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Report

Total synthesis, organocatalysis, alkyne metathesis, samarium diiodide, marine natural products, biosynthetic hypothesis, Heck-type reactions

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Catalytic Asymmetric Total Synthesis of Macrocyclic Marine Natural Product (–)-Haliclonin A

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Summary of main observation and conclusion We describe the full details of our total synthesis of haliclonin A, a macrocyclic natural product suggested to originate from a common biosynthetic intermediate as sarain A. Central to our synthetic route is the strategic employment of nitromethane for several purposes: (1) as an umpolung surrogate of an aminomethyl group; (2) as an ideal nucleophile for the highly enantioselective catalytic asymmetric conjugate addition to forge the challenging all-carbon quaternary stereogenic center that was used to induce the formations of all other chiral centers of the molecule; and (3) as a C_1N_1 building block to form the 3-azabicyclo[3.3.1]nonane framework. The realization of this strategy relied on the development of a novel organocatalytic asymmetric conjugate addition of nitromethane to 3-alkenyl cyclohex-2-enone, and the first Pd-promoted intramolecular coupling of a thiocarbamate moiety onto an electron-deficient alkene (enone) to form the 3-azabicyclo[3,3,1]nonane core. The synthesis also features a SmI_2-mediated intermolecular reductive coupling of an enone with an aldehyde, ring-closing alkene and alkyne metathesis reactions to build the two aza-macrocycles, and an unprecedented direct transformation of enol into enone.

Background and Originality Content

Containing more than 600 species, the marine sponge genus Haliclona represents one of the most prolific sources of natural products.[1] To date, more than 110 nitrogenous secondary metabolites have been isolated from classified and unclassified Haliclona sp.[1] Among them, the family of macrocyclic diamine metabolites derived from 3-alkylpyridine dimers[2] comprises structurally diverse groups as represented by manzamine A (**1** in Figure 1),[3] nakadomarin A, madangamine A, and sarain A (**2**).[4,5] Following Baldwin's seminal biosynthetic hypothesis in 1992,[6] it is now well recognized that these apparently different polycyclic alkaloids are closely related, with 3-alkyldihydropyridine dimer A as the common biosynthetic precursor (Figure 1).[5] This family of natural products exhibits a broad spectrum of bioactivities including anticancer,[3,7] anti-HIV-1,[8] and antibacterial action.[9] The intriguing structural features combined with the interesting bioactivities established their "celebrity" status within the synthetic community.[2a,5-13] However, their enantioselective total synthesis presents a formidable synthetic challenge, especially for sarain A.[11] Indeed, although tremendous efforts have been devoted to the synthesis of sarain A,[12] its total synthesis was not achieved until Overman et al.[13] published their results describing the first enantioselective total synthesis of sarain A. Moreover, this remains the only total synthesis to date.

In 2009, Shin and coworkers reported the isolation of the macrocyclic alkaloid haliclonin A (**3**) from a marine sponge *Haliclona* sp. collected from Korean waters.[14] A preliminary assessment of bioactivity showed that haliclonin A exhibited moderate antibacterial activity against several Gram-positive and -negative bacteria, and displayed moderate cytotoxicity against the K562 leukemia cell line, with an IC_{50} of 15.9 μg/mL (0.03 μmol). The structural elucidation of haliclonin A (**3**) turned out to be challenging because in the ^{13}C and ^{1}H NMR spectra, most of the

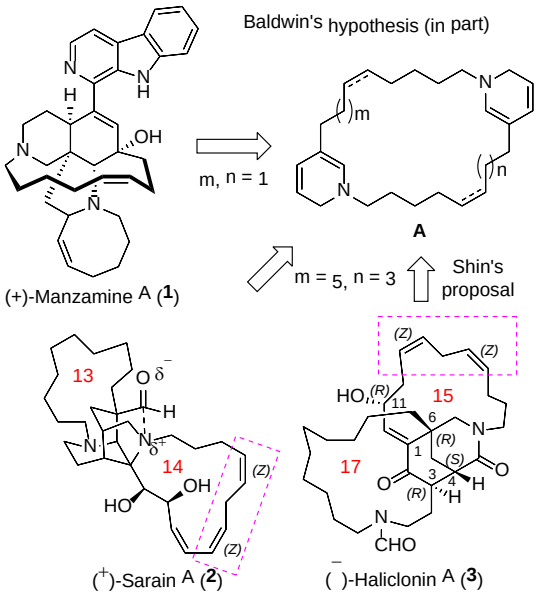
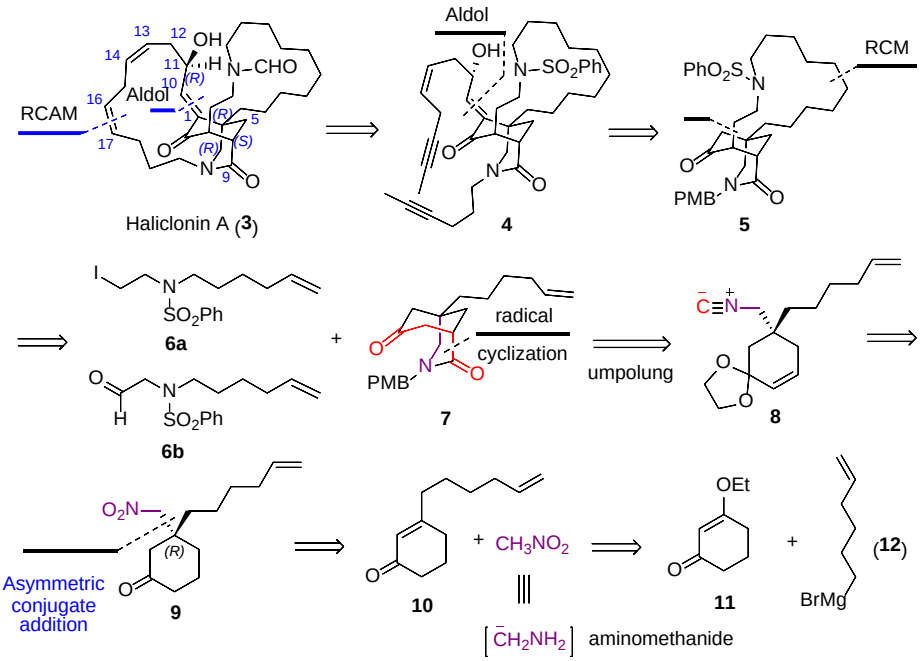


Figure 1 Biogenetic relationship within dimeric 3-alkyldihydropyridine natural products.

proton and carbon signals were paired to each other. On the basis of spectral investigations, Shin et al. suggested that compound **3** was a mixture of two rotamers with a ratio of 3:2. Moreover, the geometries of the skipped diene could not be determined because of the severe overlapping of the proton signals. A clever solution to this puzzle came from the hypothesis that haliclonin A might originate biosynthetically from 3-alkylpyridine dimers. Thus, whereas the structure of haliclonin A features the unprecedented 3-azabicyclo[3.3.1]nonane framework with an enone-diamide functionality, Shin et al suggested a possible retrobiosynthetic pathway, which converges with that of sarain A on bispyridinium intermediate A (Figure 1). Hence, the stereochemistry of the skipped diene moiety in haliclonin A (**3**) was tentatively assigned by analogy with that of sarain A (**2**). The absolute configuration of haliclonin A is another puzzle: i.e., the assigned one (1*E*,3*S*,4*R*,6*S*,11*S*) is actually the antipode of that showed in Figure 1.[17c] Consequently, the challenges for the total synthesis of haliclonin A not only come from the unprecedented tetracyclic framework with delicate functionalities, but also from the uncertainty about the relative stereochemistry for the skipped diene moiety and about the absolute configuration. With our longstanding interests in the synthesis of *N*-containing compounds,[15,16] we have embarked on a synthetic study of haliclonin A (**3**),[17a,c,e,18] which has resulted in the first total synthesis of (−)-haliclonin A.[17d] In parallel[17a,b] with our own work, significant progress has been made by Yokoshima, Fukuyama, and coworkers, who very recently disclosed a racemic synthesis of 3-azabicyclo[3.3.1]nonane skeleton with a bridge that forms the 17-membered ring.[17f] Herein, we describe the full details of our efforts to explore this intriguing molecule.

In view of the confusions discussed above regarding the stereochemistries of natural haliclonin A, our adventure started with selecting the displayed 1*E*,3*R*,4*S*,6*R*,11*R*,13*Z*,16*Z* stereoisomer of haliclonin A (**3** in Figure 1 and Scheme 1) as our synthetic target. Our initial retrosynthetic analysis of **3** is outlined in Scheme 1. We envisioned the formation of the *Z*-olefinic bond at C16–C17 and thus the 15-membered ring by a macrocyclic ring-closing alkyne metathesis (RCAM)[19] followed by a stereoselective Lindlar reduction. Fürstner[19] extensively explored the chemistry of RCAM from catalysts to reactions and its applications in the total synthesis of natural products. Next, after a retro-aldol disconnection of the side chain connected at C1, we anticipated the formation of the saturated 17-membered macrocycle by a ring-closing metathesis (RCM);[20] a methodology widely used for the construction of macrocycles.[5a,11,13,21] A disconnection at the α,β-C–C bond of the ketone is apparently simple and obvious, but the formation of this C–C bond in a regio- and stereoselective manner might be problematic. Hence the aldol reaction of **7** with **6b** was envisioned as a stepwise alternative. Given that the 3-azabicyclo[3.3.1]nonanone scaffold **7** contains a 1,4-dicarbonyl motif, an umpolung method is required for its construction. We thought that Bachi's radical lactamization method[22] might suit this need, which implied olefinic isocyanide **8** as an umpoled precursor. Finally, as the key to our strategy, we opted for nitromethane as both an umpolung surrogate of an aminomethanide[23] and a pronucleophile for the envisioned catalytic enantioselective conjugate addition to forge the challenging all-carbon quaternary stereogenic center.[24,25] The established first chiral center was expected to induce the formations of all the other three chiral centers in haliclonin A.

