The Virtue of Palladium-Catalyzed Domino Reactions — Diverse Oligocyclizations of Acyclic 2-Bromoenynes and 2-Bromoenediynes

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ABSTRACT

The domino-type combination of consecutive palladium-catalyzed cross-coupling reactions with subsequent pericyclic transformations offers a very fast access to various oligocyclic skeletons. This Account highlights all-intramolecular, intra-intermolecular, and all-intermolecular organopalladation cascades leading to 1,3,5-hexatrienes, which undergo consecutive 6π-electrocyclizations with closure of three, two, or just one ring, respectively. Sequences of cross-coupling reactions and Diels−Alder additions are also discussed, as well as tricyclizations of 2-bromoenediynes giving rise to bisannelated benzene and fulvene derivatives.

Armin de Meijere, born in 1939 in Homberg (Niederrhein), Germany, studied chemistry at the Universities of Freiburg and Göttingen, where he obtained his doctorate under the guidance of Wolfgang Lüttke. Following postdoctoral training at Yale University (Kenneth B. Wiberg) in New Haven, CT, he finished his "Habilitation" in 1971 in Göttingen. He became Full Professor at the University of Hamburg in 1977 and returned to Göttingen to succeed his former mentor in the chair of Organic Chemistry in 1989. His current research interests include the development of new cascade reactions for the efficient construction of complex organic skeletons and new small-ring building blocks to be applied in the synthesis of natural and non-natural compounds, new highly strained polycyclic compounds with interesting properties, as well as the development of new methodology based on metal-mediated and -catalyzed transformations of organic compounds.

Paultheo von Zezschwitz, born in Wolfsburg, Germany, in 1972, studied chemistry at the University of Göttingen and at the KTH Stockholm, Sweden. He obtained his doctorate in 1999 under the guidance of Armin de Meijere in Göttingen. After a postdoctoral stay at Harvard University (Eric N. Jacobsen) in Cambridge, MA, he is now working at the University of Göttingen toward his "Habilitation", in association with Armin de Meijere. His research focuses on asymmetric metal-catalyzed processes and natural product synthesis.

Stefan Bräse, born in Kiel, Germany, in 1967, studied chemistry in Göttingen, Bangor (UK), and Marseille. He obtained his doctorate in 1995 under the guidance of Armin de Meijere in Göttingen. After postdoctoral appointments at Uppsala University (Jan Bäckvall) and The Scripps Research Institute (K. C. Nicolaou), he began his independent research career at the RWTH Aachen associated with Dieter Enders in 1997 and finished his "Habilitation" in 2001. He became Professor at the University of Bonn that same year and Full Professor of Organic Chemistry at the Technical University of Karlsruhe in 2003. His research interests include asymmetric metal-catalyzed processes and combinatorial chemistry toward the synthesis of biologically active compounds.

Introduction

Carbon−carbon bond-forming reactions represent the most important processes in organic synthesis. When performed intermolecularly, they are used to couple small fragments to larger units. In intramolecular reactions, they can bring about cyclizations or bicyclizations, and thus astonishing changes of molecular structures and increases in molecular complexity. This effect can even be enhanced by repeating the same reaction type several times or combining it with a different transformation in a domino fashion.[1] Such sequential processes offer a wide range of possibilities for the efficient construction of highly complex molecules in a single procedural step, thus omitting the need for several workup and purification operations and allowing savings of both solvents and reagents. Additionally, they frequently occur with enhanced regio-, diastereo-, and even enantioselectivity for the overall transformation. Among the numerous methods for carbon−carbon bond formation, palladium-catalyzed transformations have come to play a leading role,[2] and one of the most widely applicable reactions of this type is the arylation and alkenylation of alkenes. Elaborated as a stoichiometric transformation by Heck in 1968 and for the first time executed catalytically by Mizoroki et al. in 1971, it is currently generally known as the Heck reaction and has since been developed to an increasingly important tool in organic synthesis.[3] The rapid development of new and vastly improved protocols, the discovery of diastereoselective and, since 1989, even ligand-induced enantioselective variants, has made it possible to apply the Heck reaction in elegant syntheses of various biologically active compounds. Substantial work has also led to deeper insights into the mechanism of this important cross coupling so that the key steps are now reasonably well understood.[4] This also bears on other Pd-catalyzed processes, for example, the cycloisomerization of enynes, discovered by Trost et al.,[5] which exceeds the Heck reaction in terms of atom economy. This transformation differs from the Heck reaction only in that a σ-alkenylpalladium(II) complex is generated by hydridopalladation of a triple bond. Multifold palladium-catalyzed cross-coupling reactions can either occur iteratively with oligohaloalkenes or -arenes and lead to highly substituted carbo- and heterocyclic systems.[6] On the other hand, additional carbon−carbon bonds can be formed if, after the first *syn*-addition, further intra- or intermolecular carbopalladations take place due to prevention of β-dehydropalladation. This occurs after carbopalladation of a 1,1-disubstituted alkene, when the palladium rests in a neopentyl position, or after *syn*-carbopalladation of an alkyne, when *syn*-β-dehydropalladation to form an alkyne is impossible and elimination to form an allene is energetically unfavorable. Therefore, oligocyclizations by Heck reactions generally require acyclic precursors in which a starter unit, for example, a bromoalkene, one or more

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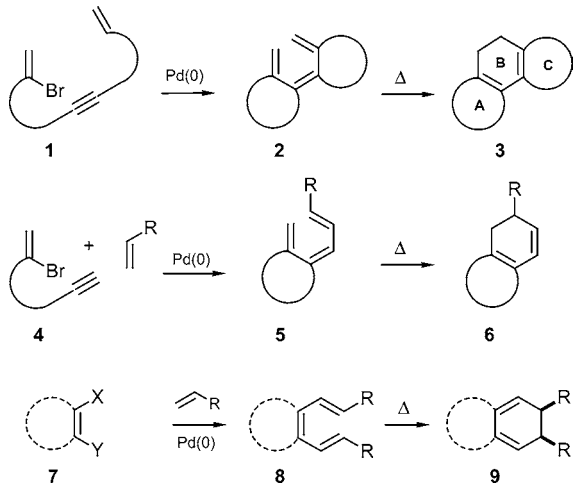
Scheme 1. Possible Domino Reactions Consisting of Heck Couplings and Consecutive 6π-Electrocyclizations



