commun.* **2012**, *48*, 1922.

[52] E. Nakamura, H. Oshino, I. Kuwajima, *J. Am. Chem. Soc.* **1986**, *108*, 3745.

[53] K. Nomura, T. Hirayama, S. Matsubara, *Chem. Asian J.* **2009**, *4*, 1298.

[54] K. Nomura, S. Matsubara, *Chem. Asian J.* **2010**, *5*, 147.

[55] a) K. Cheng, P. J. Caroll, P. J. Walsh, *Org. Lett.* **2011**, *13*, 2346; H. Y. Kim, P. J. Walsh, *Acc. Chem. Res.* **2012**, *45*, 1533.

[56] D. T. Ziegler, A. M. Steffens, T. W. Funk, *Tetrahedron Lett.* **2010**, *51*, 6726.

[57] a) P. P. Das, K. Belmore, J. K. Cha, *Angew. Chem.* **2012**, *124*, 9655; *Angew. Chem. Int. Ed.* **2012**, *51*, 9517; b) P. P. Das, B. B. Parida, J. K. Cha, *ARKIVOC* **2012**, 74.

[58] a) D. Rosa, A. Orellana, *Chem. Commun.* **2013**, *49*, 5420; b) K. Cheng, P. J. Walsh, *Org. Lett.* **2013**, *15*, 2298.

[59] B. B. Parida, P. P. Das, M. Niocel, J. K. Cha, *Org. Lett.* **2013**, *15*, 1780.

[60] For reviews on the chemistry of donor–acceptor and electrophilic cyclopropanes, see: a) P. Tang, Y. Qin, *Synthesis* **2012**, *44*, 2969; b) M. Yu, B. L. Pagenkopf, *Tetrahedron* **2005**, *61*, 321; c) H. N. C. Wong, M.-Y. Hon, C.-W. Tse, Y.-C. Yip, J. Tanko, T. Hudlicky, *Chem. Rev.* **1989**, *89*, 165; d) S. Danishefsky, *Acc. Chem. Res.* **1979**, *12*, 66; e) *The Chemistry of the Cyclopropyl Group*, *Patai Series* (Ed.: Z. Rappoport), Wiley-Interscience, New York, **1995**.

[61] For recent reports on the fragmentation of 1,1-cyclopropane diesters, see: a) S. M. Wales, M. M. Walker, J. S. Johnson, *Org. Lett.* **2013**, *15*, 2558 and references cited therein; b) Y.-Y. Zhou, L.-J. Wang, J. Li, X.-L. Sun, Y. Tang, *J. Am. Chem. Soc.* **2012**, *134*, 9066; c) J. Moran, A. G. Smith, R. M. Carris, J. S. Johnson, M. J. Krische, *J. Am. Chem. Soc.* **2011**, *133*, 18618; d) D. Marcoux, S. R. Goudreau, A. B. Charette, *J. Org. Chem.* **2009**, *74*, 8939.

[62] For monoactivated esters, see: P.-O. Delaye, D. Didier, I. Marek, *Angew. Chem.* **2013**, *125*, 5441; *Angew. Chem. Int. Ed.* **2013**, *52*, 5333 and references cited therein.

[63] a) S. Harada, H. Kiyno, T. Taguchi, Y. Hanzawa, *Tetrahedron Lett.* **1995**, *36*, 9489; b) Y. Hanzawa, S. Harada, R. Nishio, T. Taguchi, *Tetrahedron Lett.* **1994**, *35*, 9421.

[64] a) E. Tsoglin, H. Chechik, G. Karseboom, N. Chinkov, A. Stanger, I. Marek, *Adv. Synth. Catal.* **2009**, *351*, 1005; b) H. Chechik-Lankin, I. Marek, *Synthesis* **2005**, 3311; c) S. Farhat, I. Zouev, I. Marek, *Tetrahedron* **2004**, *60*, 1329.

[65] B. Canchegui, P. Bertus, J. Szymoniak, *Synlett* **2001**, 123.

[66] For representative reviews on catalytic olefin metathesis, see: a) G. C. Vougioukalakis, R. H. Grubbs, *Chem. Rev.* **2010**, *110*, 1746; b) A. M. Lozano-Vila, S. Monsaert, A. Bajek, F. Verpoort, *Chem. Rev.* **2010**, *110*, 4865; c) *Metathesis in Natural Product Synthesis* (Eds.: J. Cossy, S. Arsenyadis, C. Meyer), Wiley-VCH, Weinheim, **2010**; d) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem.* **2005**, *117*, 4564; *Angew. Chem. Int. Ed.* **2005**, *44*, 4490; e) S. T. Diver, A. J. Giessert, *Chem. Rev.* **2004**, *104*, 1317; f) *Handbook of Metathesis* (Ed.: R. H. Grubb), Wiley-VCH, Weinheim, **2003**; g) A. H. Hoveyda, *J. Org. Chem.* **2014**, *79*, 4763.