Scheme 1 Initial retrosynthetic analysis of haliclonin A (**3**)

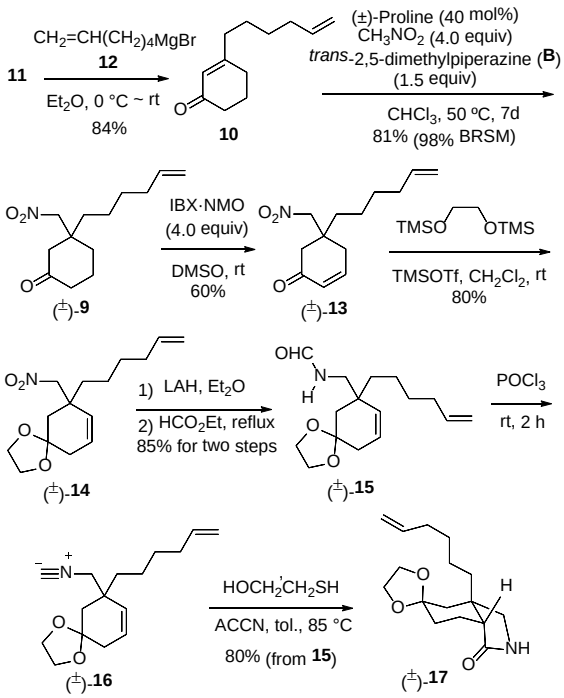


Results and Discussion

Synthesis of racemic 3-azabicyclo[3.3.1]nonane framework (7)

Radical approach. The synthesis started with commercially available 3-ethoxycyclohex-2-enone (**11**) (Scheme 2). Addition of Grignard reagent followed by acidic work-up afforded the desired 3-(hex-5-enyl)cyclohex-2-enone (**10**) in 84% yield. To test the viability of our strategy, racemic substrate **9** was prepared and used for our initial investigation. For the conjugate addition of nitromethane to enone[23,26] **10**, attempts using both organic bases (NEt_3, DBU, TMG) and inorganic bases (KF/Al_2O_3, NaOH) as well as *t*-BuOK in THF failed to yield any adduct. Under Hanessian's asymmetric conjugate addition conditions[26a] except that racemic proline was used as a catalyst, the desired adduct (±)-**9** was obtained in 15% yield, along with 84% of the recovered starting material. After optimization of reaction conditions, the yield was increased to 81% (98% BRSM, based on the recovered starting material). Nicolaou's method[27] was adopted for the transformation of cyclohexanone into the corresponding enone. Under the optimized conditions consisting of employing 4.0 equiv. of *N*-methyl-morpholine *N*-oxide (IBX·NMO) complex in DMSO for 3 days at room temperature, the desired enone (±)-**13** was obtained in 60% yield. Acetalization of (±)-**13** under Hwu's conditions[28] unexpectedly led to the olefinic bond migrated acetal (±)-**14** as the major product. At the time of our investigation, we were unaware of this unexpected result, and proceeded to the subsequent transformations.[18] Although this result did not allow us to access the desired tropinone ring system, it offered us the opportunity to examine Bachi's lactamization method for our synthesis.[22] Under Bachi's conditions (with minor modification employing 1,1′-azobis(cyclohexanecarbonitrile) as a radical initiator), the reaction of isocyanide (±)-**16**, formed in situ by the dehydration of formamide (±)-**15** with $POCl_3$, proceeded smoothly to afford the bicyclic lactam (±)-**17** in 80% yield.[18]

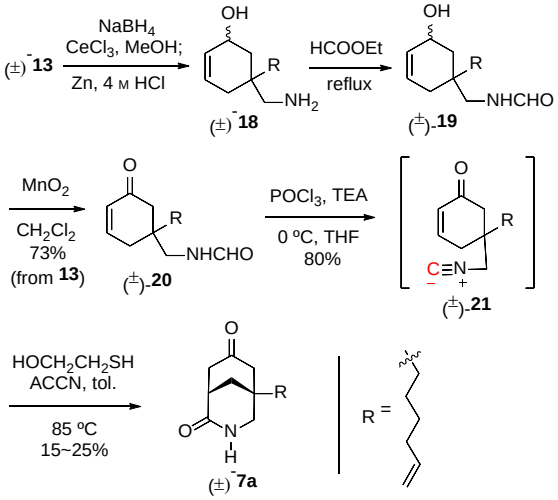
Scheme 2 Unanticipated formation of the hexahydro-1*H*-isoindole- 1,5(4*H*)-dione



To circumvent the deconjugation of enone (±)-**13** during the subsequent transformations, an alternative route was investigated. Thus, (±)-**13** was subjected to sequential chemoselective Luche's

reduction[29] of the enone ($NaBH_4$, $CeCl_3·H_2O$, MeOH) and nitro reduction (Zn, HCl, MeOH). *N*-formylation followed by oxidation of the allylic alcohol with MnO_2 afforded compound (±)-**20** in 73% overall yield from (±)-**13**. Treatment of (±)-**20** with $POCl_3$ yielded isocyanide (±)-**21**, which was used without purification in the Bachi's reaction. To our disappointment, after many trials, the desired cyclization product (±)-**7a** was always obtained in low yields (15–25%).

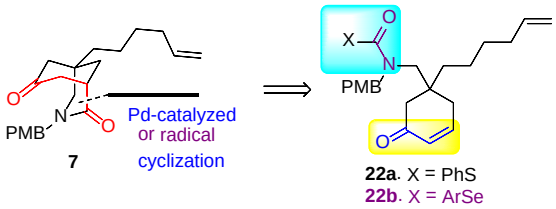
Scheme 3 Attempted construction of the 3-azabicyclo[3.3.1]nonane skeleton by Bachi's lactamization



Considering that all successful Bachi's reactions involve substrates bearing an electron-rich olefin,[18,22] the observed low yield in the formation of (±)-**7a** can be attributed to the electron-deficient nature of the alkene (i.e., enone) in (±)-**21**. Thus, we had to modify our strategy by developing another method to access the 3-azabicyclo[3.3.1]nonane framework **7**.

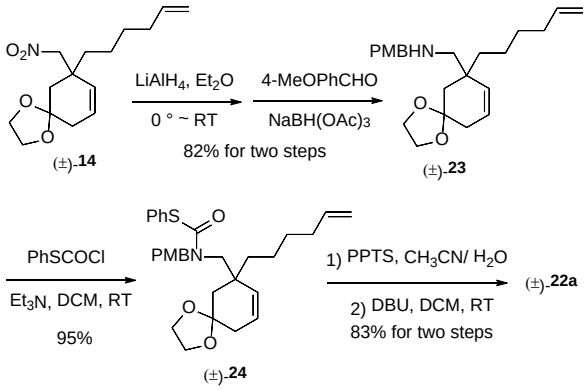
Pd-mediated Heck-type reductive cyclization approach. Although many methods have been developed for the synthesis of the 3-azabicyclo[3.3.1]nonane framework,[30] asymmetric variants are rare. Our new approach for the construction of **7** is outlined in Scheme 4. The new design called for a radical[31] or a Pd-catalyzed intramolecular coupling of thiocarbamate moiety onto an enone (**22**) in a conjugate addition manner. While similar couplings using vinyl or aryl halides as a coupling partner are well documented[32,33] and a palladium-catalyzed cyclization of a carbamoyl chloride or a *S*-phenyl carbamothioate onto electron-rich alkenes[34] has been reported, a combination of the two partners, i.e., the coupling of a carbamoyl chloride or a *S*-phenyl carbamothioate with an enone, is, to our knowledge, without precedent. Nevertheless, this transformation was crucial for our approach; therefore, we decided to explore this chemistry.

Scheme 4 Modified retrosynthetic analysis for the 3-azabicyclo[3.3.1]nonane skeleton



The synthesis of precursor (±)-**22a** is outlined in Scheme 5. Reduction of the nitro group in (±)-**14** with $LiAlH_4$, followed by reductive alkylation of the crude amine with anisaldehyde and $NaBH(OAc)_3$ in CH_2Cl_2 (room temperature, 4 h) furnished the desired PMB-protected product (±)-**23** in 82% yield over the two steps. The latter was exposed to *S*-phenyl chlorothioformate, prepared by Xu's protocol,[35] to yield (±)-**24**. Deacetalization of **24** by PPTS-catalyzed hydrolysis in MeCN/H_2O, followed by treating the resulted β,γ-cyclohexenone with DBU (1.0 equiv) in CH_2Cl_2 (4 h, room temperature) afforded the reconjugated enone (±)-**22a** in 83% yield.

Scheme 5 Synthesis of the racemic cyclization precursor **22a** as a model compound



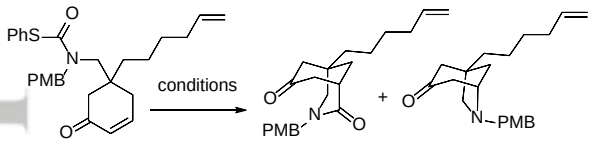
Racemic (±)-**22a** was used for screening the reaction conditions. We first attempted the intramolecular radical cyclization reaction.[31] When the $(Me_3Si)_3SiH$/ AIBN combination was used (toluene, 110 °C), the starting material (±)-**22a** remained intact, whereas the more reactive Bu_3SnH/ AIBN combination led to complex products. Therefore, we focused on transition metal-mediated cyclization reactions.[32,33] After unsuccessful trials using $Pd(OAc)_2$ or $Pd(dppb)Cl_2$ as a catalyst (cf. Table 1, entries 1, and 2), we found that, in the presence of 20 mol% of $Pd(Ph_3P)_4$, the reaction of (±)-**22a** in toluene at 110 °C for 12 h produced (±)-**7** in 12% yield, along with 4% of the decarbonylative cyclization side-product (±)-**25**, and 70% of recovered starting material (±)-**22a** (Table 1, entry 3). The reaction was not improved by adding triethylamine as an additive or ammonium formate as a reductant (Table 1, entry 4). However, to our delight, the yield of the desired product was improved by increasing the catalyst loading. Meanwhile, an increased amount of the decarbonylative side-product (±)-**25** was obtained (Table 1, entries 5 and 6).