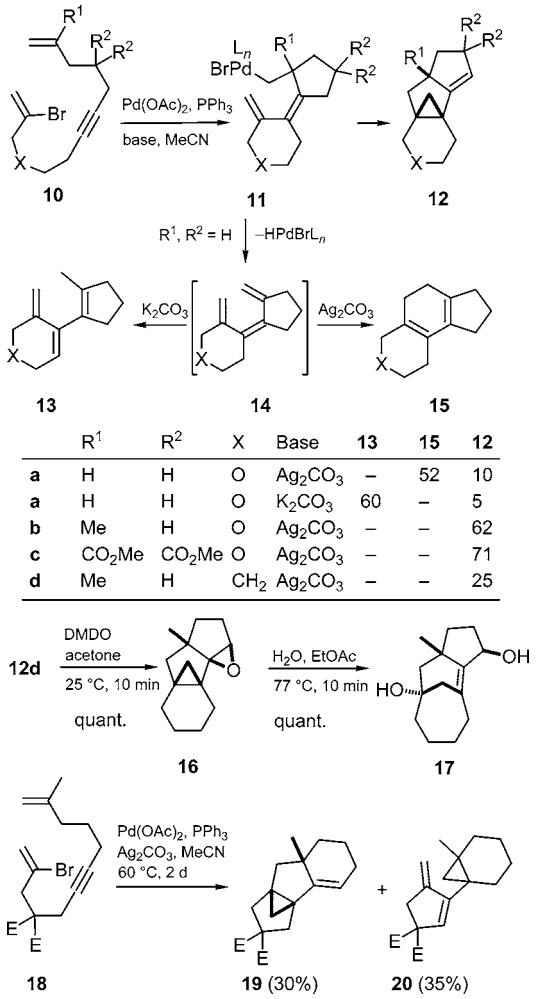
relay units, and a terminating alkene moiety, capable of β-dehydropalladation after carbopalladation, are tethered with each other. Various types of such cascade reactions have been realized, including the assembly of the steroid skeleton applying a zipper cascade by Negishi et al.,[7] or a dumbbell-mode cascade by Grigg et al.,[8] the elegant formation of a heptaspirane in a single operation by Trost et al.,[9] the first preparation of scopadulcic acid using a linear fused-mode cascade by Overman et al.,[10] and many more.[11] This Account focuses on various modes of oligocyclizations including subsequent pericyclic reactions from the authors' own laboratories.

Intramolecular Couplings of 2-Bromodienynes with Consecutive 6π-Electrocyclizations

Access to 1,3,5-hexatrienes suitable for subsequent 6π-electrocyclizations can be envisioned by three different strategies (Scheme 1). An all-intramolecular reaction of bromodienynes **1** would form dumbbell-shaped hexatrienes **2**, which should undergo 6π-electrocyclization to tricycles **3** with a central cyclohexa-1,3-diene moiety. The intra-intermolecular mode via hexatriene **5** would lead to bicycles **6**, and the all-intermolecular assembly of a dihalo(cyclo)alkene **7** with two alkenes would eventually lead to only one newly formed ring. The first possibility appeared to be especially promising because intramolecular reactions usually occur with high selectivities and hexatrienes of type **2** with a fixed *s-cis*,*s-cis*-conformation are predetermined for fast 6π-electrocyclizations.

The first realization of this concept was reported from our laboratories in 1991.[12] The oxabromodienyne precursor **10a** was set up to give the [6-6-5]-tricyclic skeleton **15a**, when performed in the presence of silver carbonate, to prevent double bond migrations in the intermediate **14**. With potassium carbonate as a base, the cross-conjugated triene **13a** was obtained along with 5% of the tetracyclic propellane **12a**, formed as a single diastereomer (Scheme 2). Subsequent work showed that the tetracycles **12b**−**d** arising from **11** by a sequence of 5-*exo*-*trig*-, 3-*exo*-*trig*-cyclization and β-dehydropalladation can be obtained

Scheme 2. Tri- and Tetracyclizations of 2-Bromodienynes



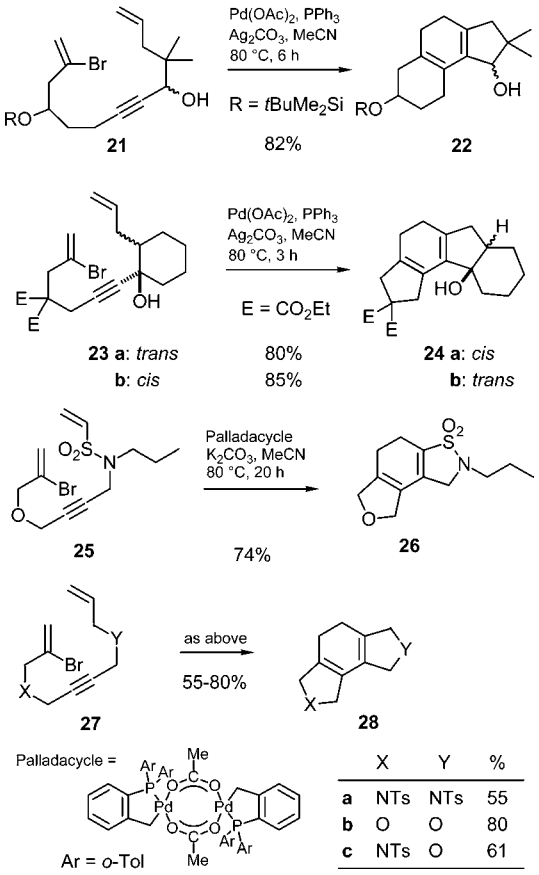
	R^1	R^2	X	Base	13	15	12
a	H	H	O	Ag_2CO_3	–	52	10
a	H	H	O	K_2CO_3	60	–	5
b	Me	H	O	Ag_2CO_3	–	–	62
c	CO_2Me	CO_2Me	O	Ag_2CO_3	–	–	71
d	Me	H	CH_2	Ag_2CO_3	–	–	25

in 62%, 71%, and 25% yield, respectively, from the corresponding acyclic precursors **10b**−**d** with substituents $R^1 \neq H$ preventing β-dehydropalladation at the intermediate stage **11**. Treatment of **12d** with dimethyldioxirane furnished the epoxide **16** as a single diastereomer. This, upon attempted recrystallization from ethyl acetate (technical grade), underwent addition of water with opening of the cyclopropane ring to yield the interesting tricycle **17** with a tetrasubstituted bridgehead double bond.[13]

Yet another reaction mode showed up with bromodienyne **18**. The expected tetracycle **19** was isolated along with the tricycle **20**, which is formed from an intermediate analogous to **11** by 3-*exo*-*trig*-carbopalladation of the tetrasubstituted double bond.[14] Obviously, the outcome of the overall reaction is controlled by the reaction conditions and the tether lengths in the precursor.

