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VIP A Two-Component Alkyne Metathesis Catalyst System with an Improved Substrate Scope and Functional Group Tolerance: Development and Applications to Natural Product Synthesis

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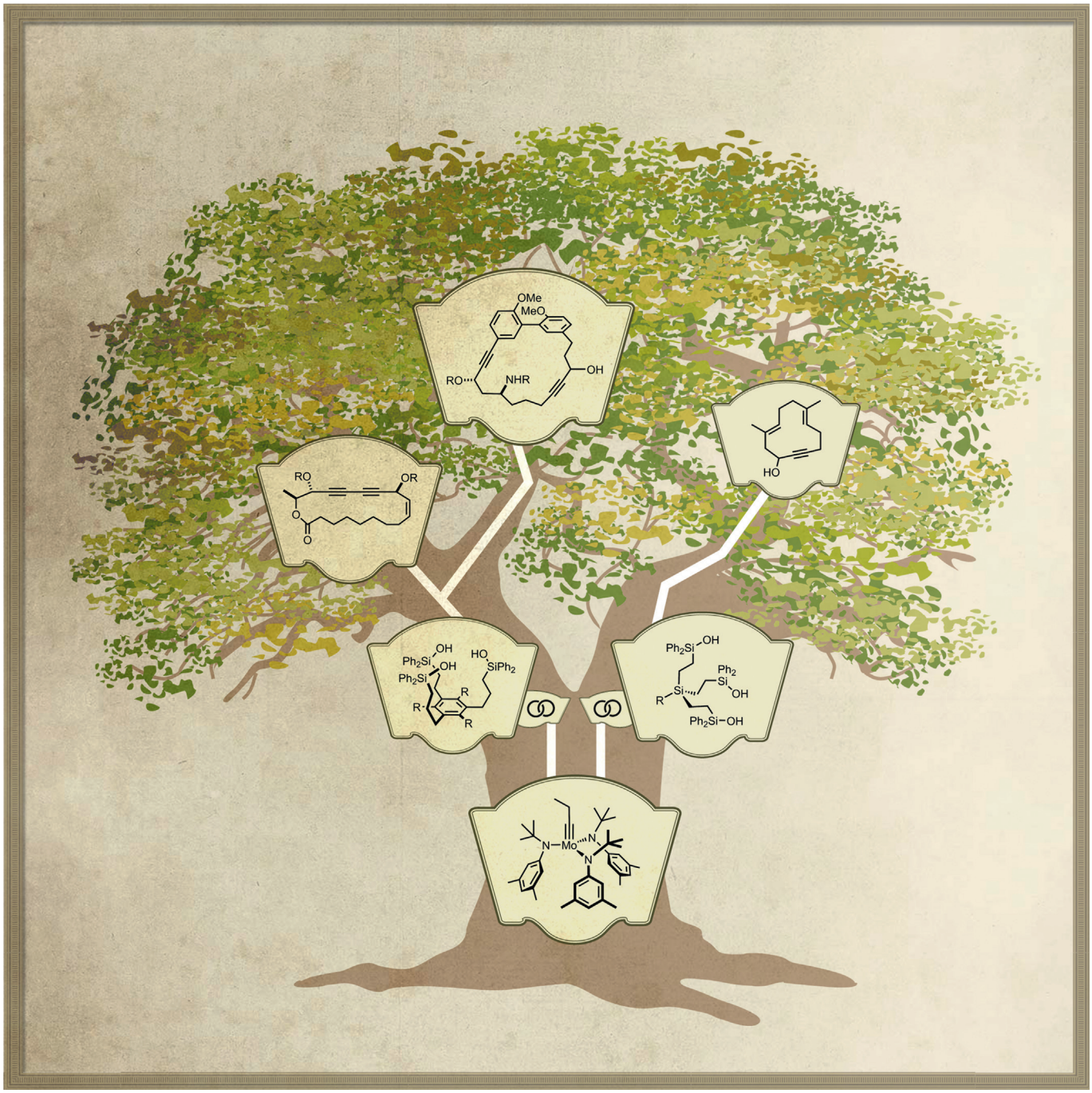
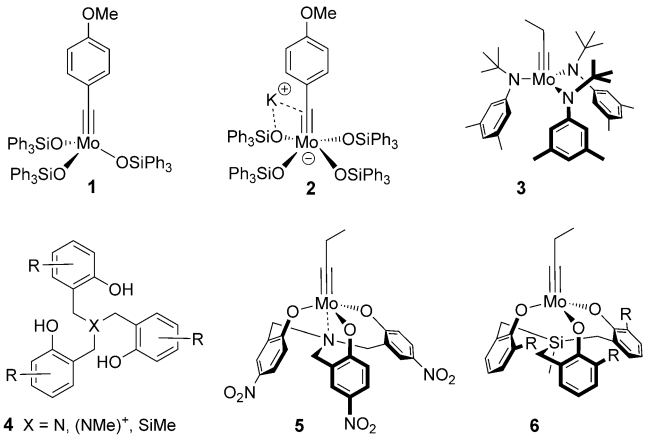


Abstract: Although molybdenum alkylidyne complexes such as **1** endowed with triarylsilanolate ligands are excellent catalysts for alkyne metathesis, they can encounter limitations when (multiple) protic sites are present in a given substrate and/or when forcing conditions are necessary. In such cases, a catalyst formed in situ upon mixing of the trisamidomolybenum alkylidyne complex **3** and the readily available trisilanol derivatives **8** or **11** shows significantly better performance. This two-component system worked well for a series of model compounds comprising primary, secondary or phenolic -OH groups, as well as for a set of challenging (bis)propargylic substrates. Its remarkable efficiency is also evident from applications to the total syntheses of manshurolide, a highly strained sesquiterpene lactone with kinase inhibitory activity, and the structurally demanding immunosuppressive cyclodiyne ivorenolide A; in either case, the standard catalyst **1** largely failed to effect the critical macrocyclization, whereas the two-component system was fully operative. A study directed toward the quinolizidine alkaloid lythrancepine I features yet another instructive example, in that a triyne substrate was metathesized with the help of **3**/**11** such that two of the triple bonds participated in ring closure, while the third one passed uncompromised. As a spin-off of this project, a much improved ruthenium catalyst for the redox isomerization of propargyl alcohols to the corresponding enones was developed.

Introduction

Alkyne metathesis has greatly benefitted from the introduction of molybdenum alkylidyne complexes endowed with silyloxy groups as ancillary ligands such as **1** and **2**,[1–5] which are distinguished by high activity as well as by a remarkable functional group tolerance.[6,7]



A rapidly growing number of applications to exceedingly challenging target molecules bears witness of their excellent profile; a few selected examples of key intermediates of previous total syntheses formed by ring closing alkyne metathesis (RCAM) catalyzed by complexes **1**, **2** or congeners[8,9] are shown below.[8–11]

While occasional limitations were encountered with sterically hindered or very electron-deficient substrates, surprisingly few functionalities seem to be incompatible.[1–6] This notion is corroborated by the results shown in Table 1, which surveys substituents that are known to be problematic for many transition metal catalysts. As can be seen, **1** is fully operational in the presence of primary alkyl iodides or bromides, an azide, a thioether, a sulfoxide, a sulfinamide, and even secondary or tertiary amines.[13–15] Suffice it to say that any of these groups is challenging—if not detrimental—for the otherwise so highly accomplished ruthenium-based olefin metathesis catalysts;[16] the latter, however, excel whenever it comes to protic substituents, where they encounter hardly any serious limitation. Although **1** and congeners also allow certain protic groups to be handled, the tolerance is not nearly as general. For example, secondary alcohol derivatives can often be transformed in acceptable yields under somewhat forcing conditions (Table 1, entries 12/13), whereas the attempted metathesis of a substrate containing a primary alcohol basically met with failure (entries 14/15).

This outcome is perhaps not overly surprising for a catalyst that owes its excellent performance to an intact siloxide ligand sphere.[1,2] It seems likely that the Ph_3SiO groups in **1** might be prone to partial or even complete exchange on exposure to a protic substrate; the more acidic and more readily accessible the protic site, the higher the likelihood for damaging the catalyst. If this analysis is true, the use of multivalent ancillary ligands might be one way to counteract this fatal exchange process. Therefore we investigated whether or not chelating siloxides improve the functional group tolerance of molybdenum alkylidyne complexes, in particular vis-à-vis protic groups.

In this context, recent contributions by Zhang and co-workers deserve mentioning, who introduced podand ligands of the general type **4** that afford chelate complexes of type **5** and **6** on reaction with **3**[17] as the precatalyst; **5** and **6** were applied with considerable success to material science, although their functional group tolerance has not been comprehensively tested.[18–22] Yet, the amine tether in **5** is positioned such that it necessarily coordinates the metal center, which in turn reduces the catalytic activity; although *N*-methylation fixes the problem, the synthesis of the required charged ligand **4b** (X = NMe^+) proved low-yielding and the solubility of the resulting cationic complex is poor.[18] Therefore, a second ligand genera-

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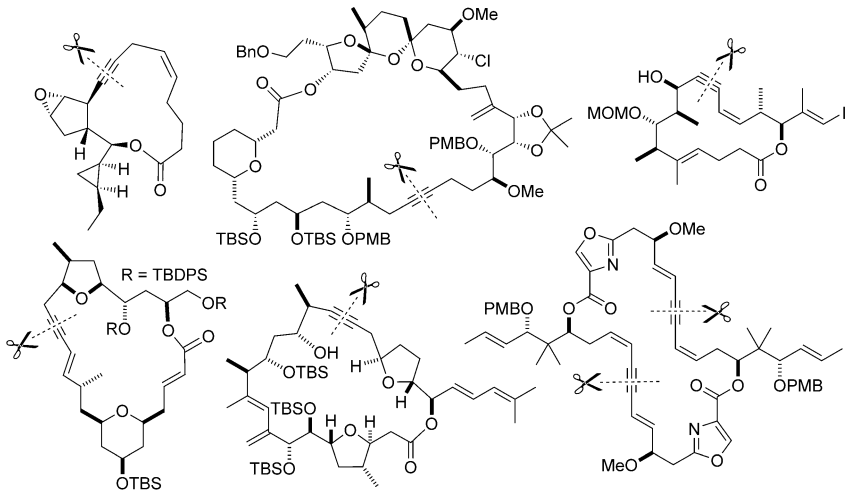
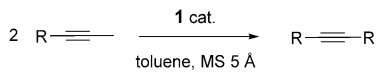
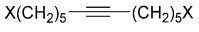
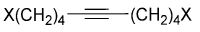
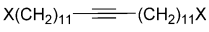
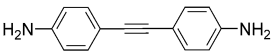
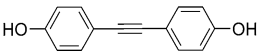
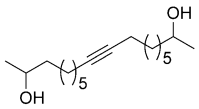
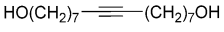


Table 1. Brief survey of the compatibility of **1** with challenging functional groups.