These results indicated that no catalytic cycle was established during the reaction. A plausible mechanism for this unprecedented

Heck-type Pd-mediated cyclization reaction is depicted in Scheme 6. The first step involves an oxidative addition of compound (±)-**22a** with Pd(0) to give Pd-complex **M1**, from which two pathways are possible. Path A is the desired one involving the intramolecular insertion reaction leading to Pd-complex **M2**. However, because the subsequent *syn*-β-elimination[35] from **M2** would lead to an anti-Bredt bridgehead enone[36] (±)-**26**, moreover, Pd and H are in a *trans*-disposition, the *syn*-β-elimination is impossible. Hence Pd-complex **M2** can only undergo hydrolysis via its tautomer **M2'** to yield (±)-**7** as the major product. Due to a lack of a *syn*-β-elimination to regenerate and recycle the Pd(0) catalyst, a stoichiometric amount of the catalyst is required for completion of the reaction. In path B, Pd-complex **M1** undergoes a decarbonylation to give Pd-complex **M3**, which goes through an intramolecular insertion reaction to give **M4**. Protolysis of Pd-complex **M4** produces the side-product (±)-**25**.

On the basis of these considerations, we conceived that by introducing a bidentate ligand, such as diphosphine dppp [1,3-bis(diphenylphosphino)pro-pane)], and running the reaction in a donor solvent, such as MeCN, one would be able to inhibit the decarbonylation of the presumed Pd-complex **M1** to give Pd-complex **M3**, and thus prevent the formation of the side-product (±)-**25**. Indeed, in the presence of 1.0 equiv of dppp, the ratio of (±)-**7**/ (±)-**25** was improved slightly (Table 1, entry 7). However, because the polarity of the product is similar to that of the by-product triphenylphosphine oxide (Ph_3PO), their separation was frustrating. To circumvent this problem, further optimization aimed at a replacing of $Pd(Ph_3P)_4$ with $Pd(OAc)_2$ was undertaken (Table 1, entries 8–10). We were pleased to find that when a combination of 1.0 equiv of $Pd(OAc)_2$ and 2.0 equiv of dppp was used as a source of Pd(0), and MeCN as a chelating solvent, the reaction proceeded smoothly at 100 °C to yield the desired product (±)-**7** in 79%. In such a manner, the side reaction leading to (±)-**25** was almost totally inhibited (Table 1, entry 10).

Table 1 Optimization of the Pd-mediated cyclization of carbamothioate-enone **22a**



(±)-**22a** (±)-**7** (±)-**25**

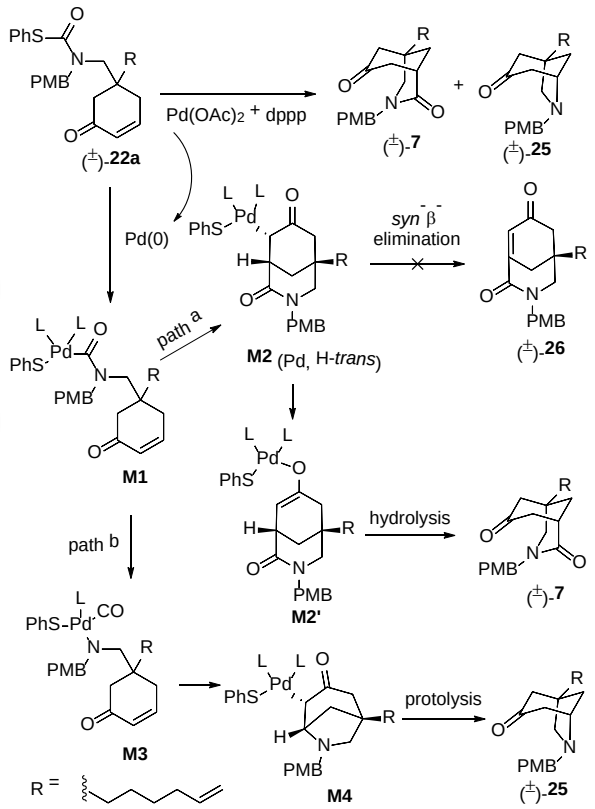
Entry	Conditions	Yield (%)[a]
1	$Pd(OAc)_2$ (0.2 equiv), Bu_4NCl, $HCOONH_4$, DMF, 120 °C	NR[b]
2	$Pd(dppb)Cl_2$ (0.2 equiv), PhMe, DPPB, 110 °C	NR[b]
3	$Pd(Ph_3P)_4$ (0.2 equiv), PhMe, 110 °C	(±)-**7** (12%), (±)-**25** (4%), (±)-**22a** (70%)
4	$Pd(Ph_3P)_4$ (0.2 equiv), Et_3N or $HCOONH_4$, PhMe, 100 °C	Low yield
5	$Pd(Ph_3P)_4$ (0.5 equiv), PhMe, 110 °C	(±)-**7** (28%), (±)-**25** (10%), (±)-**22a** (45%)
6	$Pd(Ph_3P)_4$ (1.0 equiv), PhMe, 110 °C	(±)-**7** (50%), (±)-**25** (28%)
7	$Pd(Ph_3P)_4$ (1.0 equiv), PhMe, DPPP (1.0 equiv), 110 °C	(±)-**7** (58%), (±)-**25** (15%)
8	$Pd(OAc)_2$ (1.0 equiv), DPPP (1.5 equiv), CH_3CN, rt – 90 °C	NR[b]
9	$Pd(OAc)_2$ (1.0 equiv), DPPP (1.5 equiv), CH_3CN, 100 °C	(±)-**7** (75%), (±)-**25** (5%)
10	$Pd(OAc)_2$ (1.0 equiv), DPPP (2.0 equiv), CH_3CN, 100 °C	(±)-**7** (79%), (±)-**25** (trace)

[a] Isolated yield; [b] No Reaction. DMF = *N,N*-Dimethylformamide; DPPB = 1,3-bis(diphenylphosphino) butane; DPPP = 1,3-bis(diphenylphosphino) propane; Ac = acetyl.

A concept for developing Pd-catalyzed Heck-type reductive cyclization. In an effort to develop a catalytic version of the Pd-catalyzed cyclization reaction, α-substituted cyclohexenone (±)-**33** was conceived in the hope that the methylene would provide a proton enabling a *syn*-β-elimination on the envisioned Pd intermediate (cf. **M5** and **7b** in Scheme 8).[17e] For this purpose, racemic substrate (±)-**33** was prepared. The synthesis started from the Morita–Baylis–Hillman reaction[37] of enone (±)-**13** and aldehyde **6b**. Exposing a mixture of (±)-**13** and **6b** to Bu_3P and BINOL in THF (r.t., 7 days) resulted in the formation of adduct (±)-**27** in 85% yield. This result implied that the reaction conditions are mild enough to avoid two possible competing side reactions; i.e., a Henry reaction between the nitroalkane moiety and aldehyde, and a bimolecular self-conjugate addition of the former with the enone group.

Mesylation of (±)-**27** with MsCl/ NEt_3 followed by treating the resultant mesylate with DBU afforded the elimination product (±)-**28** in 81% yield over two steps. In TFA, dienemide (±)-**28** was reduced with Et_3SiH to produce α-substituted enone (±)-**29** in 85% yield. Sequential Luche's reduction[29] and reduction of the nitro group yielded amino cyclohexenol (±)-**30**, which was subjected to reductive *N*-benzylation to yield benzylamine (±)-**31**.

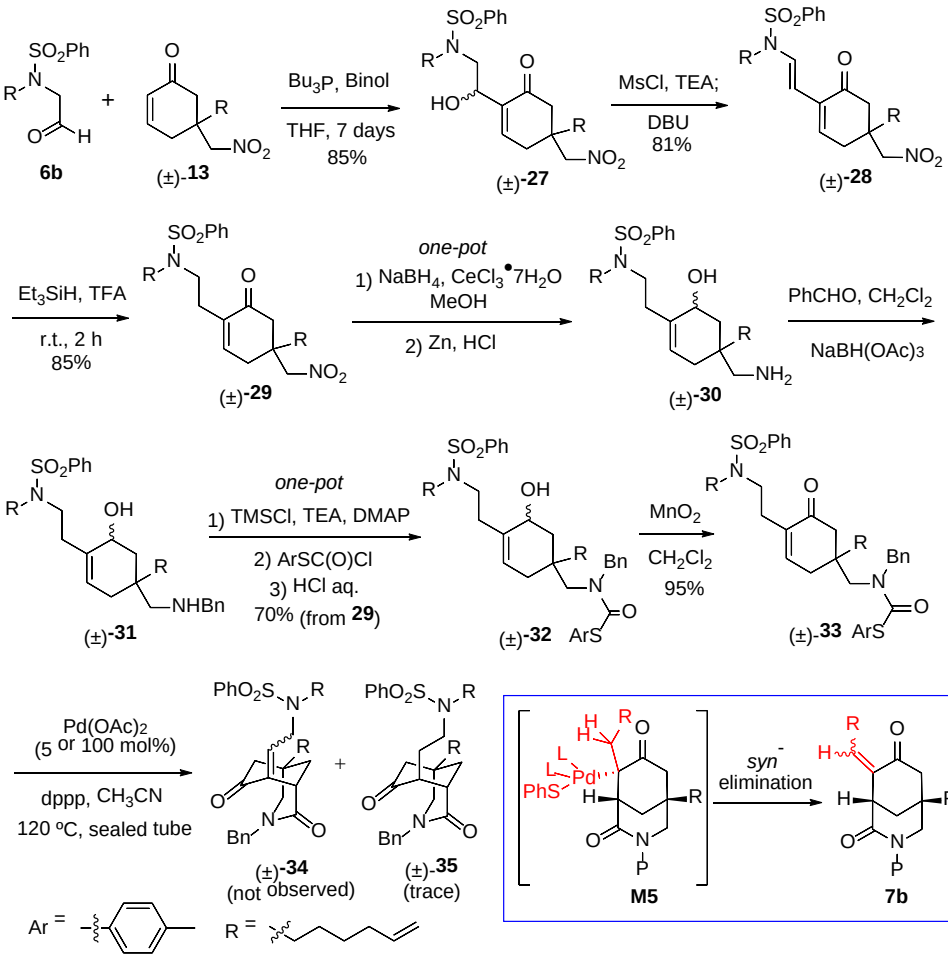
Scheme 6 Plausible mechanisms of the Pd-mediated cyclization of carbamothioate-enone **22a**



Scheme 7 Concept for developing a new Heck-type Pd-catalyzed cyclization of carbamothioate-enone