These important features initiated an extensive study of the scope and limitations of such reaction cascades with respect to various substitution patterns, ring sizes, and heteroatoms in the tethers between the unsaturated moieties. Thus, the hydroxy-substituted carbotricycle **22** was obtained in excellent yield, and so were the tetracycles **24a**,**b** with an attached cyclohexane ring by completely diastereoselective conversions of **23a**,**b** (Scheme 3).[15] Heterotricyclic compounds, such as the dihydrofurobenz-

Scheme 3. Cascade Reactions of 2-Bromodienynes with Terminal Double Bonds

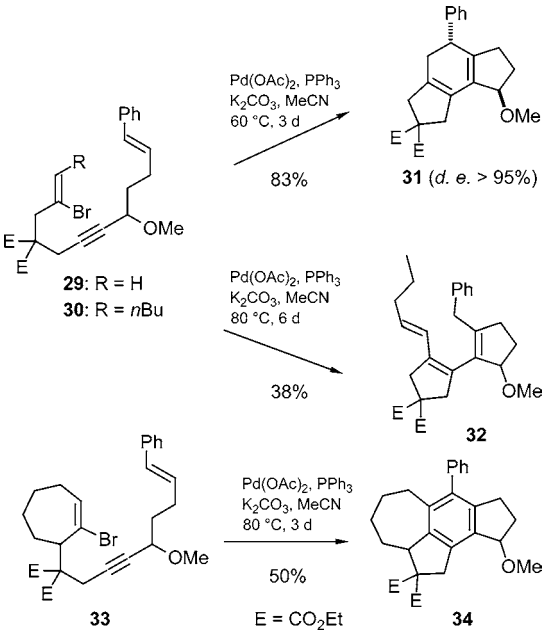


isothiazoline **26** as well as the diaza-, dioxa-, and oxaza-tricycles **28a**−**c**, were obtained in 55−80% yield.[16] The crude yield of **28a** was actually much better, and higher yields can often be obtained by carefully avoiding losses during purification. In all of these cases, the 6π-electrocyclization proceeds under the conditions of the Heck reaction and thus at remarkably low temperatures (60−100 °C).

With a phenyl substituent at the terminating unit, the 6π-electrocyclization yielded a single diastereomer **31** (Scheme 4).[17] This remarkable rotaselectivity must be caused by the methoxy substituent, which apparently favors one of the two possible disrotatory modes due to steric interactions.[18] In contrast, no electrocyclization, but an antarafacial 1,7-hydrogen shift was observed in the case of the intermediate from **30**, to give the isomeric hexatriene **32**, which did not cyclize, even at elevated temperatures. However, this problem only occurs with a (*Z*)-positioned substituent at C-1. The monocyclic bromodienyne **33** with an (*E*)-oriented substituent embedded in a seven-membered ring gave tetracycle **34** in reasonable yield, and similar results were obtained from the analogous bromodienyne with a cyclohexene moiety.[19] In these as in other cases, the initially formed cyclohexa-1,3-diene moiety underwent dehydrogenation to an aromatic ring, either under the reaction conditions or upon workup and purification.

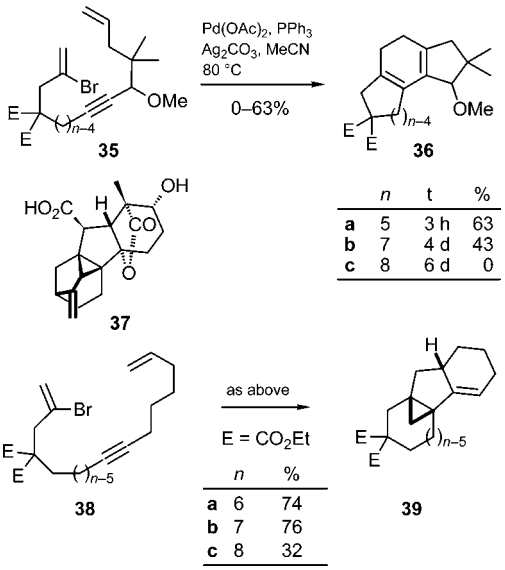
Numerous oligocyclizations were performed on variously substituted bromodienyne model compounds with

Scheme 4. Cascade Reactions of 2-Bromodienynes with Internal Double Bonds

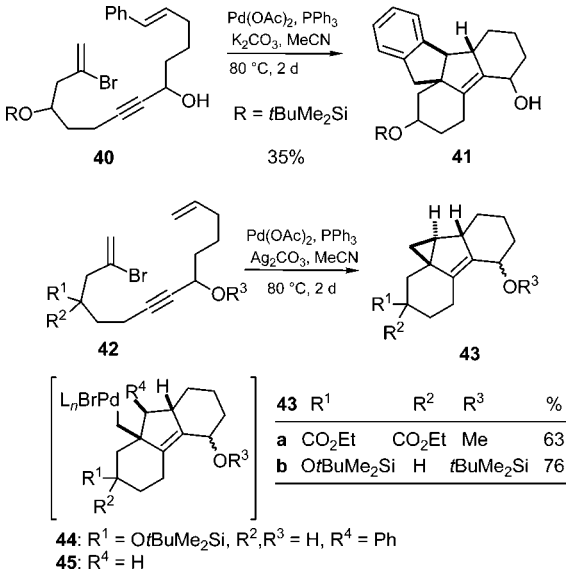


different tether lengths between the bromoene starter unit, the alkyne relay, and the alkene terminator. In the case of precursors **35a**−**c** leading to [*n*-6-5]-tricycles **36a**−**c**, the time required to form **36b** was significantly longer, and the yield of **36b** (actually isolated as a 2:1 mixture with the corresponding aromatic compound) was 20% lower (Scheme 5), whereas the [8-6-5]-tricycle **36c** was not formed at all. Attempts to assemble tricycles with six-membered A- and C-rings led to tetracycles of type **39** with cyclopropane moieties bridging the A- and B-rings just like the ones mentioned above (see Scheme 2).[20] The reasons for this anomalous reaction mode are not yet understood, but they must relate to different conformations of the key intermediates of type **11** or **14**. A related case with a decelerated 6π-electrocyclization leading to a