[67] A. H. Hoveyda, P. J. Lombardi, R. V. O'Brien, A. R. Zhugralin, *J. Am. Chem. Soc.* **2009**, *131*, 8378.

[68] a) B. M. Branan, X. Wang, P. Jankowski, J. Wicha, L. A. Paquette, *J. Org. Chem.* **1994**, *59*, 6874; b) J. K. Crandall, W. W. Conover, *J. Org. Chem.* **1978**, *43*, 1323; c) L. E. Friedrich, R. A. Leckonby, D. M. Stout, Y.-S. P. Lam, *J. Org. Chem.* **1978**, *43*, 604; d) L. E. Friedrich, R. A. Fiato, *J. Org. Chem.* **1974**, *39*, 416; e) L. E. Friedrich, R. A. Fiato, *J. Am. Chem. Soc.* **1974**, *96*, 5783; f) J. Ciabattoni, J. P. Kocienski, *J. Am. Chem. Soc.* **1971**, *93*, 4902; g) L. E. Friedrich, R. A. Cormier, *J. Org. Chem.* **1970**, *35*, 451; h) J. Ciabattoni, J. P. Kocienski, *J. Am. Chem. Soc.* **1969**, *91*, 6534.

[69] Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, K. B. Sharpless, *J. Am. Chem. Soc.* **1987**, *109*, 5765.

[70] D. Bassavaiah, B. S. Reddy, S. S. Badsara, *Chem. Rev.* **2010**, *110*, 5447.

[71] A. Basheer, M. Mishima, I. Marek, *Org. Lett.* **2011**, *13*, 4076.

[72] P. R. Khoury, J. D. Goddard, W. Tam, *Tetrahedron* **2004**, *60*, 8103.

[73] R. D. Bach, O. Dmitrenko, *J. Am. Chem. Soc.* **2004**, *126*, 4444.

[74] For reviews on cyclobutanes, see: a) T. Seiser, T. Saget, D. N. Tran, N. Cramer, *Angew. Chem.* **2011**, *123*, 7884; *Angew. Chem. Int. Ed.* **2011**, *50*, 7740; b) J. C. Namyslo, D. E. Kaufmann, *Chem. Rev.* **2003**, *103*, 1485; c) E. Lee-Ruff, G. Mladenova, *Chem. Rev.* **2003**, *103*, 1449.

[75] T. Nishimura, K. Ohe, S. Uemura, *J. Am. Chem. Soc.* **1999**, *121*, 2645.

[76] a) T. Nishimura, S. Uemura, *J. Am. Chem. Soc.* **1999**, *121*, 11010; b) A. Schweinitz, A. Chtchemelinine, A. Orellana, *Org. Lett.* **2011**, *13*, 232; c) D. Rosa, A. Chtchemelinine, A. Orellana, *Synthesis* **2012**, *44*, 1885.

[77] a) S. Matsumura, Y. Maeda, T. Nishimura, S. Uemura, *J. Am. Chem. Soc.* **2003**, *125*, 8862; b) T. Nishimura, S. Matsumura, Y. Maeda, S. Uemura, *Chem. Commun.* **2002**, 50; c) T. Nishimura, S. Matsumura, Y. Maeda, S. Uemura, *Tetrahedron Lett.* **2002**, *43*, 3037.

[78] For examples of rhodium-catalyzed C–C activation for the synthesis of cyclic compounds, see: a) N. Ishida, W. Ikemoto, M. Murakami, *J. Am. Chem. Soc.* **2014**, *136*, 5912; b) N. Ishida, S. Sawano, M. Murakami, *Nat. Commun.* **2014**, *5*, 3111; c) L. Souillart, E. Parker, N. Cramer, *Angew. Chem.* **2014**, *126*, 3045; *Angew. Chem. Int. Ed.* **2014**, *53*, 3001; d) E. Parker, N. Cramer, *Organometallics* **2014**, *33*, 780; e) L. Souillart, N. Cramer, *Chem. Sci.* **2014**, *5*, 837; f) A. Yada, S. Fujita, M. Murakami, *J. Am. Chem. Soc.* **2014**, *136*, 7217; g) T. Seiser, N. Cramer, *Chem. Eur. J.* **2010**, *16*, 3383; h) T. Seiser, O. A. Roth, N. Cramer, *Angew. Chem.* **2009**, *121*, 6438; *Angew. Chem. Int. Ed.* **2009**, *48*, 6320; i) M. Shigeno, T. Yamamoto, M. Murakami, *Chem. Eur. J.* **2009**, *15*, 12929; j) T. Seiser, N. Cramer, *Angew. Chem.* **2008**, *120*, 9435; *Angew. Chem. Int. Ed.* **2008**, *47*, 9294.

