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Iron- or Palladium Catalyzed Reaction Cascades Merging Cycloisomerization and Cross Coupling Chemistry

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Abstract: A conceptually novel reaction cascade is presented, which allows readily available enynes to be converted into functionalized 1,3-dienes comprising a stereodefined tetrasubstituted alkene unit; such compounds are difficult to make by conventional means. The overall transformation is thought to commence by formation of a metallacyclic intermediate that evolves via cleavage of an unstrained C–X bond in its backbone. This non-canonical cycloisomerization process is followed by a cross coupling step, such that reductive C–C-bond formation regenerates the necessary low-valent metal fragment and hence closes an intricate catalytic cycle. The cascade entails the formation of two new C–C bonds at the expense of the constitutional C–X entity of the substrate: importantly, the extruded group X must not be a heteroelement (X = O, NR), since activated β -C–C bonds can also be broken. This manifold was reduced to practice in two largely complementary formats: one procedure relies on the use of alkyl-Grignard reagents in combination with catalytic amounts of Fe(acac)₃, whereas the second method amalgamates cycloisomerization with Suzuki coupling by recourse to arylboronic acids and phosphine-ligated palladium catalysts.

Introduction

Enyne derivatives **A** react with various low-valent metal fragments [M] via oxidative cyclization to give metallacyclic intermediates **B** in the first place (Scheme 1).^[1, 2] This reactivity mode is a common entry point into the rich cycloisomerization and cycloaddition chemistry developed during the last decades that exploits the different possibilities by which a metallacycle can evolve.^[3-12] β -Hydride elimination is arguably the most fundamental of these downstream processes, which leads to dienes of type **C** or **D**; only in rare cases can reductive elimination with formation of a formal [2+2] cycloadduct of type **E** compete.^[13-15] In contrast, various intra- as well as intermolecular insertion reactions of π -systems are fast enough to outperform β -hydride elimination; a few prototype structures within reach are shown in Scheme 1.^[3-10]





In an attempt to further increase the portfolio of accessible structural motifs, our group has recently proposed a non-canonical reaction manifold.^[16] Specifically, we conceived that a metallacyclic intermediate of type **L** comprising a potential leaving group X in its backbone should favor ring opening over β -hydride elimination because the antibonding C–X σ^* orbital is well aligned with the electron rich C–[M] bond; this preference is amplified by the rigidity of the bicyclic core which impedes puckering of the metallacycle as necessary for cleavage of the annular C–H bond.^[17, 18] In contrast to β -hydride elimination, however, the rupture of the C–X bond does not regenerate a catalytically active low-valent metal species [M]; therefore the reaction must come to a

hold unless a separate process is juxtaposed that ensures turnover. Cross coupling was deemed adequate for this purpose, in that the reductive C–C-bond forming step would adjust the redox state of the metal fragment as necessary for entertaining a catalytic cycle.

This conceptually novel cycloisomerization/cross coupling cascade has been successfully reduced to practice with the aid of bare iron catalysts in combination with alkyl-Grignard reagents as the nucleophilic reaction partners.^[16] Iron was chosen because it is cheap and benign and had proven effective in many different cross coupling and cycloisomerization reactions.^[19] Moreover, its propensity to form ate-complexes^[20-22] could provide an additional driving force since alkylation at the stage of the ferracycle to give a charged intermediate of type **L** (M = Fe) renders the metal more electron rich. The escorting magnesium cation might engage with the leaving group; in so doing, it might well activate the C–X bond and, at the same time, relieve the transition state from possible geometric constrains. These factors are thought to synergize and hence render the overall transformation fast, facile and productive.

In fact, the many excellent results obtained with Fe(acac)₃ cat./RMgX concur with this mechanistic rationale.^[16] From a conceptual viewpoint, however, the net cycloisomerization/cross coupling cascade should not be limited to the use of iron catalysts and organomagnesium compounds; other catalyst/nucleophile combinations might increase the substrate scope and could bear advantages in terms of functional group compatibility.^[23] As outlined below, we have in fact been able to develop an alternative manifold using palladium catalysis, which nicely complements the original iron-based protocol.