Scheme 5. Variation of the Tether Length in Precursors for Palladium-Catalyzed Tricyclizations



Scheme 6. Two Unprecedented Types of Tetracyclization of 2-Bromotetradeca-1,13-diene-7-ynes



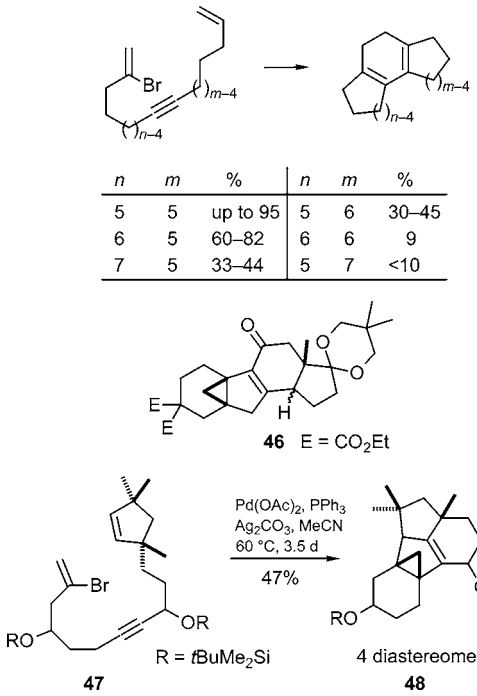
43	R^1	R^2	R^3	%
a	CO_2Et	CO_2Et	Me	63
b	O*t*BuMe$_2$Si	H	*t*BuMe$_2$Si	76

[6-6-5]-tricycle has been reported by Trost et al.[18] Thus, a retarded β-dehydropalladation or a retarded electrocyclization giving the eliminated hydridopalladium halide an opportunity to rehydropalladate the 1,3,5-hexatriene could favor an intermediate of type **11** to undergo a 5-*exo-trig*- and subsequent 3-*exo-trig*-cyclization to yield a tetracycle **39** after β-dehydropalladation. In view of its efficiency and diastereoselectivity, this Pd-catalyzed all-intramolecular cascade tetracyclization is quite interesting and potentially useful. At least one natural product, the plant growth regulator 3α-hydroxy-9,15-cyclogibberelin A (**37**), contains the same basic skeleton.[21] In addition, the initial 8-*exo-dig*-cyclization leading to **39c** is remarkable as one of the few examples of an eight-membered ring formation by a Heck reaction.[22]

Apparently, there is no rule without an exception, as certain substituents on acyclic bromodienynes set up for such tetracyclizations can cause the sequential reaction to proceed in an unprecedented direction. Thus, **40** with a terminal phenyl group apparently sequentially cyclized to the usual neopentylpalladium intermediate **44**, which, due to the proximity of the phenyl group, underwent an intramolecular electrophilic substitution to give the pentacycle **41** rather than a phenyl-substituted skeleton of type **39** (Scheme 6).[23] On the other hand, the bromodienynes **42a**,**b**, which differ from **38a** only by their 9-methoxy or 9-silyloxy substituent, respectively, eventually yielded the novel tetracyclic systems **43a**,**b** as proved by an X-ray crystal structure analysis.[20] This cascade probably also proceeds via the tricyclic intermediates **45**, but it is unclear whether **43** is simply formed by a rare γ-dehydropalladation[24] or by α-dehydrobromination to yield a palladiumcarbene complex and its subsequent β-hydride insertion.

Bromodienynes designed to lead to tricycles with a seven-membered C-ring combined with a five- or six-membered A-ring only underwent polymerization. Altogether, this sequence of all-intramolecular palladium-catalyzed 1,3,5-hexatriene formation with subsequent 6π-electrocyclization works particular well as long as five-membered rings are formed in both Heck-type cyclization steps (Scheme 7). The overall yields are not as good, when one of the Heck-type cyclizations leads to a six-membered ring, especially if this is the second cyclization step. Other tricycles are formed only in moderate yields ([7-6-5]) or as minor products ([6-6-6] and [5-6-7]). Thus, attempts to assemble the steroid skeleton from a precursor already containing the five-membered D-ring gave only minor amounts of the desired tetracycle with three six-membered rings, but the pentacycle **46** with a five-membered B-ring and a bridging cyclopropane between the A- and B-rings.[20] In this cascade oligocyclization and an analogous one of **47** leading to **48**, four new rings are formed with a remarkable increase in molecular complexity.[25]

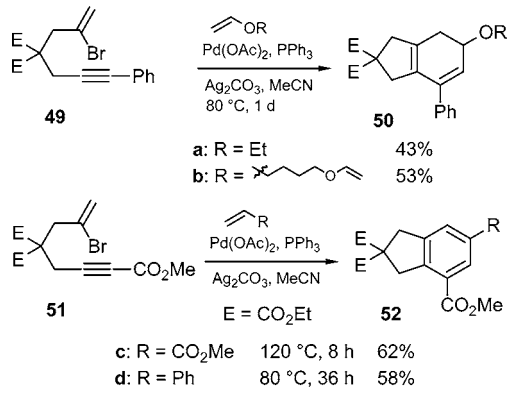
Scheme 7. Rules for Achievable Ring-Size Combinations in Palladium-Catalyzed Cascade Tricyclizations



Intra-Intermolecular Couplings of 2-Bromoenynes with Alkenes

In the envisioned sequence of an intra- and an intermolecular Heck reaction followed by 6π-electrocyclization (Scheme 1), a severe problem of chemoselectivity can occur: After oxidative addition of the bromoenyne **4** to the Pd(0) species and intramolecular carbopalladation of the triple bond, the "living" alkenylpalladium species can intermolecularly carbopalladate either the added alkene or the triple bond of another bromoenyne molecule **4**. Initially, therefore, a considerable excess of ethyl vinyl ether was employed to convert **49** to the annelated cyclohexadiene **50a** (Scheme 8). However, an excess of the alkene is not necessary, as with 1,4-bisvinyloxybutane employed stoichiometrically, the bicycle **50b** was obtained in an even better yield.[19] Apparently, selective β-alkenylation of an enol ether does take place. The intermediate

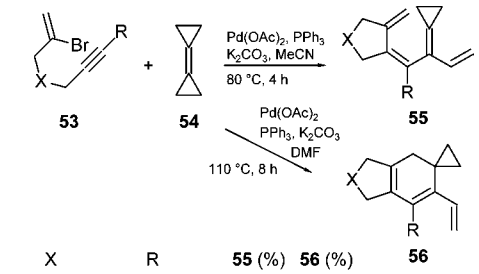
Scheme 8. Sequence of Intra- and Intermolecular Heck Reactions Followed by 6π-Electrocyclizations