Temporary in situ protection of the hydroxyl group (TMSCl, TEA, DMAP), followed by carbamation with PhSC(O)Cl and regeneration of the hydroxyl group (HCl aq.) afforded (±)-**32** in one pot. As such, (±)-**32** was prepared from (±)-**29** in an overall yield of 70%. Finally, oxidation of the allylic alcohol with MnO_2 in CH_2Cl_2 furnished the desired cyclohexenone (±)-**33** in 95% yield. To our dismay, when a mixture of (±)-**33** was treated with 5 mol% of $Pd(PPh_3)$ or $Pd(OAc)_2$ and dppp in a sealed tube, no reaction took place. Even using a stoichiometric amount of $Pd(OAc)_2$/dppp, no desired cyclization product (±)-**34** was observed and only a trace amount of reductive Heck-type coupling product (±)-**35** was detected. The failure was attributed to steric hindrance of the substrate. Notably, although our efforts to develop a catalytic Pd-promoted intramolecular Heck-type reaction was discontinued to focus on the total synthesis of haliclonin A, both the stoichiometric reaction[17c,d] and the concept for a catalytic reaction[17e] have inspired and prompted Yang's group to develop a catalytic version for related ring systems (Scheme 8), which enabled them to accomplish the total synthesis of lyconadins A–E.[38]

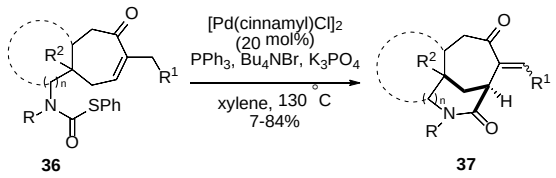
Given that we have succeeded in building the tropinone ring system **7** by the Pd-promoted intramolecular Heck-type reaction, the radical cyclization of **22b** (Scheme 4) was not investigated. It is worth mentioning that during the revision of this manuscript, this chemistry has been elegantly realized by Ishihara and coworkers in a tandem manner, which led them to achieve a formal total synthesis of (−)-haliclonin A based on our total synthesis.[17g]



Catalytic asymmetric total synthesis of haliclonin A.

Organocatalytic construction of the quaternary stereogenic carbon center. To develop a catalytic asymmetric synthesis of haliclonin A (**3**), the first reaction that we needed to investigate was the catalytic asymmetric conjugate addition of nitromethane to 3-(hex-5-enyl)-cyclohex-2-enone (**10**). Considering the high acidity of the α-protons of nitromethane, metal-catalyzed asymmetric conjugate addition[39] would not be suitable for our reaction. A survey of literature showed that only very few examples of highly enantioselective organocatalytic conjugate addition of nitroalkanes to β-substituted cyclic enones have been reported.[26b-d,f] These include one example by Ley,[26b,c] the method of Ye,[26d] and Kwiatkowski's[26f] high-pressure (10 kbar) enhanced method. In these methods, 5-pyrrolidin-2-yltetrazole (**cat-2**, Figure 2), the primary amine-thiourea catalyst containing both a 1,2-diaminocyclohexane and a cinchona alkaloid moiety (**cat-3**),[26d] and 9-amino-9-deoxy-*epi*-cinchonine (**cat-4**),[26e] were utilized as the organocatalyst, respectively (Figure 2).[40]

Scheme 8 Recently realized Pd-catalyzed cyclization of carbamothioate-enone by Yang's group[38]



We first focused on investigating the organocatalytic asymmetric conjugate addition of nitromethane to enone **10**. When Hanessian's conditions were used [L-proline/**B** (*trans*-2,5-dimethylpiperazine) in $CHCl_3$], the desired adduct **9** was formed in 81% yield, 25% *ee* (Table 2, entry 1). Switching solvent to EtOAc only resulted in a drop in yield (72%). With Ley's catalytic system **cat-2**/**B**, (*R*)-**9** was obtained in 70% yield and 89% *ee*. Running the reaction at 0 °C, the *ee* was increased to 92%; however, the yield dropped to 45%. Three bifunctional amine-squaramides (**cat-5**, **cat-6**, and **cat-7**)[41] were also examined, but all were ineffective producing adduct **9** in less than 10% yield. We next turned our attention to primary amine thiourea-type organocatalysts.[42] In this context, Wang and coworkers demonstrated that *trans*-1,2-diaminocyclohexane-based primary amine thiourea **cat-8** afforded interesting results in catalyzing the nitromethane addition to

acyclic substrate 4-phenylbut-3-en-2-one (36% yield, 93% *ee*). They further showed that by using ditrifluoromethyl derivative (*S,S*)-**cat-9**,[26e] both the yield, and enantioselectivity were improved. However, Ye and coworkers had reported that primary amine thiourea **cat-8** was inefficient (15% conversion) in catalyzing the asymmetric addition of nitromethane to cyclohex-2-enone.[26d] In view of the fact that **cat-9**[43] has not yet been used in the addition of nitroalkanes to cyclohex-2-enones, we decided to examine the (*R,R*)-**cat-9**-catalyzed asymmetric conjugate addition of nitromethane to β-substituted cyclohexanone **10**. Initial attempts at running the reaction in the presence of 20 mol% of (*R,R*)-**cat-9** in CH_2Cl_2 for 48 h at r.t. produced the desired adduct (*R*)-**9** in only 15% yield; however, an excellent enantioselectivity of 98% *ee* was observed. After many trials, it was found that by using nitromethane as solvent, running the reaction at 45 °C for 7 days, (*R*)-**9** was formed in 80% yield and 97% *ee*. Importantly, even at a 10 mmol scale, both the high enantioselectivity (97% *ee*) and yield of (*R*)-**9** (88% based on the recovery of starting material, 20%) were retained. By converting (*R*)-**9** into indole derivative (*R*)-**38**, we were able to obtain a single crystal, X-ray diffraction analysis of which showed that, fortunately, the absolute configuration of **38** and thus **9** is *R*, which is the one that we need for the enantioselective total synthesis of haliclonin A (**3**).

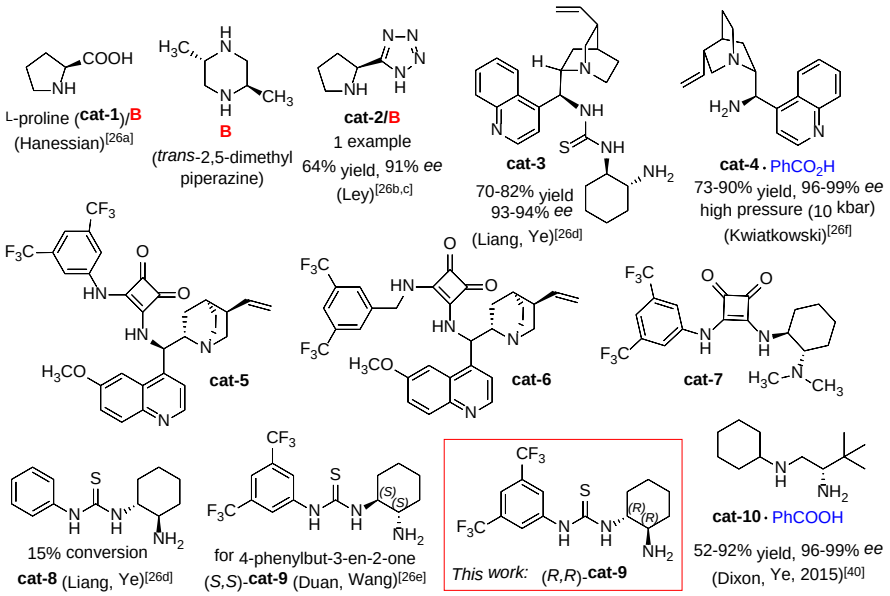


Figure 2 Some reported organocatalysts that were screened in this work for the asymmetric conjugate addition of nitromethane to cyclic enones

Table 2 Screening of organocatalysts and conditions for the asymmetric conjugate addition to β-substituted cyclohexenone

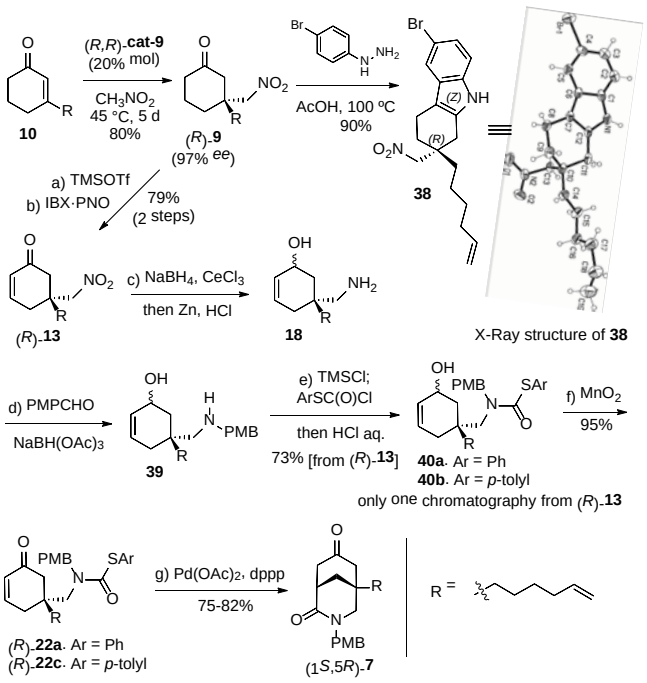
Entry	Conditions[a] ([equiv])	Yield (%)[b]	*ee* (%)[c]
1	**Cat-1** (0.40), **B** (1.5), $CHCl_3$, 50 °C, 7 d	81	26
2	**Cat-1** (0.40), **B** (1.5), EtOAc, 50 °C, 7 d	72	25
3	**Cat-2** (0.15), **B** (1.5), CH_2Cl_2, r.t., 7 d	70	89
4	**Cat-2** (0.15), **B** (1.5), $CHCl_3$, 50 °C, 4 d	75	80
5	**Cat-2** (0.15), **B** (1.5), CH_2Cl_2, 0 °C, 7 d	45	92
6	**Cat-5** (0.20), CH_2Cl_2, CH_3NO_2, r.t. to 40 °C, 7 d	<10	ND[d]
7	**Cat-6** (0.20), CH_2Cl_2, CH_3NO_2, r.t. to 40 °C, 7 d	<10	ND[d]
8	**Cat-7** (0.20), CH_2Cl_2, CH_3NO_2, r.t. to 40 °C, 7 d	<10	ND[d]
9	**Cat-9** (0.20), CH_2Cl_2, r.t., 48 h	15	98
10	**Cat-9 (0.20), CH_3NO_2[e], 45 °C, 5 d**	**80**	**97**
11	**Cat-9** (0.20), CH_3NO_2[e], 45 °C, 7 d	70 (88)[f]	97

[a] Unless otherwise specified, the reaction of **10** (0.5 mmol) with CH_3NO_2 (2.0 mmol) was carried out in 2 mL of solvent; [b] Isolated yield; [c] Determined by chiral HPLC analysis; [d] Not detected. [e] CH_3NO_2 as solvent; [f] The reaction was carried out on a 10 mmol scale, yield in parentheses is based on recovered starting material.