Results and Discussion

Iron catalyzed reaction cascades of enynes with heteroatom tethers: The readily available enyne **1** served as model compound for reaction optimization. This substrate was deemed particularly adequate since the electron deficient alkene unit will favor oxidative cyclization with formation of a metallacycle **2**, which in turn should benefit from the partial enolate character that the ester does impose.^[24] At the same time, this substituent serves as a chemical probe: it shows whether or not the iron catalyzed reaction is fast enough to outperform uncatalyzed attack of the organomagnesium reagent onto the ester. Finally, the good leaving group properties of a phenolate are thought to expedite the envisaged bond cleavage.

Table 1. Optimization of the Reaction Conditions.



Entry	Precatalyst	Loading	Additive	t [min]	Conversion	Yield ^[a]	E:Z ^[b]
		[mol%]	[mol%]		[%, NMR]		
1	Fe(acac)₃	20		≤ 20	quant.	86 %	97:3
2	Fe(acac) ₃	20	tmeda (20)	10	96	91 %	97:3
3	Fe(acac) ₃	20	dppe (20)	80	quant	82 %	97:3
4	Fe(acac) ₃	10		50	quant	91 %	97:3
5	Fe(acac) ₃	5		60	93	84 %	98:2
6	Fe(acac)₃	5		120	quant	90 %	98:2
7	Fe(acac) ₃	1		1140	93	55 %	98:2
8	FeBr ₂	20		600	quant	nd	98:2
9 10	$\mathbb{R}_{R}^{P_{1}} \mathbb{R}_{R}^{P_{1}} \mathbb{R}$	20 20		120 120	quant quant	nd nd	95:5 97:3
11	Fe Li ⁻ (tmeda)	20		180	0		

[a] Isolated yield of pure product. [b] Isomer ratio at the tetrasubstituted alkene unit; nd = not determined.

As evident from the results compiled in Table 1, addition of cyclohexylmagnesium chloride to a solution of enyne **1** and catalytic amounts of Fe(acac)₃ (20 mol%) in THF furnished dienoate **3c** in excellent yield; the reaction proceeded within minutes at low temperature. Importantly, the central tetrasubstituted alkene unit of **3c** was formed with impeccable regio- and stereoselectivity (*E*:*Z* ≥ 97:3). This outcome is consistent with intervention of a metallacyclic intermediate of type **2**, the alkenyliron unit of which eventually succumbs to cross coupling^[25-30] whereas the alkyliron side triggers ring opening. In any case, the cascade process engenders a highly selective formation of two vicinal C–C bonds at the expense of the C–O bond of the former enol ether that is cleaved during the reaction.

In practical terms, it is rewarding that the simple and ligand-free system comprising nonhygroscopic Fe(acac)₃ and RMgCl gave optimal results; additives such as tmeda or dppe are neither necessary nor beneficial. The catalyst loading could be lowered to 5 mol% without compromising the outcome, except that the reaction proceeded more slowly; the same was noticed on replacement of Fe(acac)₃ by FeBr₂. It is mechanistically relevant that the structurally well-defined Fe⁰ complex [(dippp)Fe(C₂H₄)₂] was also found to be catalytically competent (entry 9).^[31, 32] Since Grignard reagents readily reduce the analogous Fe¹ complex [(dippp)FeBr(C₂H₄)] to the Fe⁰ species, this precatalyst was similarly effective (entry 10). Surprisingly though, the bimetallic Fe⁰ complex [CpFe(C₂H₄)₂][Li(tmeda)], which had previously been used as catalyst for Alder-ene type reactions, [4+2], [2+2+2] and [5+2] cycloadditions,^[32, 33] failed to afford product **3c** under otherwise identical conditions for reasons that are currently not clear (entry 11).

Our group has recently shown that the reaction of FeX_n (n = 2, 3) with cyclohexylmagnesium chloride is a highly involved process, in which disproportionation of the transient organoiron species and/or allylic C-H activation processes will eventually interfere.^[31, 34] It was for this reason that this particular nucleophile had been chosen for reaction optimization. The fact that the cyclohexyl group was transferred almost quantitatively augured well for the scope of the reaction with regard to the nucleophilic partner. Indeed, a range of (functionalized) alkyl-Grignard reagents performed nicely (Table 2); even the isopropyl group was successfully transferred, although cross coupling reactions of secondary alkyl donors in general are often plagued by isomerization to the linear isomers via rapid M–H elimination/re-addition (entry 4);^[35] of the primary Grignard reagents investigated, only TMSCH₂MgCl failed to participate in the cascade, most likely for the β -silicon effect that is thought to stabilize the transient organoiron species.^[36] The alkyl substituent delivered by the Grignard reagent and the relocated alkenoate group were invariably found to reside on the same side of the newly formed tetrasubstituted alkene unit of the resulting major isomer. This stereochemistry was assigned by numerous NOE experiments (Figure 1) and confirmed by crystallographic data. The structure of compound **3f** in the solid state (Figure 2) is representative for a number of other cases that were