1,3,5-hexatrienes of type **5** were never isolated; obviously, they swiftly undergo 6π-electrocyclization under the conditions of their formation (80 °C), although they are conformationally less rigid than those of type **2**. In contrast, reactions of the alkoxycarbonyl-substituted bromoenyne **51** with electron-deficient alkenes led to indene derivatives **52** at 80 °C (R = Ph) and 120 °C (R = CO_2Me), respectively. This facile dehydrogenation of an initially formed cyclohexa-1,3-diene has also been observed by Parsons et al.[26] Overall, the results of this type of intra-intermolecular cascade are similar to those of the inter-intramolecular mode of coupling a bromoene with an enyne introduced by Trost et al.[27]

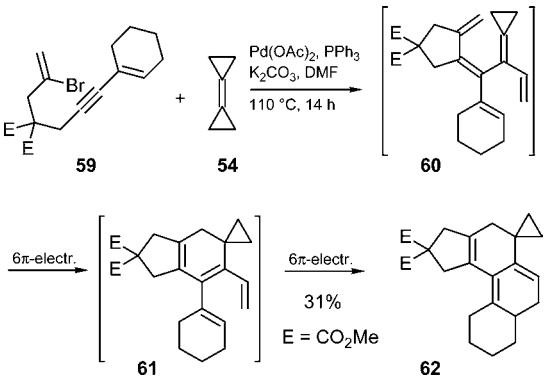
Bicyclocyclopropylidene (**54**) has proved to be particularly reactive toward carbopalladations.[28] When employed in the intra-intermolecular cascade coupling with 2-bromoenynes **53** containing bulky substituents R on the alkyne terminus, cross-conjugated tetraenes **55** were obtained in good yields (Scheme 9).[29] They arise by the rapidly occurring cyclopropylcarbinyl to homoallyl rearrangement of the intermediate **57** to **58**, which finally suffers β-dehydropalladation. NMR findings corroborate that these molecules adopt an almost 90° dihedral angle between the two diene moieties. When carried out at

Scheme 9. Intra-Intermolecular Sequence Incorporating Bicyclopropylidene with Ring-Opening Rearrangement



	X	R	**55** (%)	**56** (%)
a	$C(CO_2Me)_2$	*t*Bu	66	56
b	$C(CO_2Me)_2$	*t*$BuMe_2Si$	72	65
c	O	Ph	54	71
d	NTs	Ph	35	44

Scheme 10. Three New Rings Formed in One Procedural Step Including Two Consecutive 6π-Electrocyclizations



elevated temperature (110 °C in DMF), the reaction proceeds with a subsequent 6π-electrocyclization to yield the spiro[cyclopropane-1,4′]-bicyclo[4.3.0]nona-1(6),2-dienes **56** (up to 71%).

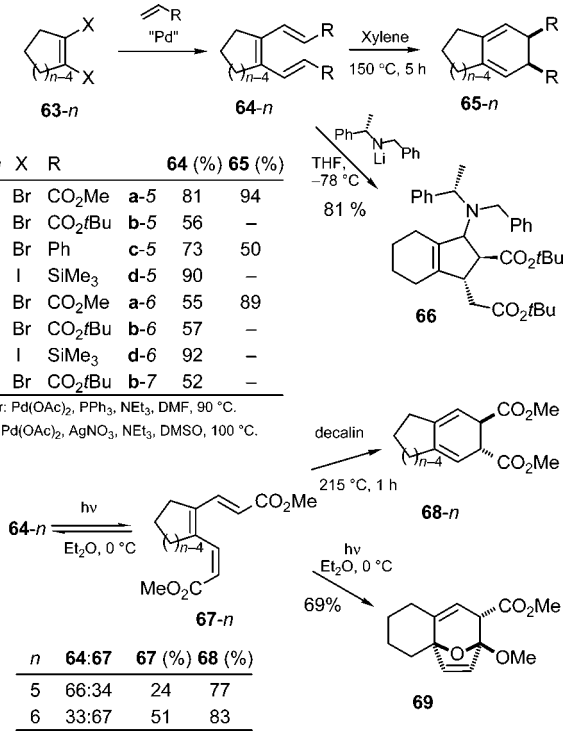
With an alkenyl substituent at the triple bond terminus as in **59** (Scheme 10), this sequence is extended in that the initially formed cross-conjugated pentaene **60** undergoes two consecutive electrocyclizations, leading to the pentacyclic product **62**.[29]

Twofold Cross-Coupling Reactions on 1,2-Difunctionalized Cycloalkenes

Toward the all-intermolecular reaction mode (see Scheme 1), (*E,Z,E*)-1,3,5-hexatrienes **64**-*n* with two identical substituents (e.g., CO_2R, Ph, $SiMe_3$) in the 1,6-positions were obtained by twofold Heck reactions of 1,2-dihalocycloalkenes **63**-*n* with correspondingly substituted alkenes (Scheme 11).[30] These *s-trans,s-trans*-oriented hexatrienes required elevated temperatures (≥150 °C) to undergo 6π-electrocyclizations to ring-annelated *cis*-disubstituted cyclohexadienes **65**-*n*. Hexatrienes **64**-*n* can also be utilized to prepare enantiopure bicyclic β-amino acids **66** by a domino-Michael addition initiated by homochiral lithium amides,[31a] strained 11-oxabicyclo[4.4.1]undeca-1,5-dienes,[31b] as well as functionalized cyclodecenones and -undecenones.[31c] Upon attempted photochemical 6π-electrocyclizations of hexatrienes **64**-*5,6*, a fast equilibrium of the (*E,Z,E*)- and its (*E,Z,Z*)-diastereomer **67**-*5,6* was established (Scheme 11).[32] Even though the photochemical conrotatory 6π-electrocyclizations could not be brought about, the *trans*-disubstituted cyclohexadienes **68**-*n* could be obtained by thermal cyclization of the isolated (*E,Z,Z*)-hexatrienes **67**-*n*. Moreover, the hexatriene **64a** with a central cyclohexene moiety, upon extended irradiation, yielded the cyclohexane-annelated 8-oxabicyclo[3.2.1]-octa-2,7-diene **69**. This unprecedented intramolecular formal hetero-Diels–Alder reaction of an ester carbonyl group with a diene unit probably proceeds as a radical reaction of the triplet excited state.[32]