Enantioselective synthesis of 3-azabicyclo[3.3.1]nonane framework (1*S*,5*R*)-7. After securing a robust method to access (*R*)-**9** in high enantioselectivity, its transformation into enone (*R*)-**13** was investigated (Scheme 9). Although in the racemic series, this was realized by a modification of Nicolaou's method (Scheme 2), this protocol presents severe limitations. First, the use of a large excess of IBX·NMO complex (4.0 equiv.) not only resulted in low atom-efficiency, but also introduced difficulties with respect to work-up and product purification. Second, the reaction can only be run on a small scale (0.5 mmol). To develop a scalable protocol to

ensure our total synthesis, an alternative method was investigated. Considering that nitroketone (*R*)-**9** contains two types of acidic α-protons, with those α- to the nitro group being much more acidic, to enable an efficient conversion of the ketone to enone, it is necessary to prevent possible deprotonation of nitro α-H that may cause side reaction and may consume reagents. To tackle this problem, a one-pot, two-step protocol involving chemoselective ketone silyl enol ether (SEE) formation was envisioned. In this regard, Nicolaou and coworkers have developed another method for ketone dehydration via the intermediacy of SEEs by using a 4-methoxypyridine-*N*-oxide (IBX·MPO) complex.[44] The authors have elegantly proved that the oxidation of SEE involves a single electron transfer. It occurred to us that this would be the method of choice for our substrate. Considering the high price of MPO, in particular for a large-scale synthesis, we opted for *N*-methylmorpholine *N*-oxide (NMO) as a less-expensive alternative. In the event, nitroketone (*R*)-**9** was treated with TMSOTf and triethylamine (0 °C, 2 h), and the SEE formed in situ was added to a solution of IBX·NMO complex in DMSO (50 °C, 8 h). In this manner, only 2.5 equiv. of IBX·NMO complex was used, and the desired enone was obtained in 72% yield. Further modification by replacing NMO with pyridine-*N*-oxide (PNO) improved the yield to 79%. It is worth noting that attempted Saegusa oxidation[45] with $Pd(OAc)_2$ led to a complex mixture of products.

After sequential reduction of the ketone and nitro groups in (*R*)-**13**, the resulting amino alcohol **18** was subjected to reductive alkylation [PMPCHO, $NaBH(OAc)_3$] to give *N*-PMB derivative **39**. The latter was converted into *S*-phenyl thiocarbamate **40a** in a one-pot reaction by sequential in situ protection of the hydroxyl group, reaction with *S*-phenyl chlorothioformate, and chemoselective removal of the silyl group. Note that only one chromatographic purification was needed from compound (*R*)-**13** to **40a** (a 73% overall yield of compound **40a** was obtained). Oxidation of **40a** with MnO_2 afforded enone (*R*)-**22a** in 95% yield, followed by the newly developed Pd-mediated Heck-type cyclization reaction to afford the desired product (1*S*,5*R*)-**7** in 79%. To avoid the high toxicity and repulsive odor of both benzenethiol and the corresponding *S*-phenyl chlorothioformate, the reagents used for the preparation of *S*-phenyl carbamothioate (*R*)-**22a**, we envisioned the use of 4-methylbenzenethiol as a safer surrogate of benzenethiol. To our delight, the corresponding *S*-(*p*-tolyl)carbamothioate (*R*)-**22c** was prepared in a similar yield (75–82%), and the cyclization of (*R*)-**22c** proceeded similarly. With the success in cyclization by Heck-type reaction, the radical cyclization reactions[31] of (*R*)-**22a,** (*R*)-**22b** and (*R*)-**22c** were not pursued.



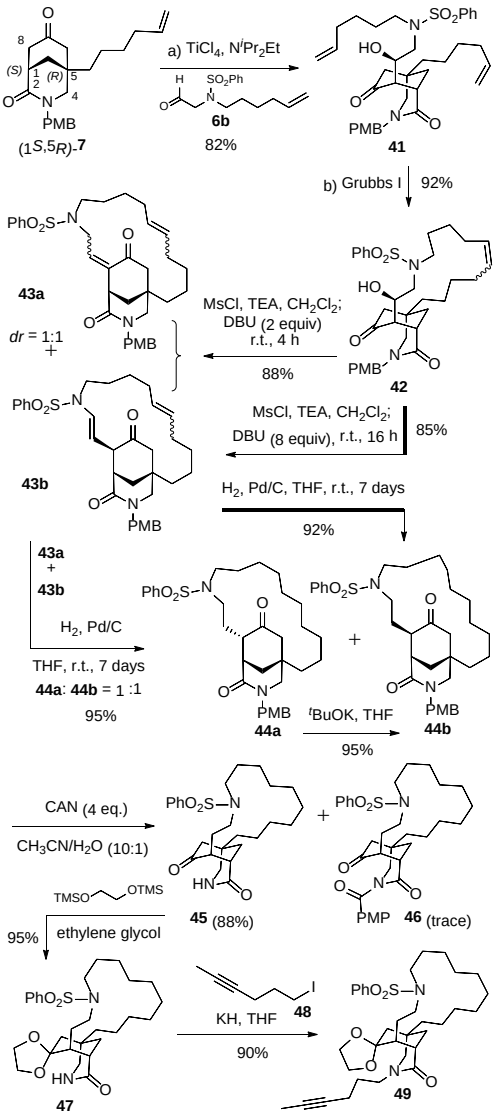
Scheme 9 Construction of the azabicyclo[3.3.1]nonane skeleton based on catalytic asymmetric conjugate addition and Pd-mediated cyclization

Construction of the tricyclic core. Having developed a seven-step enantioselective synthesis of the 3-azabicyclo[3.3.1] nonane framework (1*S*,5*R*)-**7** from **10**, in which the key Heck-type cyclization of (*R*)-**22a,c** can be run on a gram-scale, we then pursued the total synthesis of halichonin A (**3**). Our next task was the regioselective introduction of a side chain at the less-hindered α-position of the ketone. The failure to achieve a direct deprotonation–alkylation in a related ring system[18] prompted us to investigate an indirect aldol addition-based method (cf. Scheme 1). Preliminary investigation on racemic **7**[17c] allowed optimal reaction conditions to be defined. Thus, $TiCl_4$/ Hünig base-mediated aldol addition[46] of (1*S*,5*R*)-**7** with aldehyde **6b**[18] gave adduct **41** in 82% yield as a single regio- and diastereoisomer, the stereochemistry of which has been confirmed previously[17c] (Scheme 10). Subjecting diene **41** to the RCM reaction using Grubbs' first generation catalyst[20] and high dilution technique (0.0003 mol/L in CH_2Cl_2, 40 °C, 24 h)[17c] produced cyclized product **42** as an inseparable mixture of geometric isomers in 92% yield. The lack of diastereoselectivity in this reaction is of no consequence since the alkene will be saturated in a subsequent step. The subsequent mesylation and elimination with DBU merit comments. Initial attempts at mesylation of the geometric isomers **42** followed by treatment of the resultant mesylate with 2.0 equiv of DBU afforded a mixture of α,β-enone **43a** and β,γ-enone **43b** in a ratio of 1:1. Although the two diastereomers are inseparable by flash chromatography on silica gel, the observed characteristic coupling constant (J = 14.6 Hz) in the ^{1}H NMR spectrum allowed the *E*-geometry of the enesulfonamide moiety in **43b** to be deduced. The mixture of **43a** and **43b** was subjected to Pd-catalytic hydrogenation to give a mixture of **44a** and **44b** in a 1:1 ratio. We suspected that **44a** and **44b** were generated from **43a** and **43b**, respectively. To confirm this hypothesis, an in situ monitoring by ^{1}H

NMR was undertaken. It was observed that the isolated olefinic bond was saturated within 4 h, while that of enesulfonamide required about 7 days. We also observed that solvent has a profound impact on the reaction: in EtOAc, whereas the yield was only 20%, in a 1:1 (*v/v*) mixture of EtOAc and MeOH, the yield was 50%. When the reaction was run in anhydrous THF, the yield was as high as 95%, even on a gram scale. Interestingly, **44a** was efficiently converted into **44b** upon treatment with *t*-BuOK in THF (95% yield). ^{1}H NMR monitoring of the elimination reaction with DBU showed that prolonging the reaction time also resulted in a conversion of **44a** into **44b**. Based on these findings, we developed a chemoselective transformation of **42** into **43b** that was achieved simply by using 8.0 equiv of DBU for the elimination step (r.t., 16 h, yield: 85%). Catalytic hydrogenation of **43b** afforded **44b** in 92% yield with the desired aza-macrocycle in place.

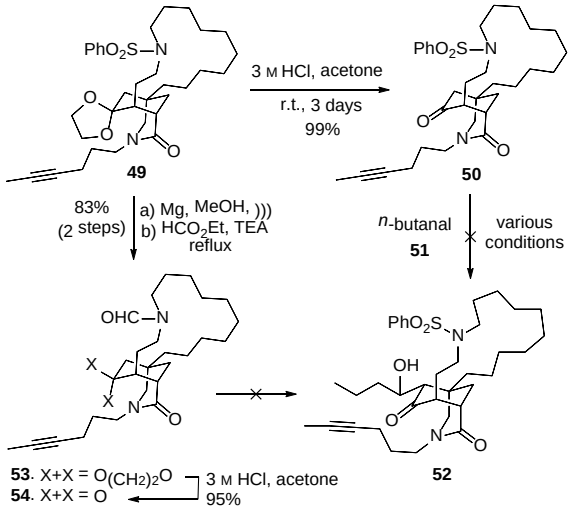
To install an alkynyl group on the amide nitrogen, the PMB group in **44b** was oxidatively cleaved with CAN in a mixture of MeCN/H_2O solvents to give **45**. We observed that the yield was highly dependent on the ratio of mixed solvent. A 4: 1 (*v/v*) mixture of MeCN/H_2O produced **45** in 60% yield, along with imide **46** in 20% yield, whereas with a 1: 1 (*v/v*) mixture of MeCN/H_2O, the yield dropped to 40%. A high yield of 88% was obtained when a 10: 1 (*v/v*) mixture of MeCN/H_2O was used. Attempted direct *N*-alkylation of **45** using alkynyl iodide **48** formed compound **50** in a low yield (10%). Thus the ketone group was first protected to give **47** in 95% yield. *N*-Deprotonation with KHMSD followed by alkylation with **48** gave the desired product **49** in 65% yield (80% BRSM). An excellent yield of 90% was obtained when KH was used as the base for the deprotonation.