equally ascertained (for three additional X-ray structures, see the Supporting Information). As an important limitation of this iron catalyzed procedure, however, we note that aryl-Grignard reagents proved largely inadequate; the expected products were obtained in low yields and proved difficult to separate from biaryl derivatives formed as by-products by competitive homo-coupling of ArMgBr; the examples shown in entries 8 and 21 are representative.



Figure 1. Representative example for the NOE-based stereochemical assignment.



Figure 2. Structure of one of the two independent molecules of compound 3f in the unit cell.

Entry	Substrate	RMgX	Product		Yield (<i>E/Z</i>) ^[b] [%]
1 2 3 4	COOMe	MeMgBr nPentMgCl C ₆ H ₁₁ MgCl iPrMgCl	COOMe	3a 3b 3c 3d	93 84 (93:7) 90 (98:2) 76 (94:6) ^[c]
5	1 Me		Me	3e	73 (90:10) ^[c]
6		├──MgBr		3f	9 (≥ 99:1)
7		OMgBr		3g	94 (≥ 99:1)
8		∽0 PhMgBr		40a	< 25 (99:1)
9	COOMe	MeMgBr	С	5a	90 (≥ 99:1)
10		├── MgBr	COOMe	5b	72 (≥ 99:1)
	4		∼∽∽ ^R		
11	6 SiMe ₃	MeMgBr	COOMe Me ₃ Si Me	7	93 (≥ 99:1)
10	COOMe		OH	0-	
12			COOMe	9a 9b	95 74 ^[e]
	8 Ph	r -	Ph		
14	MeO 10 Me	MeMgBr	MeO Me COOMe	11	89 ^[c]
			ОН		[c]
15	MeO 12 Me	MeMgBr	MeO COOMe	13	94
16	Ms N	MeMgBr	NHMs	15	64 (90.10)
10	COOMe	MEMBE	COOMe	15	04 (50.10)
	14		Me		
17		├ ──MgBr	COH OSCO Tol	17	74 (99:1) + 22 ^[f]
18	COOMe	∫ ^O MgBr	ОН	19a	81 (95:5) ^[c, g]
19	18	∽о MeMgBr	MeR	19b	64 ^[c, g]
20	Me	C ₆ H ₁₁ MgCl		19c	72 (73:27) ^[c, g]
21		PhMgBr		19d	37 (92:8) ^{,c,u, g}

Table 2. Iron catal	vzed cycloisomeriz	ation/cross.cou	pling cascade. ^[a]
	y200 0y0101501110112		ping cuscuuc.

[a] Unless stated otherwise, all reactions were carried out with Fe(acac)₃ (5 mol%) in THF at -30 °C. [b] Yield of isolated pure product; *E/Z* ratios as determined by NMR. [c] Using 20 mol% of Fe(acac)₃ as precatalyst. [d]

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Considerable homocoupling of PhMgBr was noticed; the resulting biphenyl proved difficult to separate from the product. [e] The *E/Z* ratio changes significantly with reaction time, see Text. [f] The minor product is the oxa-Michael adduct formed by 1,4-additon of the phenol –OH group to the alkenyl sulfone. [g] At 0 °C; Ms = methanesulfonyl.

Different substituents on their alkyne terminus of the enyne substrates were tolerated, including a silyl group that allows for further functionalization. In this context, it is emphasized that formation of products **9** was accompanied by a gradual but substantial loss of isomeric purity on prolonged stirring; specifically, the *Z/E* ratio for **9a** decreased from an appreciable 96:4 after 10 min to 41:59 after 90 min reaction time. We tentatively ascribe this secondary process to a high degree of charge delocalization and a certain steric congestion in the product. This major exception notwithstanding, the highly selective course of the cycloisomerization/cross coupling cascade allows isomeric pairs of products to be obtained by permutation of the alkyne terminus and the substituent R delivered by the Grignard reagent; dienoate **3b** and its stereoisomer **5a** illustrate the point.