The preparation of unsymmetrical terminally disubstituted 1,3,5-hexatrienes by twofold Heck coupling of **63**-*n* with two different alkenes cannot be achieved because the second coupling step turned out to be

Scheme 11. Twofold Heck Reactions on 1,2-Dihalocycloalkenes and Subsequent Transformations of the Products



significantly faster than the first.[6b] Sufficient differentiation could not be brought about with a triflate and a bromide leaving group as in **70**.[30] However, this substrate proved to undergo completely chemoselective Stille cross couplings with various alkenylstannanes at the triflate position, and this could be succeeded by a Heck reaction at the remaining bromide.[33] In several cases, this sequence has been carried out as a one-pot operation, for example, toward triene **71** as a versatile intermediate (Scheme 12). Thermal 6π-electrocyclization of **71** and subsequent treatment with HCl yield the ring-annelated cyclohexenone **72**. The overall result of this sequence from cyclohexanone, the precursor of **70**, is a cyclohexenone annelation complementing the well-known Robinson annelation. Direct hydrolysis of the hexatriene **71** yields dienyl ketone **73**, the enolate of which undergoes an intramolecular Michael addition to yield (91% overall) the cyclopentenone-annelation product **74**. The analogous Stille–Heck coupling sequence with 3-(tributylstannyl)allyl alcohol and *tert*-butyl acrylate furnishes the triene **75**, which, upon heating to 200 °C, undergoes 6π-electrocyclization followed by intramolecular transesterification to the tricyclic lactone **76**.

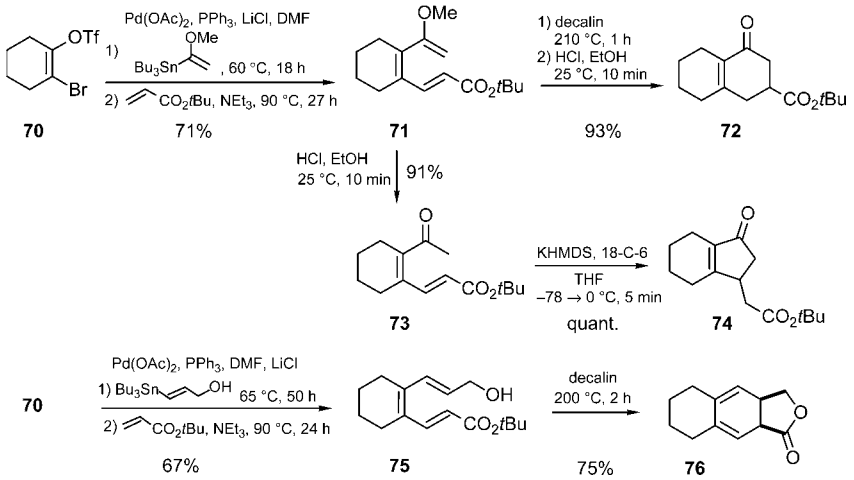
In an approach to the steroid skeleton, the 4-substituted bromoenol triflate **77** representing the A-ring was coupled to the novel bicyclo[4.3.0]nonenylstannane **78** (the CD-ring fragment) with a catalyst cocktail containing triphenylarsine and copper(I) iodide, to give bromodiene **79** in very good yield (Scheme 13).[34] Under optimized conditions at 105 °C with the thermally relatively stable palladacycle as catalyst (see Scheme 3), **79** was then coupled with *tert*-butyl acrylate leading to the hexatriene **80**, which, upon heating at 215 °C, underwent 6π-electrocyclization with complete rotaselectivity, albeit the expected product **81** was accompanied by its isomer **82** arising from subsequent 1,5-*H* shift. These steroidal products have the favorable feature of bearing a versatile substituent at C-7.

Cross Couplings with Subsequent Diels–Alder Reactions

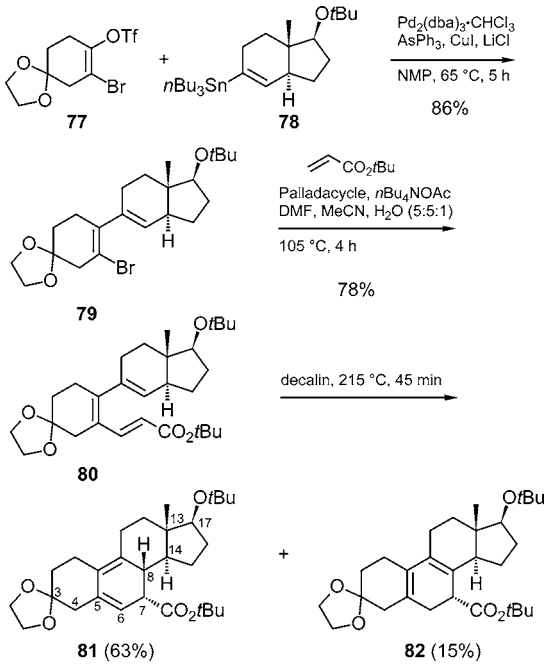
Another potentially powerful sequence arises by combining one or two intramolecular Heck-type couplings with an intra- or intermolecular Diels–Alder addition. An all-intramolecular version of such a sequence has been shown to proceed reasonably smoothly for terminally alkoxycarbonyl-substituted 2-bromotrideca-1,11-diene-6-ynes (*E*/*Z*)-**83** under palladium catalysis at 130 °C (Scheme 14). At 80 °C, the sequential reaction stops after the two consecutive Heck-type cyclizations with subsequent β-dehydropalladation only from the terminal methyl group to give *cis*/*trans*-**84**, which cannot undergo 6π-electrocyclization.[17] At 130 °C with potassium carbonate as a base, *trans*-**84** undergoes intramolecular Diels–Alder reaction to give the tetracycle **85**, while *cis*-**84** remains unchanged.