[79] a) T. Seiser, N. Cramer, *J. Am. Chem. Soc.* **2010**, *132*, 5340; b) N. Cramer, T. Seiser, *Synlett* **2011**, *4*, 449.

[80] T. Matsuda, M. Shigeno, M. Makino, M. Murakami, *Org. Lett.* **2006**, *8*, 3379.

[81] a) H. Yu, C. Wang, Y. Yang, Z.-M. Dang, *Chem. Eur. J.* **2014**, *20*, 3839; b) L. Ding, N. Ishida, M. Murakami, K. Morokuma, *J. Am. Chem. Soc.* **2014**, *136*, 169.

[82] N. Ishida, Y. Nakanishi, M. Murakami, *Angew. Chem.* **2013**, *125*, 12091; *Angew. Chem. Int. Ed.* **2013**, *52*, 11875.

[83] For examples of the C–C activation of cyclobutanones, see: a) Y. Masuda, M. Hasegawa, M. Yamashita, K. Nozaki, N. Ishida, M. Murakami, *J. Am. Chem. Soc.* **2013**, *135*, 7142; b) T. Matsuda, M. Shigeno, M. Murakami, *J. Am. Chem. Soc.* **2007**, *129*, 12086; c) T. Matsuda, M. Makino, M. Murakami, *Bull. Chem. Soc. Jpn.* **2005**, *78*, 1528; d) T. Matsuda, M. Makino, M. Murakami, *Org. Lett.* **2004**, *6*, 1257; e) M. Murakami, T. Itahashi, Y. Ito, *J. Am. Chem.*

Soc. **2002**, *124*, 13976; f) M. Murakami, T. Itahashi, H. Amii, K. Takahashi, Y. Ito, *J. Am. Chem. Soc.* **1998**, *120*, 9949.

[84] a) T. Nishimura, T. Yoshinaka, Y. Nishiguchi, Y. Maeda, S. Uemura, *Org. Lett.* **2005**, *7*, 2425; b) T. Nishimura, Y. Nishiguchi, Y. Maeda, S. Uemura, *J. Org. Chem.* **2004**, *69*, 5342; c) T. Nishimura, S. Uemura, *J. Am. Chem. Soc.* **2000**, *122*, 12049.

[85] T. Nishimura, T. Katoh, K. Takatsu, R. Shintani, T. Hayashi, *J. Am. Chem. Soc.* **2007**, *129*, 14158.

[86] Y. Terao, H. Wakui, T. Satoh, M. Miura, M. Nomura, *J. Am. Chem. Soc.* **2001**, *123*, 10407.

[87] a) P. Jones, P. Knochel, *J. Org. Chem.* **1999**, *64*, 186; b) P. Jones, N. Millot, P. Knochel, *Chem. Commun.* **1998**, 2405; c) P. Jones, P. Knochel, *Chem. Commun.* **1998**, 2407.

[88] a) M. Iwasaki, S. Hayashi, K. Hirano, H. Yorimitsu, K. Oshima, *J. Am. Chem. Soc.* **2007**, *129*, 4463; b) S. Hayashi, K. Hirano, H. Yorimitsu, K. Oshima, *J. Am. Chem. Soc.* **2006**, *128*, 2210.

[89] Y. Takada, S. Hayashi, K. Hirano, H. Yorimitsu, K. Oshima, *Org. Lett.* **2006**, *8*, 2515.

[90] M. Sai, H. Yorimitsu, K. Oshima, *Angew. Chem.* **2011**, *123*, 3352; *Angew. Chem. Int. Ed.* **2011**, *50*, 3294.

[91] S. Hayashi, K. Hirano, H. Yorimitsu, K. Oshima, *Org. Lett.* **2005**, *7*, 3577.

[92] a) R. Wakabayashi, D. Fujino, S. Hayashi, H. Yorimitsu, K. Oshima, *J. Org. Chem.* **2010**, *75*, 4337; b) S. Hayashi, K. Hirano, H. Yorimitsu, K. Oshima, *J. Am. Chem. Soc.* **2007**, *129*, 12650.