Scheme 10 Stereoselective formation of the 17-membered macrocycle to forge the tricyclic core



Construction of the multifunctional 15-membered ring. To undertake an aldol reaction to introduce the side-chain for RCAM, the acetal in **49** was cleaved with a 3 M HCl in acetone (r.t., 3 days), which afforded keto-lactam **50** in 99% yield (Scheme 11). Unexpectedly, under a variety of conditions, the aldol reaction of **50** with *n*-butanal used as a model aldehyde was unsuccessful. Considering that the failure may be due to steric hindrance, the *N*-phenylsulfonyl group in **49** was replaced with a formyl group (**54**) via a three-step protocol consisting of desulfonylation (Mg, MeOH, ultrasonic irradiation),[47] formylation (HCO_2Et, TEA, reflux), and deacetylation (3 M HCl). To our disappointment, an attempted aldol reaction of functionalized ketone **54** was also unsuccessful.

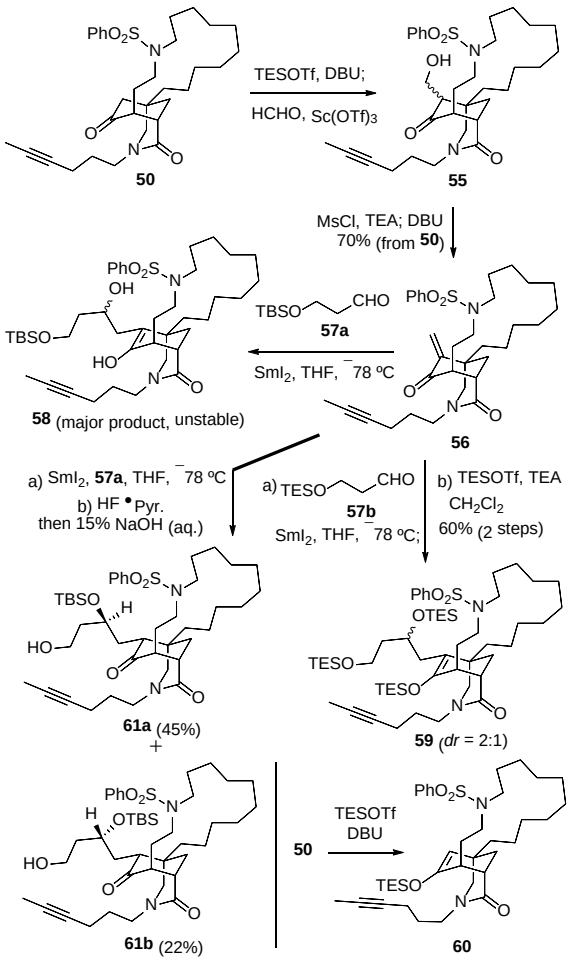
Scheme 11 Attempted direct aldol addition reactions



At this stage, a stepwise tactic employed by Li and Nicolaous in the total syntheses of anominine and tubingensin A attracted our attention.[48] Inspired by Li's work,[49] an indirect approach was pursued. Thus ketone **50** was treated with TESOTf/DBU, and the resulting SEE was subjected to the $Sc(OTf)_3$-promoted[48,49] Mukaiyama aldol reaction with formaldehyde to give the presumed α-hydroxymethylation product **55** (Scheme 12). We were unable to isolate **55** in its pure form because partial epimerization and elimination of **55** into **56** occurred during purification by column chromatography. To our delight, subjecting the diastereomeric mixture **55** to mesylation and elimination with DBU produced **56** in 70% overall yield from **50**. Enone **56** and aldehyde **57a** were reductively coupled using SmI_2 (Kagan's reagent).[50] To our surprise, the major product appeared to be enol **58**. Although the lability of enol **58** prevented its isolation in pure form, its structure was tentatively assigned on the basis of an analysis of the mass spectrum and $^1H/^{13}C$ NMR spectra of the crude material. The following experimental evidence support this hypothesis. First, when *O*-TES protected aldehyde **57b** was successively subjected to the SmI_2-mediated reductive coupling with enone **56**, and to *O*-silylation of the resulting product with TESOTf, tris-*O*-TES-protected SEE **59** was obtained as a separable mixture of two diastereomers in a 2: 1 ratio. Second, in our previous effort to undertake a direct aldol reaction of **50** (Scheme 11), we have observed the formation of SEE **60** from the corresponding ketone **50** upon treatment with TESOTf/DBU, and TESOTf/TEA was ineffective for this transformation. These observations allowed us to deduce that SEE **59** was formed by silylation of the corresponding enol. Although labile, the direct observation of the enol form of an unactivated ketone is a rare phenomenon,[51] which turned out to be crucial for us to achieve the total synthesis of haliclonin A (**3**) (*vide infra*).

To simplify product isolation and characterization, a protocol was developed to allow the isolation of the product in pure ketone form. The protocol comprised the SmI_2-mediated reductive coupling with aldehyde **57a**, *O*-silylation of the crude material with TBSOTf, selective mono-desilylation of the primary silyl ether with Olah's reagent (HF·Pyr.) in THF, and a basic work-up with a 15% aqueous solution of NaOH. In such a manner, two separable diastereomeric ketones, **61a** and **61b**, were obtained in 45% and 22% overall yield, respectively, from **56**. It is noteworthy that although intramolecular reductive coupling of enones[50] with aldehydes is known, the intermolecular version of the latter reaction is unprecedented. The stereochemistries of the two newly formed stereogenic centers were not determined at this stage, but deduced from compound **67** at a later stage (*vide infra*). The major diastereomer **61a** was employed for the total synthesis.

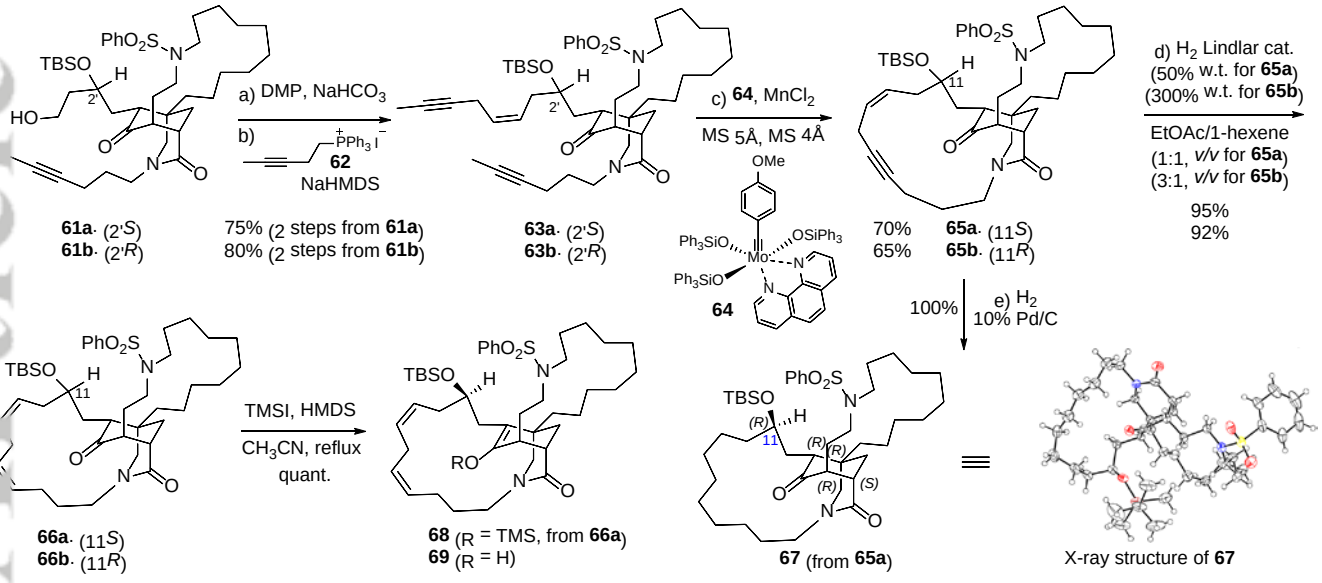
Scheme 12 Introduction of the chiral side-chain



To introduce the enyne moiety, required for the RCAM[19] reaction, diastereoisomer **61a** was subjected to successive Dess-Martin oxidation and Wittig reaction with ylide generated in situ from **62**[52] to afford enediyne **63a** in 75% yield over two steps (Scheme 13). Under Fürstner's alkyne metathesis conditions using Fürstner's catalyst generated in situ from precursor **64** and $MnCl_2$, RCAM of compound **63a** proceeded smoothly to give the tetracyclic framework of haliclonin A (**65a**) in 70% yield.[53] Controlled hydrogenation of the alkynyl group in **65a** using Lindlar catalyst afforded tetracyclic diene (13*Z*,16*Z*)-**66a** in 95% yield.[54] It is worth noting that over-reduction is a common problem in the Lindlar reduction. We tackled this problem by using a mixed solvent system

EtOAc/1-hexene (1:1, *v/v*). Following the same sequence, the minor diastereoisomer **61b** was converted into **66b** in a similar overall yield. However, this diastereoisomer (**65b**) is less reactive towards Lindlar reduction, which required the use of 300% w.t. of Lindlar catalyst and a 3:1 (*v/v*) EtOAc/1-hexene solvent system. Compound **65a** was hydrogenated to give **67** to confirm its structure by single-crystal X-ray diffraction analysis. The result indicates that the configuration at *C*11 is *R*, and the relative stereochemistry around the tetracyclic core is in agreement with that reported for the natural product. The determined absolute configuration 3*R*,4*S*,6*R*,11*R* is consistent with the displayed structure, but opposite to that descibed in the text of ref. 14.