Obviously, systems that can undergo intramolecular Diels–Alder reactions can also be set up by enyne

Scheme 12. Chemoselective Stille–Heck Coupling Sequences of 2-Bromocyclohexenyl Triflate

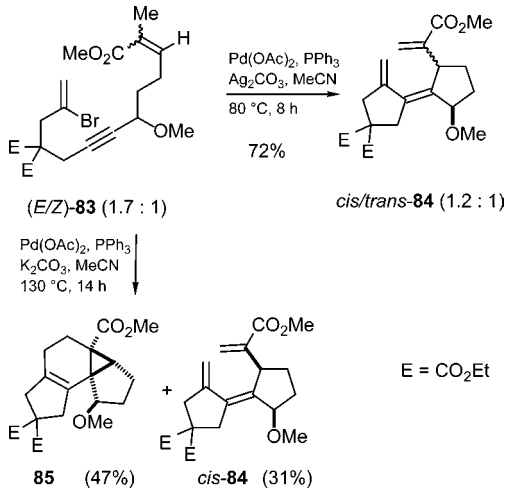


Scheme 13. Assembly of the Steroid Skeleton Using the Stille–Heck Coupling Sequence

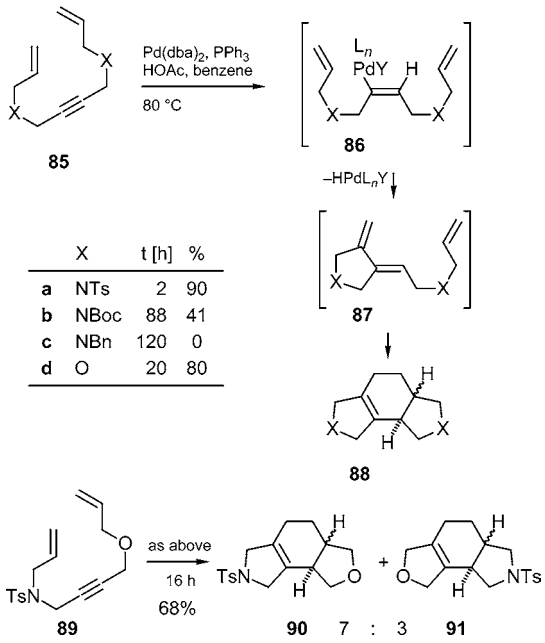


cycloisomerizations. A few examples of this domino reaction have been reported by Trost et al. employing unsymmetrical dienynes with terminal triple bonds.[35] In this way, several [6-6-5]- and [5-6-5]-carbotricycles were prepared, yet in most cases a two-step operation was necessary as the Diels–Alder addition only occurred above 140 °C. Symmetrical dienynes with a central triple bond and heteroatoms in the tethers are easily accessible and by this reaction mode can yield heterotricyclic compounds (Scheme 15). Thus, the dienynes **85** upon treatment with [Pd(dba)$_2$] in the presence of acetic acid and triphenylphosphine at 80 °C gave the diaza- and dioxatricycles **88**.[36] Yields were best (90%) with *N*-tosyl linkers; with *N*-Boc groups the reaction was slower (41% yield), and with *N*-benzyl linkers only decomposition occurred. This may be due to coordination and blocking of the catalyst by the more Lewis-basic precursors.[37]

Scheme 14. The All-Intramolecular Domino Heck–Diels–Alder Reaction



Scheme 15. A Domino of Enyne Cycloisomerization and Intramolecular [4+2] Cycloaddition



	X	t [h]	%
a	NTs	2	90
b	NBoc	88	41
c	NBn	120	0
d	O	20	80

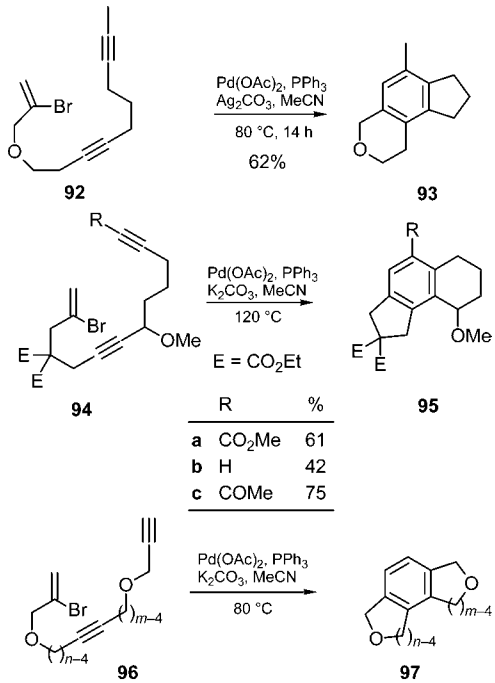
The *cis*- and *trans*-diastereomers of **88** were formed in a ratio of 1.8:1, and this ratio did not change in other solvents, at different temperatures, with other catalyst precursors, or under high pressure (10 kbar). In view of the apparent influence of the tether, the unsymmetrical oxaza-precursor **89** gave a 7:3 mixture of tricycles **90** and **91**. Obviously, the hydridopalladation of the triple bond occurred with some regioselectivity such that intramolecular carbopalladation of the allylamine predominated. It is noteworthy that these intramolecular Diels–Alder reactions of the intermediate trienes **87** already occur under the employed conditions, that is, at 80 °C.

Cycloisomerizations of 1,ω-enynes to yield 1,2-dialkylidenecycloalkanes and subsequent intermolecular Diels–Alder reactions have frequently been employed by Trost et al.[35] toward the synthesis of various natural products. Such cycloisomerizations or corresponding intramolecular Heck reactions of 2-bromoalka-1,ω-dienes can favorably be carried out in the presence of the respective dienophile to give significantly higher yields of the cross-coupling-cycloadducts.[36,38]

Tricyclizations of 2-Bromoenediynes

While the domino cyclizations of 2-bromodienynes lead to tricycles with a central cyclohexa-1,3-diene moiety (vide supra), an analogous cascade tricyclization of 2-bromoalk-1-enediynes can be applied to prepare angularly bisannelated benzene derivatives. The viability of this concept was first demonstrated by conversion of the bromoenediyne **92** to the tricycle **93** (Scheme 16),[39] while others prepared similar systems by all-intramolecular cascade cycloisomerization of triynes,[40a] or by intra-intermolecular cascade couplings of 2-bromoenynes or diynes with added alkynes.[40] Screening different substituents on the second triple bond revealed that a wide range of functionalities

Scheme 16. Angularly Bisannelated Benzene Derivatives Obtained by Palladium-Catalyzed Tricyclization Cascades