Compounds **11** and **13** indicate that even significant changes in the electronic character of the central aryl ring are largely inconsequential. In accord with previous experiences with iron catalyzed cross coupling,^[25-28, 37] the compatibility of the additional ester group in **12** further illustrates the kinetic selectivity of the process, in that the organomagnesium reagent is consumed before it gets a chance to attack the electrophilic substituent. Moreover, variations of the acceptor site (alkenyl sulfone) and of the leaving group (anilide) are possible (entries **16**, 17): the fact that product **17** is prone to undergo a secondary Michael addition of the phenol to the alkenylsulfone forecasts further opportunities for reaction development. Finally, a much more dramatic structural change is manifest in substrate **18** featuring an aliphatic backbone: the increased conformational flexibility is expected to lower the propensity for metallacycle formation; likewise, an alkoxide is a much less favorable leaving group than a phenolate. Despite these arguments, enyne **18** was readily transformed into dienoates **19** under standard conditions, except that the reaction was best carried out at 0 °C rather than –30 °C.

Iron catalyzed cascades involving C–C bond cleavage: The concept of letting a metallacycle of type **L** evolve by the cleavage of a constitutional bond rather than a peripheral C–H group is not limited to the extrusion of phenolates, alkoxides or anilides. As manifest in the examples shown in Scheme 2,

unstrained but activated C–C bonds can be cleaved analogously.^[38-41] Specifically, enyne **20** was converted into diene **21** in good yield by an overall process in which two C–C bonds are formed while another C–C bond is concomitantly broken; changing the alkyl-Grignard reagent did not affect the course (**20** \rightarrow **23**). Once again, the transformation turned out to be highly regio- and stereoselective with regard to the newly formed tetrasubstituted alkene. In contrast, the configuration of the migrating enoate proved irrelevant, since *E*-**20** and *Z*-**20** led to the exact same isomer **21** as the only detectable product.



Scheme 2. a) C₆H₁₁MgCl, Fe(acac)₃ (20 mol%), THF, -30 °C, 70 % (*E*:*Z* = 99:1). b) C₆H₁₁MgCl, Fe(acac)₃ (20 mol%), THF, -30 °C, 70 % (*E*:*Z* = 99:1). c) **22**, Fe(acac)₃ (20 mol%), THF, -15 °C, 63 % (*E*:*Z* = 98:2). d) MeMgBr, Fe(acac)₃ (20 mol%), THF, -30 °C, 67 %; E = COOMe.

The comparison with substrate **24** indicates that the malonate leaving group in **20** is mandatory for the full cascade to be passed through. While enyne **24** obviously engaged in metallacycle formation and iron catalyzed cross coupling, cleavage of the less activated C–C bond embedded into the bicyclic skeleton of the putative intermediate **25** has not taken place. The densely decorated dihydroindene derivative **26** was obtained in diastereomerically pure form upon hydrolytic work-up.

Mechanistic considerations: Although formation of ferracycles of type **L** is plausible and consistent with all available experimental data, it is not the only conceivable mechanistic scenario. Rather, a stepwise process commencing with an iron catalyzed carbometalation of the alkyne in **N**,^[42-45] followed by a Michael addition of the resulting alkenylmetal species **O** could be envisaged (Scheme 3); in this case, the resulting (C- or O-metalated) enolate **P** could be prone to elimination to give the final product **Q**. Various pieces of evidence, however, speak against such a pathway (Scheme 4).



Scheme 3. Conceivable but unlikely alternative mechanism comprising an iron catalyzed carbometalation followed by 1,4-addition/elimination.



Scheme 4. Control experiments of mechanistic relevance.

First and foremost, aryl alkynes **27** and **28** – without or with a potentially directing oxygen atom at the arene *ortho* position – both failed to undergo iron catalyzed carbomagnesiation under the chosen conditions, even when the mixtures were allowed to reach ambient temperature. Moreover, a literature report had shown that the iron catalyzed carbolithiation of the related substrate **29** is regio-unselective, furnishing the isomers **30** and **31** in a 82:18 ratio.^[42] Even if one assumes that it is the assistance provided by the flanking alkene in **6** which entails facile carbometalation^[46] without participating in metallacycle formation, the directing effect of the silyl group would almost certainly counteract any try to place the incoming [MgBr]-unit next to it;^[47] as a consequence, formation of product **7** would almost certainly be unselective. Taken together, these data speak against carbometalation as the triggering event.