Entry	Product	mol %	*t* [h]	*T* [°C]	Yield [%]
1		1	1.5	20	91 (X = Br)
2		1	15	20	96 (X = N_3)
3		4	1	20	83 (X = piperidin-1-yl)
4		3	16	20	77 (X = NHBu)
5		2	2	20	85 (X = $S(CH_2)_{11}Me$)
6		5	16	80	75 (X = $S(O)(CH_2)_{11}Me$)
7		2	3	20	80 (X = NHBoc)
8		5[a]	22	20	67 (X = NS(O)*p*-Tol)
9		5	1.5	20	78 (X = I)
10		4	14	80	52
11		4	14	80	87
12		10	14	20	34
13		7	24	80	66
14		10	14	20	0
15		10	14	110	7

[a] A solution of the catalyst in toluene was added over the course of 1 h.

tion comprising a benzylsilane tether was introduced (**4c**, X = SiMe). Since the preparation requires several steps and the derived catalysts of type **6** work best in CCl_4 as the solvent (which is particularly problematic in conceived applications to macrocyclization reactions that usually require high dilution),[18] we set out to find practical alternatives that should be easy to make on scale, retain the many proven advantages of silanol ligands,[1–4] and allow alkyne metathesis to be applied to otherwise problematic substrates.

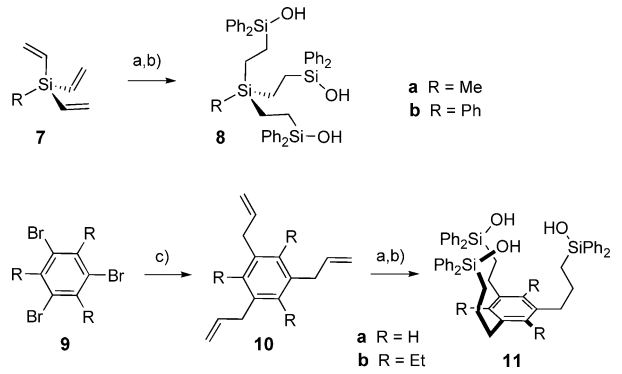
Results and Discussion

Ligand Synthesis and Evaluation

Possible chelate trisilanol ligands **8** were obtained in only one operation by hydrosilylation of **7** with diphenylchlorosilane followed by in situ hydrolysis of the Si–Cl unit (Scheme 1). As the substrates are cheap and commercial, such compounds are available in quantity. The preparation of **11a** (R = H) comprising a tethering phenyl group is only one step longer but equally scalable. With the idea in mind that a hexasubstituted arene unit might preorganize the ligand in a favorable alternating up/down conformation,[23] compound **11b** (R = Et) was prepared analogously.

For the preparation of complex **1**, Ph_3SiOH is first deprotonated and the resulting sodium (or potassium) salt is then slowly added to a solution of the readily accessible tribromoalkylidyne complex [ArC≡$MoBr_3$]·dme (Ar = *p*-$MeOC_6H_4$-).[1,2] The very poor solubility of the triple salts derived from **8** or **11**, however, precluded this procedure from being used. Therefore the protic ligands themselves were added to a solution of the trisamidomolybdenum alkylidyne complex **3**[17] in toluene; NMR inspection showed that the ligand exchange is rapid but a mixture of products is formed, independent of the addition time and the structure of the ligand precursor.[24] In contrast to the triphenolamine ligand **4a** (X = N), which caps a single alkylidyne unit with formation of the chelate complex **5**,[12] the trisilanols of type **8** and **11** act primarily as "cross-linking" agents.

In this context, the X-ray structure of compound **11b** is informative (Figure 1), which shows the expected alternating up/down pattern of the six alkyl substituents on the central benzene ring. Interestingly, all three silanol groups are oriented to the outside, away from each other. Although it is not clear if this particular conformation is retained in solution, it might provide an explanation why this compound failed to afford



Scheme 1. a) $Ph_2Si(H)Cl$, Karstedt's catalyst (0.5 mol%), toluene, 60 °C; b) H_2O, Et_3N, RT, 56% (**8a**), 58% (**8b**), 47% (**11a**), 54% (**11b**); c) allyltributylstannane, $Pd(PPh_3)_4$ (16 mol%), CsF, DMF, 120–135 °C, 76% (**10a**), 60% (**10b**); Karstedt's catalyst = platinum(0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane.

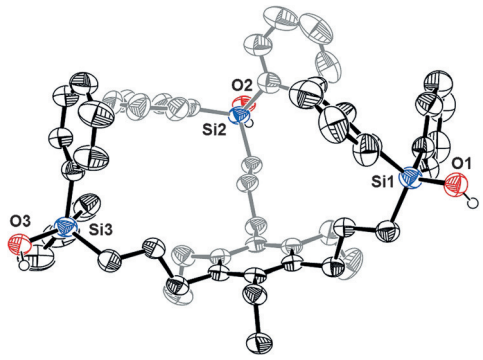


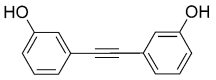
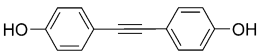
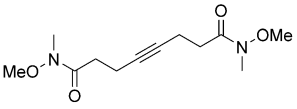
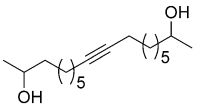
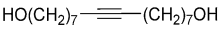
Figure 1. Structure of compound **11b** in the solid state; for details, see the Supporting Information.

a defined monomeric chelate complex on reaction with alkylidyne **3**.

The oligomeric character of the active species notwithstanding, the resulting mixtures proved effective in a number of challenging cases (Table 2). While a *meta*-propynyl phenol derivative was metathesized by **1** and **3**/**8a** or **3**/**11b** with similar ease (entries 1–3), the new catalyst system worked better for the *para*-analogue (entries 4–6). The difference is more clear-cut with the Weinreb amide derivative shown in entries 7/8, which reacted poorly with **1** but was transformed with remarkable ease with the help of **3**/**8a**; the very same is true for a secondary alcohol (entries 9–11). In the case of a substrate bearing a primary alcohol, the standard catalyst **1** failed, whereas the new two-component system furnished the desired product in respectable yields (entries 12–14).

Somewhat unexpectedly, the different trisilanol ligands **8** and **11** led to catalysts of similar activity and selectivity. Distinct differences became evident only with more elaborate substrates; the study directed toward the quinolizidine alkaloid lythrancepine I is representative, where the combination **3**/**11b** gave the best result (vide infra). In any case, the target oriented synthesis projects outlined below provide additional evidence for the superior performance of the new two-component catalyst when it comes to challenging applications.

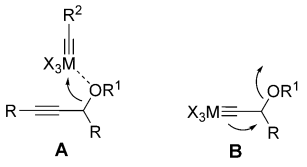
Table 2. Comparison of the performance of **1** with that of the new two-component system in homo-metathesis reactions.[a]

Entry	Catalyst	Product	*t* [h]	Yield [%]
1	**1**		14	84
2	**3**/**8a**		14	80
3	**3**/**11b**		14	80
4	**1**		14	69
5	**3**/**8a**		1	81
6	**3**/**11b**		4	84
7	**1**		16	47
8	**3**/**8a**		0.5	86
9	**1**		14	34
10	**3**/**8a**		0.5	81
11	**3**/**11b**		4	76
12	**1**		14	0
13	**3**/**8a**		14	69
14	**3**/**11b**		4	72

[a] For the sake of comparison, all reactions were performed at ambient temperature with 10 mol% of catalyst in toluene in the presence of MS 5 Å.

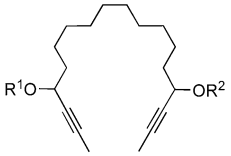
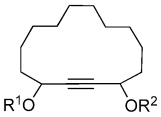
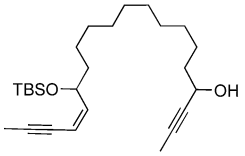
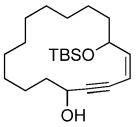
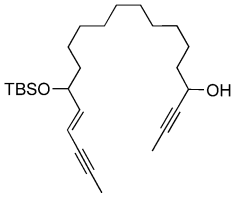
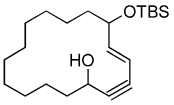
Propargylic and Bis-Propargylic Alcohol Derivatives

Until recently, it had been basically impossible to subject propargyl alcohol derivatives to alkyne metathesis mainly for two reasons: all well-defined alkyne metathesis catalysts are Schrock alkylidynes, and as such comprise an early transition metal in its highest possible oxidation state.[25,26] Unless appropriately tempered by the ligand set, the Lewis acidity inherent to such complexes endangers substituents at any activated position; propargylic alcohol derivatives fall into this category (see the generic structure **A**) for the resonance stabilization of the resulting carbocations. Even if this serious pitfall is overcome and the chosen catalyst engages productively with the triple bond, the ensuing alkylidyne of type **B** might decompose by extrusion of the potential leaving group next to the nucleophilic site.



Only after the advent of complex **1** and congeners has this important gap in substrate scope been closed, at least in part.[3] A couple of exigent applications to natural product total synthesis are encouraging (a representative example is shown in the Introduction), but the number of successful cases is still small and certain limitations persist.[27–31] Most notably, only substrates comprised of only *one* propargylic site but one regular alkyne have been successfully metathesized. In con-

Table 3. Ring closing metathesis of bis-propargylic and related substrates.[a]

Entry	Substrate	Product		Yield [%][b] 1	Yield [%][b] 3/11 b
1			$R^1=R^2=$MOM	54	70
2			$R^1=$MOM, $R^2=$OH	0	67
3			$R^1=R^2=$TES	0	71
4			$R^1=$TES, $R^2=$OH	0	64
5			$R^1=R^2=$OH	0	53
6			$R^1=R^2=$Ac	0	0
7				0	90
8				0	76

[a] All reactions were performed with a catalyst loading of 20 mol% in refluxing toluene (1 mM) in the presence of MS 5 Å. [b] Isolated yields.

trast, compounds, in which both triple bonds bear propargylic leaving groups, largely fail to react when exposed to **1** even under forcing conditions (see Table 3); only a fully MOM-protected derivative was a positive outlier (entry 1). Despite the modest yield, this result does indicate that there is nothing inherently wrong with the projected ring closure of bis-propargylic substrates; rather, the problem must be due to an incompetence of the standard catalyst.

Therefore it seemed worthwhile to test the new two-component system. Gratifyingly, the use of **3**/**11 b** allowed all substrates to be converted into the corresponding products, except for the ester derivative shown in entry 6, which remained unchanged for reasons that are not entirely clear. The additional substrates shown in entries 7 and 8 corroborate the trend, in that **1** failed completely whereas **3**/**11 b** gave the corresponding strained cyclic enynes with flanking -OR groups in good to excellent yield.