Scheme 13 Formation of the 15-membered macrocycle to build the tetracyclic core



Completion of the total synthesis of (–)-haliclonin A: The end game. Although we were very close to the target, the last battle, the dehydration of ketone to form the enone moiety turned out to be quite challenging. After many unsuccessful attempts for a direct dehydration of **66a** using IBX,[27] $Pd(TFA)_2$,[55] DDQ, etc., we investigated an indirect method via silyl enol ethers. To our surprise, compound **66a** was reluctant to deprotonation with a strong base (LDA, KH) at –78 °C, whereas at a temperature higher than –30 °C, the substrate was destroyed. An alternative method utilizing TMSOTf-TEA combination was also unrewarding. Finally, we were pleased to find that compound **66a** could be quantitatively converted into the corresponding SEE **68** by exposure to TMSI/HMDS in refluxing MeCN,[56] as confirmed by ^{1}H NMR spectroscopic analysis. Attempts to purify the product by flash chromatography on SiO_2 resulted in partial decomposition to give the corresponding enol **69**, possibly stabilized by H-bonding with the nitrogen atom of the lactam. For the subsequent oxidation of SEE to enone, as shown in Table 3, more than fifteen methods and conditions[30,44,17e,57] were tried, but all failed to yield the desired enone **70**. Nevertheless, careful analysis of the results gave us useful information. As can be seen from entries 1, 14, and 15, although the oxidation with $Pd(OAc)_2$[45] and $AZADO^+BF_4$ (Iwabuchi's oxidant)[57] failed to give any product, a combination of the two reagents led to the formation of enone **70**, albeit in only 5% yield.

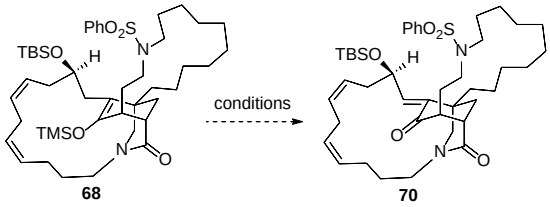


Table **3** Attempted conversion of SEE **68** into enone **70**

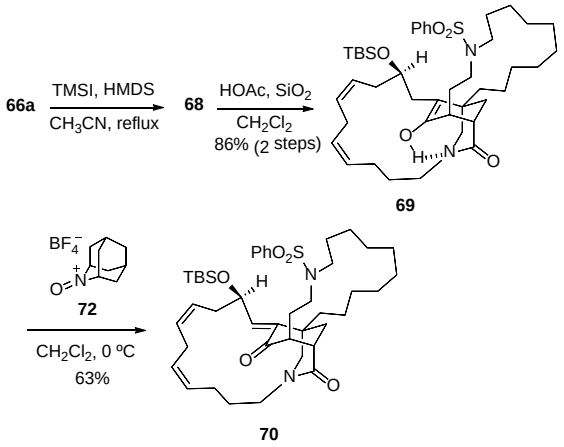
Entry	Conditions (equiv.)	Yield (%)[a]
1	$Pd(OAc)_2$ (5.0), CH_3CN, r.t.	0[b]
2	$Pd(OTFA)_2$ (5.0), CH_3CN, r.t.	Decomposed
3	$Pd(OAc)_2$ (5.0), DMSO, r.t.	0
4	$Pd(OAc)_2$ (5.0), DMSO, 80 °C	Decomposed
5	$Pd_2(dba)_3$ (0.2), **71**[c] (5.0), CH_3CN, reflux	NR[d]
6	PhSeCl (2.0), DCM, –78 °C to –20 °C	NR
7	PhSeCl (1.1), DCM, r.t.	0
8	IBX (2.5), PNO (2.6), DMSO, r.t.	NR
9	IBX (2.5), PNO (2.6), DMSO, 80 °C	Decomposed
10	DDQ (4.0), CH_3CN, r.t.	NR
11	DDQ (4.0), CH_3CN, reflux	Decomposed
12	CAN (2.5), DMF, 0 °C	Decomposed
13	**72**[e] (1.5), DCM, r.t.	NR

14	**72** (1.5), CH_3CN, r.t.	NR
15	**72** (1.5), $Pd(OAc)_2$ (2.0), CH_3CN, r.t.	5[b,f]

[a] Crude yield determined by ^1H NMR spectroscopic analysis; [b] Compound **68** partially decomposed; [c] **71**: Diallyl carbonate; [d] No reaction; [e] **72**: AZADO$^+BF_4^-$ (Iwabuchi's oxidant); [f] Enone **70** is labile.

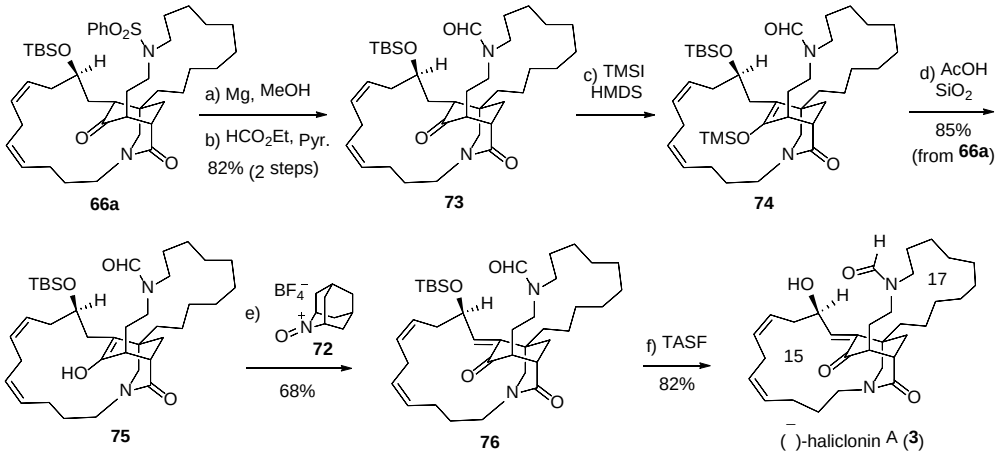
Considering the lability of SEE **68**, we supposed that $Pd(OAc)_2$ might play the role of promoting the cleavage of SEE **68** to give enol **69**, and the latter was oxidized by AZADO$^+BF_4$. To test this idea, SEE **68** was treated with HOAc/ SiO_2, which gave enol **69** in 86% yield from **66a**. Enol **69** is sufficiently stable to allow a chromatographic purification. To our delight, oxidation of enol **69** with AZADO$^+BF_4^-$ (**72**) at 0 °C furnished the desired enone **70** in 63% yield.

Scheme 14 Conversion of ketone **66a** into enone **70**



To complete the total synthesis, compound **66a** was desulfonylated by reaction with Mg in methanol under ultrasonic irradiation,[47] and the resulting crude amine was formylated with ethyl formate/ pyridine to give diamide **73** in 82% yield over two steps (Scheme 15). Ketone **73** was treated with TMSI-HMDS in refluxing acetonitrile[56] to yield enol **75**, and the latter was exposed to HOAc/ silica gel to give enol **75**. Oxidation of enol **75** produced the desired enone **76** in 68% yield. The geometry of the enone **76** was not determined at this stage, but deduced from the final product **3**. *To the best of our knowledge, this represents the first example of direct conversion of an enol into an enone.* Finally desilylation of **76** with tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF)[58] afforded (–)-haliclonin A (**3**) in 82% yield. The sense of optical rotation and spectral (^1H and ^{13}C NMR, the ratio of rotamers = 3: 2) data of our synthetic compound fully matched those reported for the natural haliclonin A (**3**), but a difference exists for the values of specific rotation {synthetic **1**: $[\alpha]_D^{20}$ –42.1 (*c* 1.0, MeOH); natural **1**: $[\alpha]_D^{20}$ –23.6 (*c* 0.14, MeOH)[14]}. The fact that the synthetic compound displayed the same sign of optical rotation as that of the natural product implies that the absolute configuration of natural (–)-haliclonin A (**3**) is 3*R*,4*S*,6*R*,11*R*, which is in agreement with the structure displayed in Figure 1 of ref. 14 (cf. Figure 1), but different from that suggested in the text of ref. 14 (3*S*,4*R*,6*S*,11*S*).

Scheme 15 Completion of the total synthesis of (–)-haliclonin A



Conclusions

We have accomplished the catalytic enantioselective total synthesis of (–)-haliclonin A (**3**). Through this campaign, the structure of natural haliclonin A (**3**) including the stereochemistry of the skipped diene moiety has been confirmed, and its absolute configuration was clarified as 1*E*,3*R*,4*S*,6*R*,11*R*,13*Z*,16*Z*. This

conclusion in turn confirmed Shin's hypothesis about the biosynthetic relationship between haliclonin A and sarain A. In the course of this work, some new chemistries have been developed, which include the thiourea (*R*,*R*)-**cat-9**-catalyzed asymmetric conjugate addition of nitromethane with 3-substituted cyclohex-2-enone, Pd-promoted intramolecular coupling of thiocarbamate moiety with an enone in a conjugate addition manner, SmI_2-mediated bimolecular reductive coupling of enone with aldehyde, and direct transformation of enol into enone. The value of these methods and/ or concepts is highlighted by the development of a catalytic version of the Pd-catalyzed intramolecular coupling of thiocarbamates with enones developed by Yang and coworkers.

Experimental

The general procedure and all the characterization data of the synthetic intermediates as well as the procedures used to prepare them are listed in the Supporting Materials online. Known compounds were recorded in the previous report.[17c,d,18]

Crystallographic data for compounds **38** (CCDC 1442504) and **87** (CCDC 1442503) have been deposited at the Cambridge Crystallographic Data Centre.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2020xxxxx.

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References

[1] Zhu, J.-Y.; Liu, Y.; Liu, Z.-J.; Wang, H.; Zhang, H.-W. Bioactive Nitrogenous Secondary Metabolites from the Marine Sponge Genus *Haliclona*. *Mar. Drugs* **2019**, *17*: 682.

[2] (a) Cheng, B.-C.; Reyes, J. Recent Progress on the Total Syntheses of Macrocyclic Diamine Alkaloids *Nat. Prod. Rep.* **2020**, *37*, 322−337. (b) Tribalat, M.-A.; Marra, M. V.; McCormack, G. P.; Thomas, O. P. Does the Chemical Diversity of the Order Haplosclerida (Phylum Porifera: Class Demospongia) Fit with Current Taxonomic Classification? *Planta Med.* **2016**, *82*, 843−856.