Scheme 5. a) $C_6H_{11}MgCl$, $Fe(acac)_3$ (20 mol%), THF, $-30 \degree C$, 53 % (34:35 = 3.8:1). b) MeMgBr, $Fe(acac)_3$ (1 equiv.), THF, $-30 \degree C \rightarrow RT$, quant. (NMR, 39:40 = 69:31).

The examples compiled in Scheme 5 show that a Michael acceptor unit is not needed either for the cascade to proceed. Specifically, compound **32** bearing a terminal alkene rather than an enoate entity did engage in the full cascade. As expected, the activated malonate unit allowed even C–C-bond cleavage to occur, although the slower overall reaction rate (compared to **20**) allowed hydride transfer to compete with cross coupling of the cyclohexyl unit.^[48] In line with the results outlined above, the reaction of the unactivated substrate **37** stopped prior to bond cleavage. Arguably most telling in mechanistic term, however, is the fact that traces of product **40** were detected in the crude material, in which *two* methyl groups derived from MeMgBr got incorporated, one on either end of the original enyne π -system; this compound accounted for up to 31 % when the Fe(acac)₃ loading was increased to one equivalent. This outcome speaks for a metallacyclic atecomplex of type **38** as the key reactive intermediate, in which the iron center is already loaded with (at least) two methyl substituents.^[20-22] Since Csp²–Me coupling is arguably easier than Csp³–Me coupling, **39** is expected to be the major product after work-up, whereas **40** eventually accumulates on prolonged reaction time and/or under more forcing conditions.

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Palladium catalyzed cycloisomerization/cross coupling cascade: Although many iron catalyzed cross coupling reactions are distinguished by remarkable (kinetic) functional group compatibility,^[25-28, 37] the need for organomagnesium reagents RMgX as the preferred coupling partners implies certain limitations. Another notable shortcoming is the fact that only alkyl-Grignard reagents will engage in the iron catalyzed cascade, whereas their aryl counterpart gave rather poor results. Therefore we set out to establish alternative procedures that accommodate alternative nucleophilic partners.



Scheme 6. Example of a chlorosilane-assisted, nickel catalyzed cycloisomerization/cross coupling cascade.

Although some success was attained with organozinc reagents in the presence of nickel catalysts (Scheme 6),^[49] the merger of the venerable Suzuki coupling^[50] with the new enyne cycloisomerization chemistry was more rewarding. To this end, however, the reaction conditions had to be carefully optimized, not least because the active palladium catalyst proved rather unstable under the quite forcing conditions that turned out to be necessary; rapid precipitation of Pd-black was observed in most cases. Best results were secured with $Pd(OAc)_2$ in combination with SPhos as the ligand,^[51] K₃PO₄ as the base, and degassed 1,4-dioxane/water (1:2) at 90 °C; interestingly, it is beneficial to complement the mixture with EtOAc as an additive (10 equiv.), whereas the use of EtOAc as the solvent gave inferior results. It is also important to note that the use of the corresponding arylboronic acid rather than the popular pinacol boronates was mandatory.



Scheme 7. Palladium catalyzed cycloisomerization/cross coupling cascade. [a] The reaction has to be stopped after \leq 10 min to avoid (partial) Michael addition of the phenole to the enoate.

Under these conditions, the method allowed aryl groups of largely different character to be transferred with good to excellent yields (Scheme 7).^[52] If the aryl substituent is electron rich as in compounds **40g** and **40h**, the reaction has to be stopped immediately once full conversion is reached, since prolonged stirring results in oxa-Michael addition of the phenol unit to the enoate. As expected, it proved unnecessary that the enyne substrate itself comprises an aromatic ring as evident from the formation of products **43** and **44**. The regio- and stereoselectivity of the palladium catalyzed transformation were outstanding in all cases investigated in that a single geometric isomer was formed within the limits of detection of NMR and GC/MS. We take this rewarding and consistent pattern as an indication that the palladium catalyzed cascade follows a pathway similar to that of the iron catalyzed process, even though a more thorough mechanistic investigation is needed to confirm or disprove this notion.