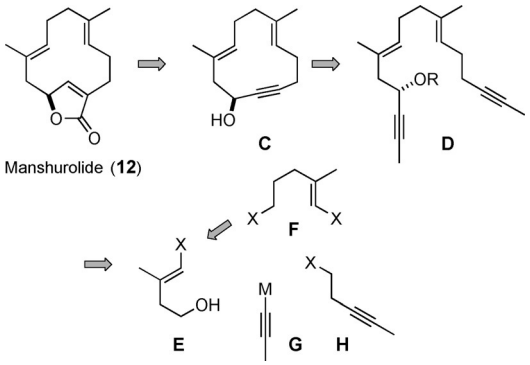
Although these results represent a step forward in preparative terms, they are mechanistically perplexing. The triphenylsilanolate ligands in **1** and the new cross-linking silanolates **8** and **11** are arguably too similar in electronic terms to explain the reactivity difference. Therefore we wondered if the substituents on the alkylidyne unit of the precatalysts (aryl in **1** versus ethyl in **3**) also play a role. To test this hypothesis, Ph_3SiOH was added to a solution of **3** in toluene;[32] indeed, the resulting mixture was able to convert the mono-TES protected substrate shown in entry 4; the conversion, however, remained incomplete (ca. 60%) and a mixture of the desired cyclic monomer and the cyclic dimer was formed, whereas **3**/**11 b** afforded the product in an isolated yield of 64%. On the one hand, this control experiment suggests that the difficulty in converting bis-propargylic substrates arises—to a large part—from the initiation step, which has not been recognized as a possible limiting factor in previous discussions of alkyne metathesis.[6,7] Precatalysts with an unbranched alkyl substituent on their alkylidyne unit seem to have a distinct advantage in this regard. This aspect provides valuable guidance for further catalyst optimization, although it needs to be seen if and how it can be reconciled with stability considerations. On the other hand, the lower net efficiency of **3**/Ph_3SiOH (ratio 1:3) compared to **3**/**11 b** indicates that a chelating or cross-linking ligand set provides additional advantages, be it for a higher resistance toward protic groups and/or for higher thermal stability since all tested bis-propargylic substrates required rather forcing conditions.

Total Synthesis of Manshurolide

The metathesis of propargylic alcohol derivatives has the charm of providing access to many different structural motives when combined with appropriate post-metathetic transformations of this functional group.[33] Previous work from this laboratory showcased this aspect by engaging such products, inter alia, into a ruthenium-catalyzed redox isomerization/transannular Michael addition process en route to the biphenyl alkaloid lythranidine,[27] into a hydroxyl-directed *trans*-hydrostannation/methyl-Stille coupling sequence for the total synthesis of the antibiotic 5,6-dihydrocineromycin B,[29] or into an intricate gold-catalyzed [3,3]-sigmatropic rearrangement/transannular hydroalkoxylation cascade as the key step of a recent total synthesis of the cytotoxic macrolide enigmazole A.[31] We conjectured that butenolides are another important structural motif commonly found in nature that should be within reach.

The sesquiterpene lactone manshurolide (**12**), isolated from the stems of the climbing plant *Aristolochia manushuriensis* Kom., was deemed an interesting and relevant target (Scheme 2).[35] Compound **12** has been shown to inhibit mitogen-activated protein (MAP) kinases signaling pathways by selective interference with the extracellular kinase ERK1/2.[36] MAP kinases are implicated in a number of critical physiological processes, including mitosis, gene expression, cell motility, and programmed cell death, and therefore represent potential biological targets for drug development. From the purely chemical viewpoint, the three *E*-configured alkenes within the 12-membered ring of **12** impose substantial strain; this issue will arguably be potentiated at the stage of the envisaged propargyl alcohol precursor of type **C**, which is therefore deemed a serious testing ground for the alkyne metathesis catalysts at hand.

Commercial **13** served as convenient starting point, which was subjected to a zirconium-assisted carboalumination/iodination to give product **14** (Scheme 3).[37,38] One part of the sample was then subjected to oxidation and the resulting alde-

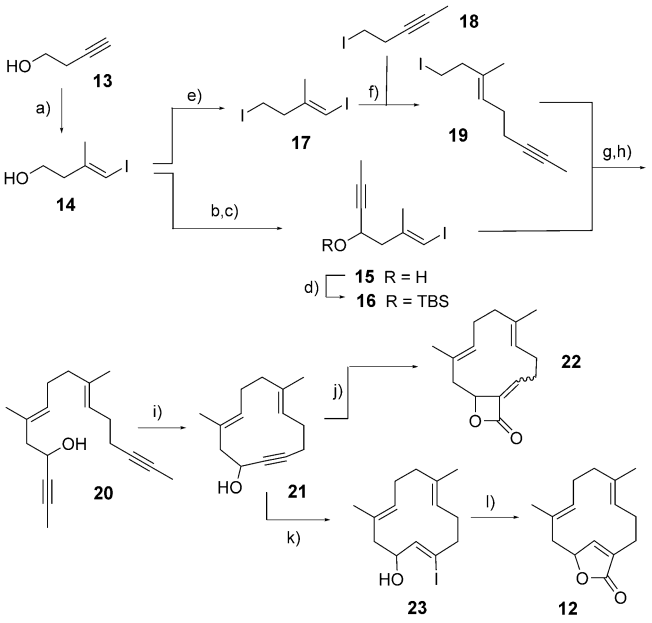


Scheme 2. Retrosynthetic analysis of manshurolide (**12**); the configuration is drawn as shown in the isolation paper.[34]

hyde reacted with propynylmagnesium bromide to give the required building block **15**. The second half of the material was transformed into the corresponding iodide **17**;[37] as expected, this compound could be selectively cross coupled at the alkenyl halide site under standard palladium catalysis when treated with the organozinc reagent derived from **18**.[39] Unfortunately, attempted coupling of **19** and unprotected **15** failed, whereas the derived TBS-ether **16** was well behaved under the conditions of the 9-MeO-9-BBN variant of the Suzuki coupling previously developed in our laboratory.[40]

Prior to the crucial macrocyclization, the bulky silyl group had to be removed;[41] the resulting propargyl alcohol **20** was then subjected to RCAM using either **1** or **3**/**8b** as the catalyst, the efficiency of which proved strikingly different: while **1** failed completely and **20** was largely recovered, the new two-component system **3**/**8b** afforded cycloalkyne **21** in excellent yield, even though unusually high dilution (0.5 mM) was mandatory to counteract competing oligomerization. This technical issue notwithstanding, this example provides a nice illustration of the superior performance of **3**/**8b** in exigent cases, which is tentatively ascribed to the stability of the catalyst toward the protic substrate even in refluxing toluene.

We had envisaged to install the yet missing butenolide ring in a single step by direct carbonylation of the propargyl alcohol subunit of **21** according to a literature procedure.[42] Despite many attempts, these efforts were to no avail; only the corresponding β-lactone **22** could be isolated from the crude material, albeit in low yield. In any case, the problem was fixed by a classical hydroxyl-directed hydroalumination/iodination,[43,44] followed by palladium-catalyzed carbonylation of the resulting product **23**. This step was best achieved by following the conditions previously optimized by our group in a different synthetic context.[45] Specifically, the use of $Pd(tfa)_2$ in combination with DPE-Phos as the ligand in a mixed solvent system proved highly effective, furnishing the desired butenolide almost quantitatively. Overall, this route provided manshurolide (**12**) in only nine steps with >17% overall yield for the longest linear sequence. Moreover, the tactics manifest in this approach should have a good chance to be applicable to other targets featuring a butenolide ring-fused to a macrocyclic skeleton too, which is a common structural motif in nature.[46]

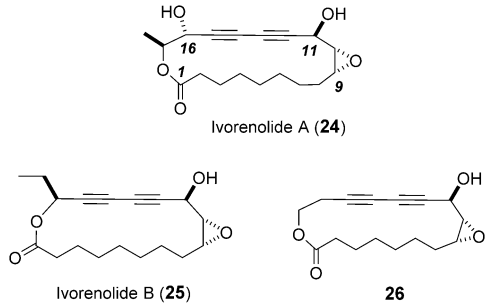


Scheme 3. a) (i) Cp_2ZrCl_2(22 mol%), $AlMe_3$, CH_2Cl_2, −25 °C→RT; (ii) I_2, Et_2O, −25 °C→RT, 65%; b) DMP, CH_2Cl_2, 0 °C→RT; c) propynylmagnesium bromide, THF, 0 °C→RT, 82% (over both steps); d) TBSCl, imidazole, DMF, 0 °C, 87%; e) I_2, PPh_3, imidazole, Et_2O/MeCN, 72%; f) (i) **18**, *t*BuLi, Et_2O, −78 °C, $ZnBr_2$, then **17**; (ii) $(dppf)PdCl_2$(2 mol%), THF, 80%; g) (i) **19**, *t*BuLi, Et_2O, −78 °C, then 9-MeO-9-BBN, −78 °C→RT; (ii) $(dppf)PdCl_2$(10 mol%), K_3PO_4, DMF, 50 °C, 60%; h) CSA cat., MeOH, 0 °C, 82%; i) **3** (10 mol%), **8b** (10 mol%), MS 5 Å, toluene, reflux, 82%; j) $Pd_2(dba)_3{\cdot}CHCl_3$ (4 mol%), dppb (8 mol%), CH_2Cl_2, CO (41 bar), H_2 (14 bar), 95 °C, ca. 17%; k) (i) Red-Al, Et_2O, 0 °C→RT; (ii) I_2, Et_2O, −25 °C, 97%; l) $Pd(tfa)_2$ (15 mol%), DPE-Phos (15 mol%), CO (1 bar), $Et_2N(iPr)$, MeCN/MeOH (4:1), 95%; BBN = 9-borabicyclononane; Cp = cyclopentadienyl; CSA = camphorsulfonic acid; dba = dibenzylideneacetone; DMP = Dess–Martin periodinane; DPE-Phos = bis[(2-diphenylphosphino)phenyl]ether; dppb = 1,4-bis(diphenylphosphino)butane; dppf = 1,1′-bis(diphenylphosphino)ferrocene; MS = molecular sieves; TBS = *tert*-butyldimethylsilyl; tfa = trifluoroacetate.

The spectral data of the synthetic sample matched those of the natural product in all respects. Surprisingly, however, the rotatory power of the enantiomers (obtained by separation on a chiral stationary phase) was found to be almost an order of magnitude larger than the $[\alpha]_D$ reported in the literature.[47] For this massive discrepancy and the uncertainty of the original stereochemical assignment,[34] we refrain from drawing a final conclusion as to the absolute configuration of natural manshurolide.

Total Synthesis of Ivorenolide A

An arguably even more challenging target is ivorenolide A (**24**), a potential lead in the quest for novel immunosuppressive agents for medical use.[48,49] Compound **24** was isolated together with its one-carbon shorter homologue ivorenolide B (**25**)[50] from the stem bark of the mahogany *Khayaivorensis* A. Chev. (Meliaceae); it was found to inhibit concanavalin A-induced T-cell proliferation as well as lipopolysaccharide-induced B-cell proliferation with selectivity indices comparable to or better than those of the clinically approved drugs cyclosporine A and periplocoside A.