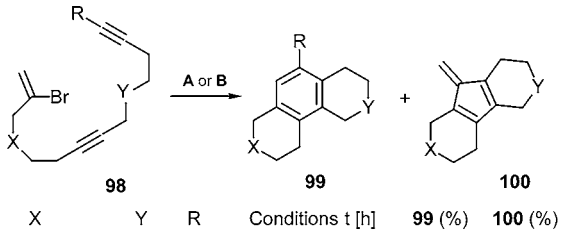


	R	%
a	CO_2Me	61
b	H	42
c	COMe	75

	n	*m*	t [h]	%		*n*	*m*	t [h]	%
a	5	5	2	50	**d**	6	5	2	33
b	5	6	2	48	**e**	7	5	1	13
c	5	7	2	4	**f**	8	5	1.5	0

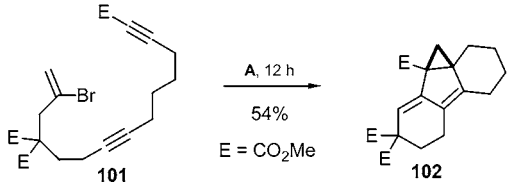
including just terminal triple bonds are compatible with this methodology, as all precursors **94** cleanly reacted to the tricycles **95**. A set of easily accessible dioxa-compounds **96** was also subjected to the cyclization conditions to evaluate the influence of different tether lengths. The outcome showed similarities to the cascade couplings of 2-bromodienynes in that the reaction gave good results when five- or six-membered rings are formed, but was less efficient for the preparation of larger rings.[41]

Scheme 17. Cascade Cyclizations of 2-Bromotetradec-1-ene-7,13-diynes

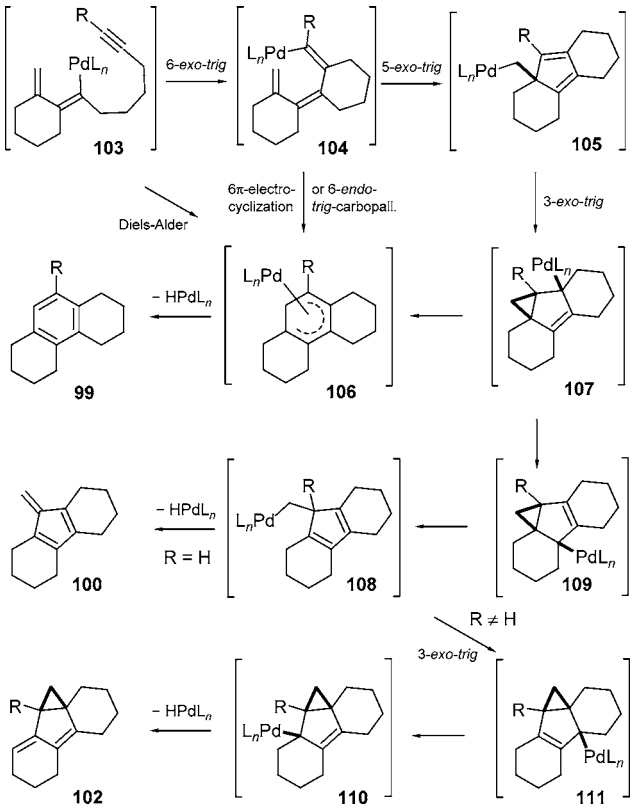


	X	Y	R	Conditions	t [h]	**99** (%)	**100** (%)
a	O	O	H	**B**	2	0	52
b	$C(CO_2Me)_2$	CH_2	H	**A**	1	0	74
c	$C(CO_2Me)_2$	CH_2	*t*$BuMe_2Si$	**A**	20	79	0
d	$C(CO_2Et)_2$	CH_2	Ph	**B**	10	40	0

A: $Pd(OAc)_2$, PPh_3, K_2CO_3, MeCN, 60 °C. **B**: $Pd(OAc)_2$, PPh_3, HCO_2Na, DMF, 60 °C.



Scheme 18. Mechanistic Considerations Concerning the Various Cascade Cyclizations of Enediynes



Just as with the cascade tricyclizations of 2-bromodienynes (see above), unexpected results were obtained when trying to access [6-6-6]-tricycles, in this case octahydrophenanthrene derivatives, from 2-bromotetradec-1-ene-7,13-diynes **98** (Scheme 17). The aromatic compounds **99** were only obtained from precursors **98c**,**d** with a *tert*-butyldimethylsilyl or a phenyl substituent on the triple bond, and the bisannelated fulvene derivatives **100a**,**b** arose from precursors with terminal triple bonds.[42,43] Yet another reaction mode showed up with the alkoxycarbonyl-substituted **101** which furnished a tetracyclic product with the skeleton **102** as ascertained by extensive NMR studies.[44]

These results presented the clue to a rationalization of the three different cascade cyclization modes (Scheme 18). The bisannelated arenes **99** could arise either from intermediate **103** by an intramolecular [4+2] cycloaddition or alternatively from **104** by either 6π-electrocyclization or 6-*endo-trig* carbopalladation, all leading to a palladated bisannelated cyclohexadiene derivative **106** that eventually undergoes β-dehydropalladation to an arene **99**. In view of the observed formation of fulvenes **100** as well as the tetracyclic product **102**, both with a central five-membered ring, and the finding by Negishi et al. that perceived 6-*endo-trig* carbopalladations actually occur as sequences of 5- and 3-*exo-trig* cyclizations with subsequent cyclopropylcarbinyl- to homoallylpalladium rearrangement,[45] the intermediate **106** leading to products of type **99** most probably also arises from intermediates **105** and **107** en route to products of types **102** and **100**. All of these σ- and π-allylpalladium species **105**−**109** are connected with

each other by cyclopropylcarbinyl to homoallyl or σ-π-σ-allylpalladium rearrangements. Fulvenes are formed from **108** by β-dehydropalladation, and the tetracyclic product **102** is formed by yet another sequence of 3-*exo-trig* carbopalladation, allyl shift, and β-dehydropalladation.

Conclusion and Future Perspectives

Although the Heck reaction at first glance appears to be just a, albeit very versatile, new direct synthesis of disubstituted alkenes, the skillful execution of this reaction on appropriate substrates as a sequential or domino-type transformation can lead to an impressive increase in molecular complexity in a single or just a few operations. According to the systematic studies presented here, the reaction mode for a given substrate can be predicted in most cases. Yet, there is ample room for more unexpected routes to other oligocyclic skeletons. This fact ensures that research on these types of transformations is far from being complete, and therefore at least the next decade will see a continuing growth and advancement of this chemistry. This will undoubtedly lead to an ever-increasing use of the Heck reaction in natural product synthesis as well as in industrial processes, especially for the production of fine chemicals such as pharmaceuticals and modern agrochemicals.

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