Scheme 8. a) 49, $Pd(OAc)_2$ (20 mol%), SPhos (40 mol%), K_3PO_4 , EtOAc (10 equiv.), $H_2O/1,4$ -dioxane, (2:1), 90 °C, 63 %. b) 50, $Pd(OAc)_2$ (20 mol%), SPhos (40 mol%), K_3PO_4 , EtOAc (10 equiv.), $H_2O/1,4$ dioxane, (2:1), 90 °C, 67 %. c) $B_2(OH)_4$, $Pd(OAc)_2$ (20 mol%), SPhos (40 mol%), K_3PO_4 , EtOAc (10 equiv.), $H_2O/1,4$ -dioxane, (2:1), 90 °C, 69 %. d) 51, MeLi, then $Pd_2(dba)_3$ (20 mol%), [Et₃O·BF₄], 0 °C \rightarrow RT, 70 %; dba = dibenzylideneacetone.

As expected, an alkenylboronic acid also performed well as the nucleophile (Scheme 8), whereas attempted use of alkylboronic acids met with failure. This limitation is it overly grave since alkyl groups transfer exceedingly well under iron catalysis (see above); if they carry substituents that are incompatible with the use of Grignard reagents, the corresponding 9-alkyl-9-BBN reagent can be used,^[53, 54] although removal of the extra boron residues tends to make the purification of the crude material more cumbersome. Moreover, product **48** shows that boryl transfer is possible:^[55] interestingly though, the use of tetrahydroxydiboron resulted in selective reduction of the triple bond of the substrate to give **47**, without any borylative cyclization being detectable. This somewhat counterintuitive outcome has precedent in the literature.^[56] In contrast, activation of B₂(pin)₂ with MeLi generated a suitable boryl-transfer agent, although the purification of the resulting product proved difficult, most likely because the released phenolate is non-innocent vis-à-vis the boron

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moiety. The problem was solved by in situ O-alkylation with Meerwein salt, which furnished the elaborate building block **48** in respectable yield.^[57]

Conclusions

Two different incarnations of a conceptually novel reaction cascade are presented herein, which allow cycloisomerization to be merged with cross coupling chemistry in a non-canonical way. One procedure makes use of cheap, benign and ligand-free iron catalysts in combination with alkyl-Grignard reagents as nucleophiles, whereas the other protocol relies on phosphine-ligated palladium catalysts in combination with arylboronic acids. The overall transformation opens a highly regio- and stereoselective entry into dienoates comprising a tetrasubstituted double bond with up to four different (functionalized) substituents as handles for further functionalization. Compounds of this and related types are exceedingly difficult to make in stereodefined format otherwise;^[58] therefore their chemistry is underdeveloped, despite the many opportunities that the dense array of functional groups may provide. Moreover, we note a possibility for parallel synthesis inherent to the new route, which could be relevant given a certain structural relationship of the resulting products with compounds as important as the anticancer agent tamoxifen.^[59]



The two experimental procedures are largely complementary to each other, because they make use of different nucleophilic reaction partners (RMgX versus ArB(OH)₂). This rewarding aspect notwithstanding, we cannot help but emphasize the enormous reactivity difference: whereas the iron chemistry proceeds rapidly at temperatures as low as -30 °C, all palladium-based reactions required heating to +90 °C to ensure reasonable rates and full conversion. The exceedingly high driving force of the iron catalyzed process manifest in this differential is thought to indicate considerable opportunity for discovery of yet other chemically unorthodox but synthetically enabling transformations leading to the formation of one or more C–C-bonds. Our laboratory has already

encountered a few such cases in the past, wherein iron unlocks reactivity that is difficult or even impossible to harness otherwise;^[60] we plan to continue our quest into this promising chemical territory.

Experimental Section

All experimental details can be found in the Supporting Information. This material includes crystallographic abstracts, compound characterization data and copies of spectra of new compounds.

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For the Table of Contents



Non-Traditional: Iron as well as palladium catalysis allows cycloisomerization chemistry to be merged with cross coupling via metallacyclic intermediates that evolve in an unorthodox fashion into highly substituted 1,3-dienes. The overall reaction cascades entail formation of two new C–C bonds, while an unstrained C–X bond (X = O, NR, C(COOR)₂) in the substrate backbone is concomitantly broken.

Keywords: cross coupling · cycloisomerization · 1,3-dienes · iron catalysis · metallacycles · palladium