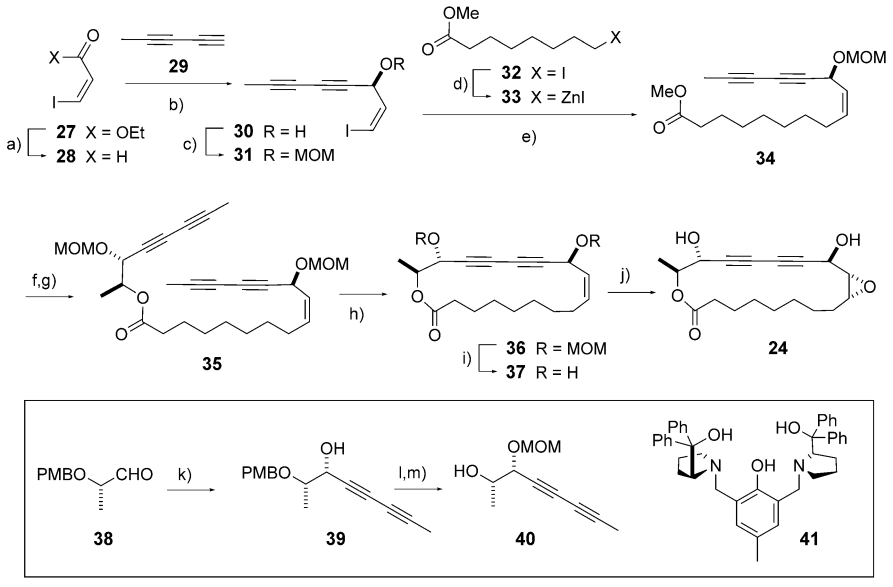
While the known routes to these structurally unique targets used conventional macrolactonization,[48–50] we saw an opportunity to employ RCAM as the key strategic element. Such a strategy, however, bears considerable risk as the conspicuous 1,3-diyne substructure might be prone to ring contraction and/or competing oligomerization if the catalyst is kinetically competent to attack the strained product once formed.[51] These issues notwithstanding, we have recently been able to communicate a concise entry into ivorenolide B (**25**) as well as the non-natural analogue **26** for biological testing.[30,52]

In view of this success, we were stunned that our initial attempts to extend the program to the parent compound ivorenolide A (**24**) faced major problems. This particular compound features exocyclic propargylic -OH groups on either side of the triple bonds and hence shows the exact substitution pattern recognized in the model study as rendering the initiation step difficult. Since this hurdle can be overcome in many cases with the help of the two-component catalyst system **3**/**11 b** in lieu of **1**, it seemed sensible to reinvestigate the total synthesis of this unusual lead compound.

The streamlined preparation of the cyclization precursor is shown in Scheme 4. It commences with an asymmetric addition of 1,3-pentadiyne (**29**)[53] to 3-iodoacrolein (**28**), which worked best under the conditions described by Trost and coworkers using (*R*,*R*)-ProPhenol (**41**) as ligand;[54] the modest *ee* of 70% is not unexpected for a nucleophilic partner as slim as **29**, but must be seen in the light of the fact that the available alternative protocols gave inferior results[55] or failed completely.[56] Product **30** is unstable and had to be processed without delay into the carboxylic acid building block by a sequence of MOM-protection, Negishi cross-coupling with the organozinc reagent **33**,[39,57] and saponification of the methyl ester terminus in **34**.

The second fragment was also secured by a Trost alkynylation[54] of the lactic-acid derived aldehyde **38**, which furnished compound **39** in enantio- and diastereomerically pure form after flash chromatography. Following a routine protecting group maneuver, the derived alcohol **40** was esterified under Yamaguchi conditions to give the required cyclization precursor **35** in appreciable yield.[58] This protocol proved more convenient than the EDC-mediated esterification previously used in our route to ivorenolide B (**25**).[30]

In concord with our model study on bis-propargylic substrates (vide supra), **35** underwent a clean and productive cyclization when exposed to catalytic amounts of **3**/**11 b** in toluene in the presence of molecular sieves to sequester the released hexadiyne byproduct (Table 4). In contrast, this critical step was problematic when the standard catalyst **1** was used, which afforded only modest yields despite the higher loading. Together with the manshurolide example outlined in the previous section, this particular transformation therefore illustrates the power of the novel two-component catalyst system.



Scheme 4. a) Dibal-H, CH_2Cl_2, −78 °C, 86%; b) **29**, Me_2Zn, (*R*,*R*)-**41** (10 mol%), $Ph_3P{=}O$ (20 mol%), toluene, 4 °C, 86% (70% *ee*); c) MOMCl, *i*$PrNEt_2$, CH_2Cl_2, 86%; d) Zn, THF, 40 °C; e) $(Ph_3P)_2PdCl_2$ (5 mol%), tmeda, THF, 50 °C, 75%; f) LiOH, THF/MeOH (2:1), 95%; g) 2,4,6-trichlorobenzoic acid chloride, Et_3N, toluene, 0 °C, then **40**, DMAP, RT, 79%; h) **3** (20 mol%), **11 b** (20 mol%), toluene, MS 5 Å, 60 °C, 78%; i) aq. HCl, EtOH, 70 °C, 64%; j) *m*CPBA, CH_2Cl_2, 74%; k) **29**, Me_2Zn, (*R*,*R*)-**41** (10 mol%), $Ph_3P{=}O$ (20 mol%), toluene, 4 °C, 61%; l) MOMCl, *i*Pr_2NEt, CH_2Cl_2, 85%; m) DDQ, CH_2Cl_2, pH 7 buffer, 0 °C, 72%; DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone; Dibal-H = diisobutylaluminum hydride; DMAP = 4-dimethylaminopyridine; *m*CPBA = *meta*-chloroperbenzoic acid; MOM = methoxymethyl; TBAF = tetra-*n*-butylammonium fluoride; tmeda = *N*,*N*,*N*′,*N*′-tetramethylethylendiamine.

Table 4. Comparison of the performance of different catalysts in the RCAM reaction of substrate **35** with formation of cyclodiyne **36**.[a]

Entry	Catalyst	Loading [mol%]	T [°C]	t [h]	Yield [%]
1	**1**	35	60	4	38
2	**1**	35	120	4	33
3	**3**/**11 b**	20	60	1	78
4	**3**/**11 b**	20	120	<1	75

[a] All reactions were performed in toluene (0.008 M) in the presence of MS 5 Å.

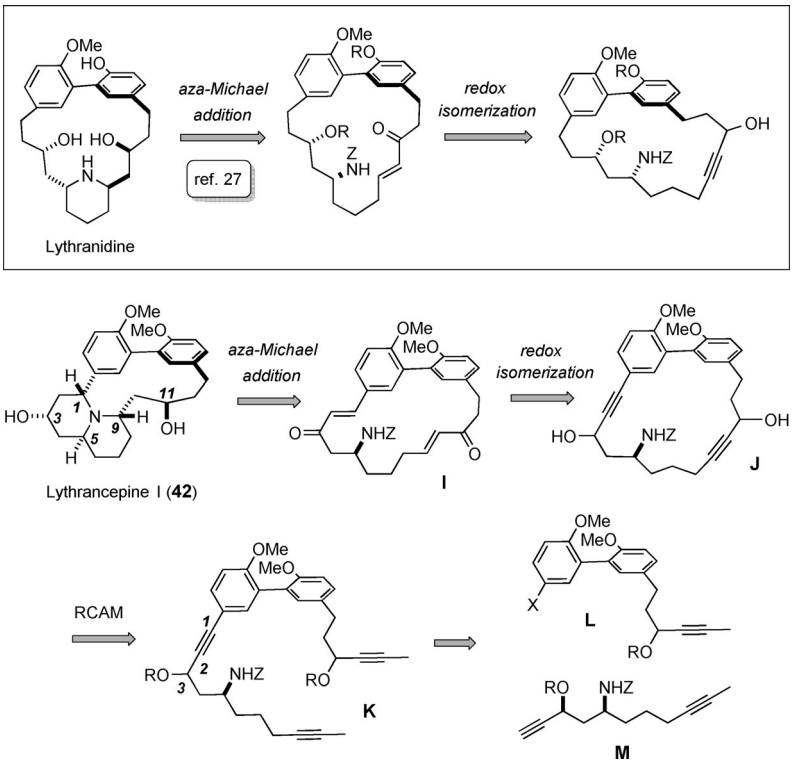
Compound **36** intercepts a previous total synthesis of **24**;[48] hence the remaining two steps were carried out in analogy to this literature precedent. To this end, **36** was deprotected under acidic conditions and the resulting diol **37** subjected to a substrate controlled stereoselective epoxidation, which occurred selectively at the double bond and left the propargylic alkynes untouched. Synthetic ivorenolide A (**24**) was identical with the natural product in all spectroscopic and analytical regards.[48] With only nine steps and an overall yield of $\geq$13% (longest linear sequence from commercial starting materials), the new route described herein is not only competitive (compare ref. [48]: 15 steps, 22%; ref. [49]: 17 steps, 13.4%) but also chemically instructive with regard to the remaining challenges of alkyne metathesis chemistry and how they can possibly be solved.

Studies toward (+)-Lythrancepine I

The first asymmetric synthesis of the biphenyl alkaloid (−)-lythranidine previously reported by our group had been based on an unprecedented sequence comprised of a RCAM reaction to form a macrocyclic propargyl alcohol skeleton followed by a ruthenium-catalyzed redox isomerization and a transannular aza-Michael addition to build the signature *trans*-substituted piperidine ring (Scheme 5).[27] It seemed reasonable to assume that a related—but clearly more involved—strategy might bring the quinolizidine alkaloid (+)-lythrancepine I (**42**) into reach, which is representative for a large family of natural products isolated from plants of the *Lythraceae* genus (Scheme 5).[59–62] Ideally, an intricate cascade comprised of two consecutive transannular aza-Michael reactions should transform a bis-enone of type **I** into the target after reduction of the carbonyls; **I** in turn could be accessed by twofold redox isomerization of a substrate such as **J**, which might be closed by RCAM from an acyclic triyne **K** comprising two propargylic entities and one regular alkyne.

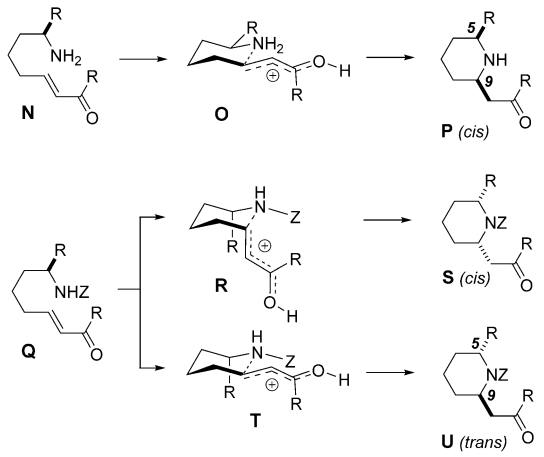
This plan bears considerable risks, with the most obvious possible pitfalls being as follows:

i) The stereochemical course of the aza-Michael tandem is difficult to predict, even though a sufficiently large *N*-substituent Z is almost certainly necessary to reach the critical *trans*-relationship between H5 and H9 in the first place (Scheme 6):[63] in its absence, a transition state of type **O** with a diequatorial orientation of the incipient 2,6-substitu-



Scheme 5. Key strategic elements of our previous total synthesis of lythranidine (ref. [27]) and their possible implementation into the synthesis of lythrancepine I (**42**); the helicity of the biaryl axis in **42** is known to be induced by the preexisting chiral centers, see ref. [62]; R, Z = protecting groups.

ents is favored that converts the substrate **N** into a *cis*-piperidine **P**. A transition state of type **T** leading to the *trans*-piperidine **U** can only be envisaged if Z ≠ H;[64] in this case, the actual *cis*/*trans* ratio will depend on the differential between the allylic strain in **T** and the transannular strain of the 1,3-diaxial substituents in the diastereomeric transition state **R**. Once a first *trans*-piperidine is in place, the second cyclization meant to yield the desired quinolizidine core of the target compound **42** might be under thermodynamic control.[65]



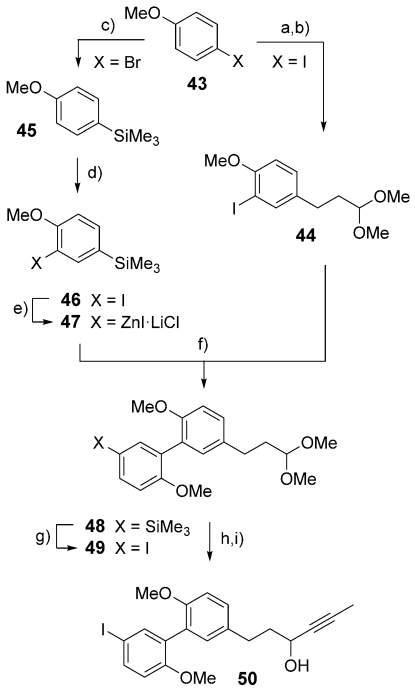
Scheme 6. Rationale for the formation of 2,6-disubstituted piperidines by aza-Michael addition; Z = generic *N*-protecting group of sufficient size to induce 1,3-allylic strain; lythrancepine numbering.

ii) It is difficult to predict if the transannular context of the envisaged Michael addition cascade imposes additional constraints.[66]

iii) We are unaware of any precedent in which two redox isomerizations were carried out concomitantly (see **J**→**I**);[67,68] with several heteroelements and nucleophilic C-atoms present within the congested framework of a substrate of type **J**, many side tracks are conceivable.

iv) For the macrocyclic frame in **J** to be forged, two out of three triple bonds in the cyclization precursor **K** have to participate in metathesis while the third one has to pass untouched; although this type of selectivity is unprecedented, we presumed that a bulky protecting group R on the propargyl alcohol at C3 might turn the adjacent C1–C2 triple bond into an innocent by-stander during RCAM.

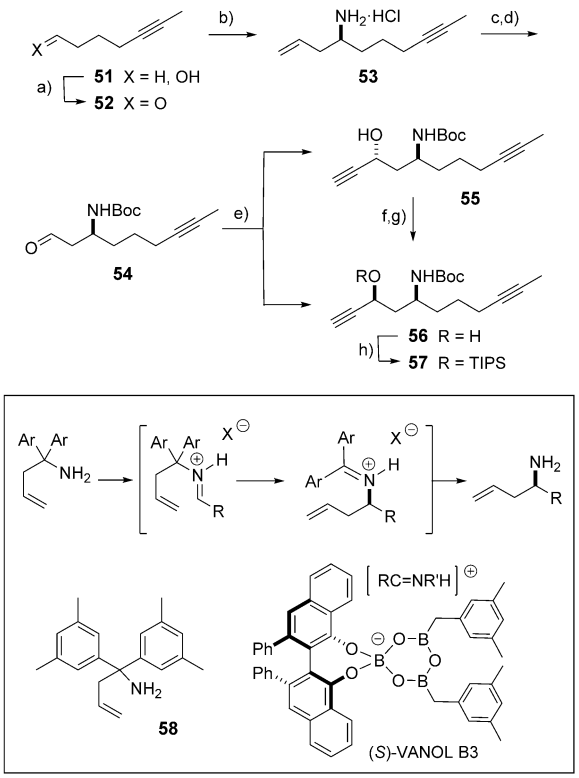
Based on this analysis and encouraged by the successful total synthesis of the sister compound lythranidine,[27] the synthesis of **42** was tackled as shown in Scheme 7. A Heck coupling of **43** (X = I) with allyl alcohol[69] furnished multigram amounts of the corresponding aldehyde, which was selectively iodinated on treatment with Ag_2SO_4 and iodine in MeOH as the preferred solvent;[70] under these conditions, concomitant acetal formation was observed. The resulting compound **44** was subjected to a Negishi reaction,[37] which was rendered remarkably effective by the SPhos ligand[71] in combination with $Pd(OAc)_2$. The required organozinc reagent **47** was derived from iodide **46** bearing a TMS group as a masked site for downstream fragment coupling. To this end, the biaryl **48** was treated with NIS in MeCN,[72] the aldehyde group was unveiled and reacted with propynyllithium to install the first propargyl alcohol entity; this latter step was much more effective when stoichiometric amounts of $LaCl_3 \cdot 2\,LiCl$ were added.[73] Overall, this sequence proved productive and scalable, providing more than five grams of **50** for further elaboration.



Scheme 7. a) Allyl alcohol, $Pd(OAc)_2$ (1 mol%), $NaHCO_3$, TBAC, DMF, 50 °C, 81%; b) Ag_2SO_4, I_2, MeOH, 87%; c) *n*BuLi, TMSCl, THF, −78 °C→RT, 99%; d) *n*BuLi, tmeda, Et_2O, then I_2, THF, −78 °C→RT, 82%; e) Zn, LiCl, TMSCl, 1,2-dibromoethane, THF, 80 °C; f) $Pd(OAc)_2$ (2 mol%), SPhos (4 mol%), THF, 93%; g) NIS, MeCN, 73%; h) PPTS, acetone/H_2O, 50 °C, quant.; i) propynyllithium, $LaCl_3 \cdot 2\,LiCl$, THF, 0 °C, 87%; NIS = *N*-iodosuccinimide; PPTS = pyridinium *p*-toluenesulfonate; TBAC = tetra-*n*-butyl-ammonium chloride; tmeda = *N*,*N*,*N*′,*N*′-tetramethylethylendiamine.

As model studies had suggested that the efficiency of a redox isomerization of an acyclic β-aminoalcohol derivative depends on the stereostructure, with a 1,3-*syn* relationship being beneficial,[74] the second required building block was formed in this particular stereochemical format (Scheme 8). A Stahl oxidation[75] proved convenient for the preparation of aldehyde **52**, which was converted into the homoallylic amine **53** on treatment with **58**[76] in the presence of catalytic amounts of the (*S*)-VANOL B3 catalyst (generated in situ) and co-catalytic benzoic acid;[77] not only did this asymmetric aza-Cope reaction scale well, but it afforded the desired product **53** with impeccable enantiomeric excess (98% *ee* as determined after *N*-Boc protection).

After routine *N*-protection of **53**, the seemingly simple ozonolysis of the double bond proved erratic in that variable but substantial amounts of the secondary ozonide were present in



Scheme 8. a) TEMPO (5 mol%), $[Cu(MeCN)_4]BF_4$ (5 mol%), bipy (5 mol%), air, NMI (10 mol%), MeCN, 91%; b) **58**, (*S*)-VANOL B3 (5 mol%), benzoic acid (5 mol%), MS 5 Å, *m*-xylene, 60 °C, then aq. HCl, THF, 91%; c) Boc_2O, Et_3N, CH_2Cl_2, 0 °C→RT, 89% (98% *ee*); d) O_3, *N*-methylmorpholine-*N*-oxide, CH_2Cl_2, 0 °C, 76%; e) ethynylmagnesium bromide, Et_2O, −78 °C→RT, **56** (39%) + **55** (33%); f) DMP, CH_2Cl_2, 0 °C→RT, 87%; g) $LiAl(OtBu)_3H$, LiCl, Et_2O, 0 °C, 92%; h) TIPSCl, imidazole, DMAP, CH_2Cl_2, 0 °C→RT, 84%; bipy = 2,2′-bipyridine; Boc = *tert*-butyloxycarbonyl; DMAP = 4-dimethylaminopyridine; NMI = *N*-methyl-imidazole; TIPS = tri(isopropyl)silyl.

the mixture even after extended exposure of the crude material to excess PPh_3. This problem was circumvented by running the ozonolysis in the presence of *N*-methylmorpholine-*N*-oxide which prevents secondary ozonides from being formed (presumably by trapping the preceding carbonyl oxide derived from the primary ozonide);[78] close monitoring of the reaction allowed any significant degradation of the triple bond to be avoided. This method proved safe and scalable, affording aldehyde **54** in well reproducible yield. Likewise, the subsequent formation of the propargyl alcohol moiety required some optimization. As none of the tested asymmetric protocols allowed the ethynyl residue (or a silyl protected equivalent) to be introduced satisfactorily,[79] we resorted to the substrate controlled addition of ethynylmagnesium bromide, separation of the diastereomers, and subsequent conversion of the *anti*-isomer **55** into **56** by oxidation/*syn*-reduction. This sequence was well suited for material throughput and further optimization of the addition step therefore postponed to a later stage. Final TIPS-protection gave more than three grams of the required building block **57**; this bulky silyl ether was supposed to shield the flanking triple bond during the projected regioselective alkyne metathesis reaction.

Gratifyingly, this expectation proved correct: thus, a Sonogashira coupling of **50** with **57** afforded triyne **59** (Scheme 9) which was cyclized within 15 min on treatment with the two-component system **3**/**11b** in refluxing toluene to give the desired product **60** in 66% yield (2.23 g scale). As evident from Table 5, the standard catalyst **1** was largely incompetent, in that it led to low conversion as well as to an unfavorable product distribution. Moreover, the data reveal subtle differences amongst the novel trisilanol ligands, which were hardly noticeable in the model studies outlined above. The trend that the phenyl-tethered ligands **11** give better results than their more flexible relatives **8** is consistent with the excellent performance of **11b** in the ivorenolide project.

Table 5. Catalyst screening for the formation of product **60**.[a]

Entry	Catalyst	*T* [°C]	HPLC [rel.%][b] Conversion	**60**	Σ of Dimers[c]	Yield [%][d]
1	**1**	80	45	16	20	nd
2	**3**/**8a**	80	75	66	8	41
3	**3**/**8b**	80	79	70	9	52
4	**3**/**11a**	80	92	84	8	58
5	**3**/**11b**	80	91	83	8	60
6	**3**/**11b**[e]	110	90	84	6	66

[a] For the sake of comparison, all reactions were performed with 20 mol% of catalyst in toluene (0.002 M) in the presence of MS 5 Å. [b] Data of the HPLC analysis of the crude reaction mixtures. [c] The sum of the cyclic dimer and an acyclic dimer is given. [d] Isolated yield of **60**. [e] With 18 mol% catalyst loading.

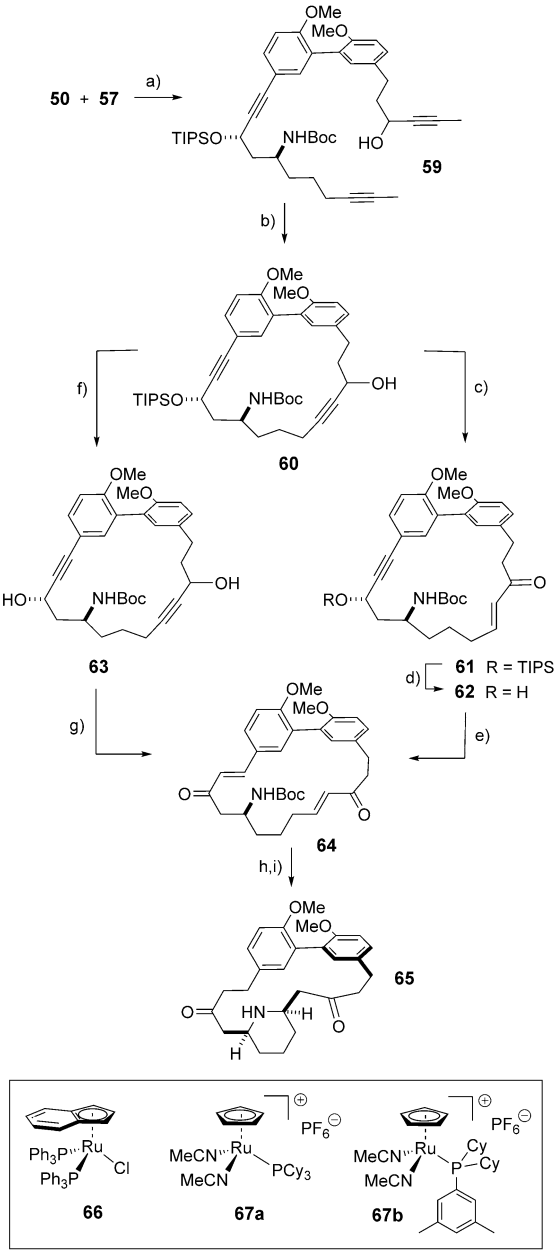
A particular challenge of this project deserves brief mentioning at this point: Once the macrocycle is closed all NMR spectra are difficult to interpret by virtue of massive line broadening and/or multiple signal sets; in compounds **60** and **63**, the complexity is further increased by the presence of diastereomers. Yet, the structural assignments are unambiguous; in all cases could the data sets be deconvoluted and the signals be attributed to individual interconverting conformers by extensive 1D and 2D experimentation at variable temperatures (for details, see the Supporting Information).

With ample material at hand, the stage was set for the two redox isomerizations meant to lead to a bis-enone of type **I**. By virtue of the protecting group pattern in **60**, it was possible to perform this transformation either in two consecutive steps or, after cleavage of the TIPS-ether, in one pot. The more conservative stepwise approach taught us that the conversion of **60** into enone **61** was easier (47%, 10 mol% catalyst loading) than the subsequent redox isomerization of **62** into **64** (< 40%, 40 mol% catalyst loading), but neither step was satisfactory under the standard conditions using catalyst **66**/$In(OTf)_3$.[67,68] An extensive optimization exercise was therefore inevitable. In essence, it was found that replacement of **66** by cationic mono-phosphine complexes of type **67** (conveniently prepared in situ)[80] and substitution of camphor-10-sulfonic acid (CSA) co-catalyst by NH_4PF_6 greatly improved the outcome. Best results in the first step were obtained with **67a** bearing commercial PCy_3 as the ligand, whereas **67b** carrying

the newly optimized Cy_2P(3,5-dimethylphenyl) ligand worked decisively better for the second isomerization;[81] this modification allowed the yield to be improved to respectable 55%. Complex **67b** was also the catalyst of choice for the one-pot double redox isomerization of diol **63** into **64** (43–47%, corresponding to ~69% per step; 400–500 mg scale). To fully appreciate this outcome one has to keep in mind that the literature conditions (**66**/CSA cat.) failed completely when applied to this particular substrate. In any case, complexes of type **67** seem to be powerful catalysts that merit attention in the context of redox isomerization chemistry in general; the good performance of the new ancillary ligand in **67b** and the inherent modularity of the catalyst preparation promise a potentially broad scope of this new method.[82]

At this stage, however, the projected total synthesis of (+)-lythrancepine I (**42**) came to an end, since **64** resisted all attempts to engage it in transannular aza-Michael reactions under a large variety of conditions as long as the *N*-Boc group was in place. This failure was unanticipated because a related transformation had served our previous total synthesis of the sister compound (−)-lythranidine very well (see Scheme 5).[27] Steric factors are more likely the malefactor than the stiffness of the di-unsaturated macrocyclic frame, since the deprotected amine derived from **64** readily cyclized with formation of piperidine **65** as the major product; as expected, however, the *cis*- rather than *trans*-piperidine was favored in this case (*cis*/*trans* 7.9:1). Changing the temperature, solvent and/or the base did not allow this stereochemical outcome to be significantly improved or even inverted.[83] This result corroborates that a bulky *N*-substituent is essential to enforce formation of an 2,6-*trans*-disubstituted piperidine, as contemplated during the retrosynthetic planning (Scheme 6). Preliminary attempts at forging the quinolizidine core via π-acid catalysis or under free radical conditions were also unfruitful.[74]

The envisaged route to (+)-lythrancepine I (**42**) was therefore abandoned at this point and the project is back at the strategic planning stage. Yet, the selective metathesis of two out of three triple bonds present in compound **59** is without precedent; this possibility illustrates the power of the methodology and might provide inspiration for other projects. Moreover, we are convinced of the utility of the much improved conditions for the redox isomerization of propargylic alcohols.



Scheme 9. a) $(Ph_3P)_2PdCl_2$ (5 mol%), CuI (10 mol%), Et_3N, DMF, 69%; b) **3** (18 mol%), **11b** (18 mol%), MS 5 Å, toluene, reflux, 66%; c) **67a** (10 mol%), CSA (10 mol%), THF, 80 °C, 74%; d) TBAF, HOAc, THF, 0 °C→RT, quant.; e) **67b** (10 mol%), NH_4PF_6 (10 mol%), THF, 80 °C, 55%; f) TBAF, HOAc, THF, 0 °C→RT, 99%; g) **67b** (20 mol%), NH_4PF_6 (20 mol%), THF, 80 °C, 47%; h) trifluoroacetic acid, CH_2Cl_2, 0 °C; i) DBU, CH_2Cl_2, −90 °C, 88% (dr = 7.9:1); CSA = camphor-10-sulfonic acid.

Conclusion

Although the structurally well-defined and commercially available trisilanolate complex **1** will continue to serve alkyne metathesis well,[1,2] it finds limitations when it comes to converting substrates comprising protic functionality and/or when forcing conditions are needed. In such cases, a catalyst mixture formed in situ from the trisamido molybdenum alkylidyne complex **3**[17] and the easily made trisilanol ligands **8** or **11** can help out. The fact that a multivalent ligand set together with an alkyl (rather than aryl) substituent on the alkylidyne residue of the precatalyst leads to a superior performance provides important guidance for future catalyst design.

The new two-component system excels in reactions of alkynes bearing primary, secondary or phenolic -OH groups, as well as in reactions of (bis)propargylic alcohol derivatives. This aspect is nicely illustrated by the total syntheses of the MAPK-inhibitory sesquiterpene manshurolide (**12**), the immunosuppressive macrolide ivorenolide A (**24**), as well as by a study toward the structurally unusual cyclophanic quinolizidine alkaloid lythrancepine I (**42**). This latter study also features the first example of an alkyne metathesis reaction of a substrate com-

prising three different triple bonds, two of which were selectively addressed while the third one remained untouched. As a valuable spin-off of the lythrancepine project, a powerful new ruthenium catalyst system for redox isomerization of propargyl alcohols to the corresponding enones was established that should be of interest well beyond the present context.

Experimental Section

All experimental details can be found in the Supporting Information. The material includes compound characterization and copies of spectra of new compounds.

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[1] J. Heppekausen, R. Stade, R. Goddard, A. Fürstner, *J. Am. Chem. Soc.* **2010**, *132*, 11045 – 11057.

[2] J. Heppekausen, R. Stade, A. Kondoh, G. Seidel, R. Goddard, A. Fürstner, *Chem. Eur. J.* **2012**, *18*, 10281 – 10299.

[3] P. Persich, J. Llaveria, R. Lhermet, T. de Haro, R. Stade, A. Kondoh, A. Fürstner, *Chem. Eur. J.* **2013**, *19*, 13047 – 13058.

[4] See also: A. D. Lackner, A. Fürstner, *Angew. Chem. Int. Ed.* **2015**, *54*, 12814 – 12818; *Angew. Chem.* **2015**, *127*, 13005 – 13009.

[5] For the use of molybdenum amido complexes as functional group tolerant alkyne metathesis catalysts, see: a) A. Fürstner, C. Mathes, C. W. Lehmann, *J. Am. Chem. Soc.* **1999**, *121*, 9453 – 9454; b) A. Fürstner, C. Mathes, C. W. Lehmann, *Chem. Eur. J.* **2001**, *7*, 5299 – 5317; c) A. Fürstner, K. Grela, C. Mathes, C. W. Lehmann, *J. Am. Chem. Soc.* **2000**, *122*, 11799 – 11805; d) A. Fürstner, K. Radkowski, J. Grabowski, C. Wirtz, R. Mynott, *J. Org. Chem.* **2000**, *65*, 8758 – 8762; e) W. Zhang, S. Kraft, J. S. Moore, *J. Am. Chem. Soc.* **2004**, *126*, 329 – 335.

[6] a) A. Fürstner, *Angew. Chem. Int. Ed.* **2013**, *52*, 2794 – 2819; *Angew. Chem.* **2013**, *125*, 2860 – 2887; b) A. Fürstner, *Science* **2013**, *341*, 1229713.

[7] a) W. Zhang, J. S. Moore, *Adv. Synth. Catal.* **2007**, *349*, 93 – 120; b) R. R. Schrock, C. Czekelius, *Adv. Synth. Catal.* **2007**, *349*, 55 – 77; c) A. Mortreux, O. Coutelier, *J. Mol. Catal. A* **2006**, *254*, 96 – 104; d) A. Fürstner, P. W. Davies, *Chem. Commun.* **2005**, 2307 – 2320.

[8] a) K. J. Ralston, H. C. Ramstadius, R. C. Brewster, H. S. Niblock, A. N. Hulme, *Angew. Chem. Int. Ed.* **2015**, *54*, 7086 – 7090; *Angew. Chem.* **2015**, *127*, 7192 – 7196; b) C. M. Neuhaus, M. Liniger, M. Stieger, K.-H. Altmann, *Angew. Chem. Int. Ed.* **2013**, *52*, 5866 – 5870; *Angew. Chem.* **2013**, *125*, 5978 – 5983; c) J. Burnley, W. R. Jackson, A. J. Robinson, *J. Org. Chem.* **2015**, *80*, 9057 – 9063; d) L.-D. Guo, X.-Z. Huang, S.-P. Luo, W.-S. Cao, Y.-P. Ruan, J.-L. Ye, P.-Q. Huang, *Angew. Chem. Int. Ed.* **2016**, *55*, 4064 – 4068; *Angew. Chem.* **2016**, *128*, 4132 – 4136; e) A. Guy, C. Oger, J. Heppekausen, C. Signorini, C. De Felice, A. Fürstner, T. Durand, J.-M. Galano, *Chem. Eur. J.* **2014**, *20*, 6374 – 6380; f) G. Herstad, P. P. Molesworth, C. M. Miller, T. Benneche, M. A. Tius, *Tetrahedron* **2016**, *72*, 2084 – 2093.

[9] a) V. Hickmann, A. Kondoh, B. Gabor, M. Alcarazo, A. Fürstner, *J. Am. Chem. Soc.* **2011**, *133*, 13471 – 13480; b) S. Benson, M.-P. Collin, A. Arlt, B. Gabor, R. Goddard, A. Fürstner, *Angew. Chem. Int. Ed.* **2011**, *50*, 8739 – 8744; *Angew. Chem.* **2011**, *123*, 8898 – 8903; c) G. Valot, C. S. Regens, D. P. O'Malley, E. Godineau, H. Takikawa, A. Fürstner, *Angew. Chem. Int. Ed.* **2013**, *52*, 9534 – 9538; *Angew. Chem.* **2013**, *125*, 9713 – 9717; d) G. Valot, D. Maihol, C. S. Regens, D. P. O'Malley, E. Godineau, H. Takikawa, P. Philipps, A. Fürstner, *Chem. Eur. J.* **2015**, *21*, 2398 – 2408; e) J. Willwacher, B. Heggen, C. Wirtz, W. Thiel, A. Fürstner, *Chem. Eur. J.* **2015**, *21*, 10416 – 10430; f) L. Hoffmeister, P. Persich, A. Fürstner, *Chem. Eur. J.* **2014**, *20*, 4396 – 4402.

[10] See also: a) M. G. Nilson, R. L. Funk, *Org. Lett.* **2010**, *12*, 4912 – 4915; b) M. Fouché, L. Rooney, A. G. M. Barrett, *J. Org. Chem.* **2012**, *77*, 3060 – 3070.

[11] a) K. Micoine, A. Fürstner, *J. Am. Chem. Soc.* **2010**, *132*, 14064 – 14066; b) K. Micoine, P. Persich, J. Llaveria, M.-H. Lam, A. Maderna, F. Loganzo, A. Fürstner, *Chem. Eur. J.* **2013**, *19*, 7370 – 7383; c) W. Chaładaj, M. Corbet, A. Fürstner, *Angew. Chem. Int. Ed.* **2012**, *51*, 6929 – 6933; *Angew. Chem.* **2012**, *124*, 7035 – 7039; d) L. Hoffmeister, T. Fukuda, G. Pototschnig, A. Fürstner, *Chem. Eur. J.* **2015**, *21*, 4529 – 4533; e) L. Brewitz, J. Llaveria, A. Yada, A. Fürstner, *Chem. Eur. J.* **2013**, *19*, 4532 – 4537.

[12] Actually, complex **5** is dimeric in the solid state by virtue of one phenoxide O-atom serving as a bridging ligand, see ref. [18a].

[13] These results stand in line with our previous findings that **1**, **2** and congeners tolerate various kinds of nitrogen- and/or sulfur containing aromatic heterocycles, including pyridines, thiophenes, thiazoles, oxazoles, and carbazoles, see ref. [1–11].

[14] For an impressive illustration of the compatibility with tertiary amines, see the total synthesis of haliclonacyclamine C: B. J. Smith, G. A. Sulikowski, *Angew. Chem. Int. Ed.* **2010**, *49*, 1599 – 1602; *Angew. Chem.* **2010**, *122*, 1643 – 1646.

[15] It needs to be emphasized, however, that attempted cross metathesis reactions of azide- or *tert*-amine containing acetylene derivatives with terminal alkynes failed for unknown reasons, cf: R. Lhermet, A. Fürstner, *Chem. Eur. J.* **2014**, *20*, 13188 – 13193.

[16] a) T. M. Trnka, R. H. Grubbs, *Acc. Chem. Res.* **2001**, *34*, 18 – 29; b) A. Fürstner, *Angew. Chem. Int. Ed.* **2000**, *39*, 3012 – 3043; *Angew. Chem.* **2000**, *112*, 3140 – 3172; c) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem. Int. Ed.* **2005**, *44*, 4490 – 4527; *Angew. Chem.* **2005**, *117*, 4564 – 4601; d) A. H. Hoveyda, A. R. Zhugralin, *Nature* **2007**, *450*, 243 – 251; e) A. Fürstner, *Chem. Commun.* **2011**, *47*, 6505 – 6511.

[17] W. Zhang, Y. Lu, J. S. Moore, *Org. Synth.* **2007**, *84*, 163 – 176.

[18] a) K. Jyothish, W. Zhang, *Angew. Chem. Int. Ed.* **2011**, *50*, 3435 – 3438; *Angew. Chem.* **2011**, *123*, 3497 – 3500; b) H. Yang, Z. Liu, W. Zhang, *Adv. Synth. Catal.* **2013**, *355*, 885 – 890.

[19] K. Jyothish, Q. Wang, W. Zhang, *Adv. Synth. Catal.* **2012**, *354*, 2073 – 2078.

[20] For applications, see: a) D. W. Paley, D. F. Sedbrook, J. Decatur, F. R. Fischer, M. L. Steigerwald, C. Nuckolls, *Angew. Chem. Int. Ed.* **2013**, *52*, 4591 – 4594; *Angew. Chem.* **2013**, *125*, 4689 – 4692; b) K. Hu, H. Yang, W. Zhang, Y. Qin, *Chem. Sci.* **2013**, *4*, 3649 – 3653; c) Y. Zhu, H. Yang, Y. Jin, W. Zhang, *Chem. Mater.* **2013**, *25*, 3718 – 3723; d) Q. Wang, C. Zhang, B. C. Noll, H. Long, Y. Jin, W. Zhang, *Angew. Chem. Int. Ed.* **2014**, *53*, 10663 – 10667; *Angew. Chem.* **2014**, *126*, 10839 – 10843; e) Z. Chen, D. W. Paley, L. Wei, A. L. Weisman, R. A. Friesner, C. Nuckolls, W. Min, *J. Am. Chem. Soc.* **2014**, *136*, 8027 – 8033; f) Q. Wang, C. Yu, H. Long, Y. Du, Y. Jin, W. Zhang, *Angew. Chem. Int. Ed.* **2015**, *54*, 7550 – 7554; *Angew. Chem.* **2015**, *127*, 7660 – 7664.

[21] For the use of an ONO-pincer ligand, which leads to a less active but more selective catalyst for living metathesis polymerizations of strained alkynes, see: D. E. Bellone, J. Bours, E. H. Menke, F. R. Fischer, *J. Am. Chem. Soc.* **2015**, *137*, 850 – 856.

[22] For metal alkylidyne complexes with pincer ligands, the catalytic activity and functional group tolerance of which has not been thoroughly investigated, see: M. E. O'Reilly, I. Ghiviriga, K. A. Abboud, A. S. Veige, *J. Am. Chem. Soc.* **2012**, *134*, 11185 – 11195.

[23] Compare: M. Fukawa, T. Sato, Y. Kabe, *Chem. Commun.* **2015**, *51*, 14746 – 14749.

[24] This situation did not change when yet other trisilanols with shorter or longer tethers between the silanol groups were used; S. Schaubach, projected doctoral thesis, TU Dortmund.

[25] R. R. Schrock, *Chem. Rev.* **2002**, *102*, 145 – 179.

[26] R. R. Schrock, *Angew. Chem. Int. Ed.* **2006**, *45*, 3748 – 3759; *Angew. Chem.* **2006**, *118*, 3832 – 3844.

[27] K. Gebauer, A. Fürstner, *Angew. Chem. Int. Ed.* **2014**, *53*, 6393 – 6396; *Angew. Chem.* **2014**, *126*, 6511 – 6514.

[28] a) J. Willwacher, N. Kausch-Busies, A. Fürstner, *Angew. Chem. Int. Ed.* **2012**, *51*, 12041 – 12046; *Angew. Chem.* **2012**, *124*, 12207 – 12212; b) D. Mailhol, J. Willwacher, N. Kausch-Busies, E. E. Rubitski, Z. Sobol, M. Schuler, M.-H. Lam, S. Musto, F. Loganzo, A. Maderna, A. Fürstner, *J. Am. Chem. Soc.* **2014**, *136*, 15719 – 15729.

[29] S. M. Rummelt, J. Preindl, H. Sommer, A. Fürstner, *Angew. Chem. Int. Ed.* **2015**, *54*, 6241 – 6245; *Angew. Chem.* **2015**, *127*, 6339 – 6343.

[30] F. Ungeheuer, A. Fürstner, *Chem. Eur. J.* **2015**, *21*, 11387 – 11392.

[31] A. Ahlers, T. de Haro, B. Gabor, A. Fürstner, *Angew. Chem. Int. Ed.* **2016**, *55*, 1406 – 1411; *Angew. Chem.* **2016**, *128*, 1428 – 1433.

[32] Such mixtures were previously used in material science, see: a) S. W. Sisco, J. S. Moore, *J. Am. Chem. Soc.* **2012**, *134*, 9114 – 9117; b) A. D. Finke, D. E. Gross, A. Han, J. S. Moore, *J. Am. Chem. Soc.* **2011**, *133*, 14063 – 14070; c) S. W. Sisco, J. S. Moore, *Chem. Sci.* **2014**, *5*, 81 – 85; d) S. W. Sisco, B. M. Larson, J. S. Moore, *Macromolecules* **2014**, *47*, 3829 – 3836.

[33] E. B. Bauer, *Synthesis* **2012**, 1131 – 1151.

[34] The published X-ray data do not allow for an unambiguous assignment of the absolute configuration; we thank Prof. C. W. Lehmann, this Institute, for this assessment.

[35] G. Rücker, C. W. Ming, R. Mayer, G. Will, A. Güllmann, *Phytochemistry* **1990**, *29*, 983 – 985.

[36] Z.-B. Cheng, W.-W. Shao, Y.-N. Liu, Q. Liao, T.-T. Lin, X.-Y. Shen, S. Yin, *J. Nat. Prod.* **2013**, *76*, 664 – 671.

[37] E. Negishi, S.-Y. Liou, C. Xu, S. Huo, *Org. Lett.* **2002**, *4*, 261 – 264.

[38] P. Wipf, S. Lim, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1068 – 1071; *Angew. Chem.* **1993**, *105*, 1095 – 1097.

[39] E. Negishi, *Bull. Chem. Soc. Jpn.* **2007**, *80*, 233 – 257.

[40] a) G. Seidel, A. Fürstner, *Chem. Commun.* **2012**, *48*, 2055 – 2070; b) A. Fürstner, G. Seidel, *Tetrahedron* **1995**, *51*, 11165 – 11176.

[41] Macrocyclization can also be enforced with the TBS-group in place using complex **1** in refluxing toluene; the yield was moderate (29–55%) and significant amounts of dimeric product as well as anisole transfer from the alkylidyne group rendered product isolation difficult.

[42] W.-Y. Yu, H. Alper, *J. Org. Chem.* **1997**, *62*, 5684 – 5687.

[43] S. E. Denmark, T. K. Jones, *J. Org. Chem.* **1982**, *47*, 4595 – 4597.

[44] a) K. Lehr, R. Mariz, L. Leseurre, B. Gabor, A. Fürstner, *Angew. Chem. Int. Ed.* **2011**, *50*, 11373 – 11377; *Angew. Chem.* **2011**, *123*, 11575 – 11579; b) K. Lehr, S. Schulthoff, Y. Ueda, R. Mariz, L. Leseurre, B. Gabor, A. Fürstner, *Chem. Eur. J.* **2015**, *21*, 219 – 227.

[45] A. Kondoh, A. Arlt, B. Gabor, A. Fürstner, *Chem. Eur. J.* **2013**, *19*, 7731 – 7738.

[46] For representative examples, see the following and literature cited therein: J.-C. Han, C.-C. Li, *Synlett* **2015**, 1289 – 1304.

[47] The isolation paper (ref. [35]) reports an $[\alpha]_D^{24} = +56^\circ$ (EtOH, $c = 0.79$), whereas the two enantiomers obtained by separation of the racemic synthetic sample showed the following rotatory power (in the order, in which the enantiomers were eluting from the column, cf. the Supporting Information): $[\alpha]_D^{20} = +519.8^\circ$ ($c = 0.5$, EtOH); $[\alpha]_D^{20} = -508.1^\circ$ ($c = 0.53$, EtOH).

[48] B. Zhang, Y. Wang, S.-P. Yang, Y. Zhou, W.-B. Wu, W. Tang, J.-P. Zuo, Y. Li, J.-M. Yue, *J. Am. Chem. Soc.* **2012**, *134*, 20605 – 20608.

[49] D. K. Mohapatra, G. Umamaheshwar, R. N. Rao, T. S. Rao, S. Kumar, J. S. Yadav, *Org. Lett.* **2015**, *17*, 979 – 981.

[50] Y. Wang, Q.-F. Liu, J.-J. Xue, Y. Zhou, H.-C. Yu, S.-P. Yang, B. Zhang, J.-P. Zuo, Y. Li, J.-M. Yue, *Org. Lett.* **2014**, *16*, 2062 – 2065.

[51] S. Lysenko, J. Volbeda, P. G. Jones, M. Tamm, *Angew. Chem. Int. Ed.* **2012**, *51*, 6757 – 6761; *Angew. Chem.* **2012**, *124*, 6861 – 6865.

[52] In our publication (ref. [30]), ivorenolide A was erroneously depicted as a 17-membered rather than 18-membered macrolide; we apologize for this mistake in the drawing of the structure.

[53] L. Brandsma, *Synthesis of Acetylenes, Allenes and Cumulenes. Methods and Techniques*, Elsevier, Oxford, **2004**.

[54] B. M. Trost, V. S. Chan, D. Yamamoto, *J. Am. Chem. Soc.* **2010**, *132*, 5186 – 5192.

[55] M. Turlington, Y. Du, S. G. Ostrum, V. Santosh, K. Wren, T. Lin, M. Sabat, L. Pu, *J. Am. Chem. Soc.* **2011**, *133*, 11780 – 11794.

[56] S. Reber, T. F. Knöpfel, E. M. Carreira, *Tetrahedron* **2003**, *59*, 6813 – 6817.

[57] In our previous synthesis of ivorenolide B (ref. [30]), the same organozinc reagent was prepared on treatment of iodide **32** with zinc dust in DMF; we found that the use of zinc dust activated with TMSCl/1,2-dibromoethane in THF according to a method described by Knochel is more convenient and productive, cf: A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040 – 6044; *Angew. Chem.* **2006**, *118*, 6186 – 6190.

[58] a) J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989 – 1993; b) A. Parenty, X. Moreau, J.-M. Campagne, *Chem. Rev.* **2006**, *106*, 911 – 939.

[59] E. Fujita, K. Bessho, Y. Saeki, M. Ochiai, K. Fuji, *Lloydia* **1971**, *34*, 306 – 309.

[60] a) E. Fujita, Y. Saeki, *J. Chem. Soc. D* **1971**, 368 – 369; b) E. Fujita, Y. Saeki, *J. Chem. Soc. Perkin Trans. 1* **1972**, 2141 – 2146; c) E. Fujita, Y. Saeki, *J. Chem. Soc. Perkin Trans. 1* **1973**, 297 – 301; d) E. Fujita, Y. Saeki, *Chem. Pharm. Bull.* **1971**, *19*, 1515 – 1516.

[61] M. J. Barrow, P. D. Cradwick, G. A. Sim, *J. Chem. Soc. Perkin Trans. 2* **1974**, 1812 – 1818.

[62] For the only total synthesis of a member of this series, see: a) D. J. Hart, W. P. Hong, *J. Org. Chem.* **1985**, *50*, 3670 – 3672; b) D. J. Hart, W. P. Hong, L. Y. Hsu, *J. Org. Chem.* **1987**, *52*, 4665 – 4673.

[63] For the formation of disubstituted piperidines by 5-*exo* cyclization reactions, see: a) C. Zhong, Y. Wang, A. W. Hung, S. L. Schreiber, D. W. Young, *Org. Lett.* **2011**, *13*, 5556 – 5559; b) I. J. McAlpine, R. W. Armstrong, *Tetrahedron Lett.* **2000**, *41*, 1849 – 1853; c) S. Chandrasekhar, G. S. K. Babu, C. R. Reddy, *Tetrahedron: Asymmetry* **2009**, *20*, 2216 – 2219; d) S. Fustero, S. Monteagudo, M. Sánchez-Roselló, S. Flores, P. Barrio, C. del Pozo, *Chem. Eur. J.* **2010**, *16*, 9835 – 9845; e) P. Radha Krischna, B. K. Reddy, *Tetrahedron: Asymmetry* **2013**, *24*, 758 – 763.

[64] P. Beak, W. K. Lee, *J. Org. Chem.* **1993**, *58*, 1109 – 1117.

[65] A. O. Maldaner, R. A. Pilli, *Synlett* **2004**, 1343 – 1346.

[66] Reviews: a) P. A. Clarke, A. T. Reeder, J. Winn, *Synthesis* **2009**, 691 – 709; b) E. Reyes, U. Uria, L. Carrillo, J. L. Vicario, *Tetrahedron* **2014**, *70*, 9461 – 9484.

[67] a) B. M. Trost, R. C. Livingston, *J. Am. Chem. Soc.* **1995**, *117*, 9586 – 9587; b) B. M. Trost, R. C. Livingston, *J. Am. Chem. Soc.* **2008**, *130*, 11970 – 11978.

[68] a) B. M. Trost, N. Maulide, R. C. Livingston, *J. Am. Chem. Soc.* **2008**, *130*, 16502 – 16503; b) B. M. Trost, A. C. Gutierrez, R. C. Livingston, *Org. Lett.* **2009**, *11*, 2539 – 2542; c) B. M. Trost, A. Breder, B. M. O'Keefe, M. Rao, A. W. Franz, *J. Am. Chem. Soc.* **2011**, *133*, 4766 – 4769; d) B. M. Trost, A. Breder, *Org. Lett.* **2011**, *13*, 398 – 401; e) B. M. Trost, A. Breder, B. Kai, *Org. Lett.* **2012**, *14*, 1708 – 1711.

[69] L. F. Tietze, K. Kahle, T. Raschke, *Chem. Eur. J.* **2002**, *8*, 401 – 407.

[70] In our hands, much better results were obtained on larger scale with MeOH than EtOH as the solvent which had previously been used for similar transformations, see: S. Wing-Wah, *Tetrahedron Lett.* **1993**, *34*, 6223 – 6224.

[71] D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 27 – 50.

[72] A. Kuboki, C. Maeda, T. Arishige, K. Kuyama, M. Hamabata, S. Ohira, *Tetrahedron Lett.* **2008**, *49*, 4516 – 4518.

[73] a) A. Krasovskiy, F. Kopp, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 497 – 500; *Angew. Chem.* **2006**, *118*, 511 – 515; b) A. Metzger, A. Gavryushin, P. Knochel, *Synlett* **2009**, 1433 – 1436.

[74] K. Gebauer, doctoral thesis, TU Dortmund, **2016**.

[75] a) J. M. Hoover, S. S. Stahl, *J. Am. Chem. Soc.* **2011**, *133*, 16901 – 16910; b) B. L. Ryland, S. S. Stahl, *Angew. Chem. Int. Ed.* **2014**, *53*, 8824 – 8838; *Angew. Chem.* **2014**, *126*, 8968 – 8983.

[76] H. Ren, W. D. Wulff, *J. Am. Chem. Soc.* **2011**, *133*, 5656 – 5659.

[77] G. Hu, A. K. Gupta, R. H. Huang, M. Mukherjee, W. D. Wulff, *J. Am. Chem. Soc.* **2010**, *132*, 14669 – 14675.

[78] C. Schwartz, J. Raible, K. Mott, P. H. Dussault, *Org. Lett.* **2006**, *8*, 3199 – 3201.

[79] Note that substrate and product are aminoalcohol derivatives, which themselves might ligate acetylide reagents and hence intervene in an attempted asymmetric addition process.

[80] These catalysts were conveniently prepared in situ from $[CpRu(MeCN)_3]PF_6$ and the corresponding phosphine according to: E. Rüba, W. Simanko, K. Mauthner, K. M. Soldouzi, C. Slugovc, K. Mereiter, R. Schmid, K. Kirchner, *Organometallics* **1999**, *18*, 3843 – 3850; control experiments showed that isolated **67a** or **67b** lead to the same outcome.

[81] The Supporting Information contains the procedure for the preparation of $Cy_2P(C_6H_3Me_2)$.

[82] A variety of aryl (aryl)dicyclohexylphosphines with different substitution patterns on the aromatic ring were prepared according to: M. Murata, S. L. Buchwald, *Tetrahedron* **2004**, *60*, 7397 – 7403. It was observed that minor changes in ligand architecture had strong impact on the catalytic activity of the resulting ruthenium complexes in the given transformation, see ref. [74].

[83] Moreover, the minor *trans*-isomer is configurationally unstable and rapidly converts to the *cis*-configured product **65** under basic or acidic conditions.

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