[3] Sakai, R.; Higa, T.; Jefford, C. W.; Benardinelli, G.; Manzamine, A. A Novel Antitumor Alkaloid from a Sponge. *J. Am. Chem. Soc.* **1986**, *108*, 6404–6405.

[4] (a) Cimino, G.; Scognamiglio, G.; Spinella, A.; Trivellone, E. Structural Studies on Saraine A. *J. Nat. Prod*. **1990**, *53*, 1519−1525. (b) Guo, Y.; Madaio, A.; Trivellone, E.; Scognamiglio, G.; Cimino, G. Structural and Stereochemical Studies of Saraines: Macrocyclic Alkaloids of the Sponge *Reniera sarai*. *Tetrahedron* **1996**, *52*, 8341−8348.

[5] Delpech, B. *Chapter Four - The Saraine Alkaloids*, In: The Alkaloids: Chemistry and Biology; vol. *73*, 223−329. Hans-Joachim, K., Ed.; Academic Press: London, **2014**.

[6] (a) Baldwin, J. E.; Whitehead, R. C. On the Biosynthesis of Manzamines. *Tetrahedron Lett.* **1992**, *33*, 2059−2062. (b) Baldwin, J. E.; Ciaridge, T. D. W.; Culshaw, A. J.; Heupel, F. A.; Lee, V.; Spring, D. R.; Whitehead, R. C.; Boughtflower, R. J.; Mutton, I. M.; Upton, R. J. Investigations into the Manzamine Alkaloid Biosynthetic Hypothesis. *Angew. Chem. Int. Ed.* **1998**, *37*, 2661−2663. For a review, see: (c) Duval, R.; Poupon, E. Biomimetic Synthesis of Manzamine Alkaloids. in Biomimetic Organic Synthesis. pp 181−224; Biomimetic Organic Synthesis. Eds. Poupon, E. and Nay, B. Wiley-VCH: Weinheim, **2011**.

[7] Karan, D.; Dubey, S.; Pirisi, L.; Nagel, A.; Pina, I.; Choo, Y. M.; Hamann, M. T. The Marine Natural Product Manzamine A Inhibits Cervical Cancer by Targeting the SIX1 Protein. *J. Nat. Prod.* **2020**, *83*, 286−295.

[8] Yousaf, M.; Hammond, N. L.; Peng, J.-N.; Wahyuono, S.; McIntosh, K. A.; Charman, W. N.; Mayer, A. M. S.; Hamann, M. T. New Manzamine Alkaloids from An Indo-Pacific Sponge. Pharmacokinetics, Oral Availability, and the Significant Activity of Several Manzamines Against HIV-I, AIDS Opportunistic Infections, and Inflammatory Diseases. *J. Med. Chem.* **2004**, *47*, 3512−3517.

[9] Hamann, M. T. The Manzamines as an Example of the Unique Structural Classes Available for the Discovery and Optimization of Infectious Disease Controls Based on Marine Natural Products. *Curr. Pharm. Design* **2007**, *13*, 653−660.

[10] For a review on synthetic studies, see: Matzanke, N.; Gregg, R. J.; Weinreb, S. M. Biomimetic and Synthetic Approaches to Marine Sponge Alkaloids Derived from Bis-pyridine Macrocycles. A review. *Org. Prep. Proced. Int.* **1998**, *30*, 1−51.

[11] For enantioselective total syntheses: Madangamines: (a) Ballette, R.; Perez, M.; Proto, S.; Amat, M.; Bosch, J. Total Synthesis of (+)-Madangamine D. *Angew. Chem. Int. Ed.* **2014**, *53*, 6202−6205. Manzamines: (b) Toma, T.; Kita, Y.; Fukuyama, T. Total Synthesis of (+)-Manzamine A. *J. Am. Chem. Soc.* **2010**, *132*, 10233−10235. (c) Humphrey, J. M.; Liao, Y.-S.; Ali, A.; Rein, T.; Wong, Y.-L.; Chen, H.-J.; Courtney, A. K.; Martin, S. F. Enantioselective Total Syntheses of Manzamine A and Related Alkaloids. *J. Am. Chem. Soc.* **2002**, *124*, 8584−8592. Nakadomarin A: (d) Clark, J. S.; Xu, C. Total Synthesis of (−)-Nakadomarin A. *Angew. Chem. Int. Ed.* **2016**, *55*, 4332–4335. (e) Bonazzi, S.; Cheng, B.; Wzorek, J. S.; Evans, D. A. Total Synthesis of (−)-Nakadomarin A. *J. Am. Chem. Soc.* **2013**, *135*, 9338−9341. (f) Cheng, B.; Wu, F.-F.; Yang, X.-B.; Zhou, Y.-D.; Wan, X.-L.; Zhai, H.-B. Efficient Total Synthesis of Marine Alkaloid (−)-Nakadomarin A. *Chem. Eur. J.* **2011**, *17*, 12569−12572. (g) Martin, D. B. C.; Vanderwal, C. D. Concise Synthesis of (−)-Nakadomarin A. *Angew. Chem. Int. Ed.* **2010**, *49*, 2830−2832. (h) Jakubec, P.; Cockfield, D. M.; Dixon, D. J. Total Synthesis of (−)-Nakadomarin A. *J. Am. Chem. Soc.* **2009**, *131*, 16632−16633. (i) Young, I. S.; Kerr, M. A. Total Synthesis of (+)-Nakadomarin A. *J. Am. Chem. Soc.* **2007**, *129*, 1465−1469. (j) Nagata, T.; Nakagawa, M.; Nishida, A. The First Total Synthesis of Nakadomarin A. *J. Am. Chem. Soc.* **2003**, *125*, 7484−7485, Correction: *J. Am. Chem. Soc.* **2003**, *125*, 13618−13618.

[12] For reviews on synthetic studies, see: (a) Sisko, J.; Weinreb, S. M. Construction of the Tricyclic Core of the Marine Alkaloid Sarain A. *J. Org. Chem.* **1991**, *56*, 3210−3211. (b) Heathcock, C. H.; Clasby, M.; Griffith, D. A.; Henke, B. R.; Sharp, M. J. Progress toward the Synthesis of Sarain A. *Synlett* **1995**, 467−474. (c) Sung, M. J.; Lee, H. I.; Chong, Y.;

Cha, J. K. Facile Synthesis of the Tricyclic Core of Sarain A. 3-Oxidopyridinium Betaine Cycloaddition Approach. *Org. Lett.* **1999**, *1*, 2017−2019. (d) Price Mortimer, A. J.; Pang, P. S.; Aliev, A. E.; Tocher, D. A.; Porter, M. J. Concise Synthesis of Bicyclic Aminals and Their Evaluation as Precursors to the Sarain core. *Org. Biomol. Chem.* **2008**, *6*, 2941−2951. (e) Yang, R.-F.; Huang, P.-Q. Studies towards an Enantioselective Total Synthesis of Sarain A: A Concise Asymmetric Construction of the Diazatricyclic Core. *Chem. Eur. J.* **2010**, *16*, 10319−10322. (f) Franklin, A. I.; Bensa, D.; Adams, H.; Coldham, I. Transannular Dipolar Cycloaddition as an Approach Towards the Synthesis of the Core Ring System of the Sarain Alkaloids. *Org. Biomol. Chem.* **2011**, *9*, 1901−1907. (g) Wang, Y.; Leng, L. Y.; Liu, Y.; Dai, G. Y.; Xue, F. L.; Chen, Z. H.; Meng, J.; Wen, G. H.; Xiao, Y. X.; Liu, X. Y.; Qin, Y. Asymmetric Synthesis of an Advanced Tetracyclic Framework of (+)-Sarain A. *Org. Lett.* **2018**, *20*, 6701–6704.

[13] (a) Garg, N. K.; Hiebert, S.; Overman, L. E. Total Synthesis of (−)-Sarain A. *Angew. Chem. Int. Ed.* **2006**, *45*, 2912−2915. (b) Becker, M.; Chua, H.; P.; Downham, R.; Douglas, C. J.; Garg, N. K.; Hiebert, S.; Jaroch, S.; Matsuoka, R. T.; Middleton, J. A.; Ng, F. W.; Overman, L. E. Total Synthesis of (−)-Sarain A. *J. Am. Chem. Soc.* **2007**, *129*, 11987−12002, Correction: *J. Am. Chem. Soc.* **2018**, *140*, 5319−5319. (c) Higo, T.; Ukegawa, T.; Yokoshima, S.; Fukuyama, T. Formal Synthesis of Sarain A: Intramolecular Cycloaddition of an Eight-Membered Cyclic Nitrone to Construct the 2-Azabicyclo[3.3.1]nonane Framework. *Angew. Chem. Int. Ed.* **2015**, *54*, 7367−7370.

[14] Jang, K. J.; Kang, G. W.; Jeon, J.; Lim, C.; Lee, H. S.; Sim, C. J.; Oh, K. B.; Shin, J. Haliclonin A, a New Macrocyclic Diamide from the Sponge *Haliclona* sp. *Org. Lett*. **2009**, *11*, 1713−1716.

[15] (a) Ou, W.; Han, F.; Hu, X.-N.; Chen, H.; Huang, P.-Q. Iridium-Catalyzed Reductive Alkylations of Secondary Amides. *Angew. Chem. Int. Ed*. **2018**, *57*, 11354−11358. (b) Wu, D.-P.; He, Q.; Chen, D.-H.; Ye, J.-L; Huang, P.-Q. A Stepwise Annulation for the Transformation of Cyclic Ketones to Fused 6 and 7-Membered Cyclic Enimines and Enones. *Chin. J. Chem.* **2019**, *37*, 315−322. (c) Geng, H.; Huang, P.-Q. Ketone Synthesis by Direct, Orthogonal Chemoselective Hydroacylation of Alkenes with Amides: Use of Alkenes as Surrogates of Alkyl Carbanions. *Chin. J. Chem.* **2019**, *37*, 811−816. (d) Wang, S.-R.; Huang, P.-Q. Cross-coupling of Secondary Amides with Tertiary Amides: The Use of Tertiary Amides as Surrogates of Alkyl Carbanions for Ketone Synthesis. *Chin. J. Chem.* **2019**, *37*, 887−891. (e) Liu, Y.-P.; Zhu, C.-J.; Yu, C.-C.; Wang, A.-E; Huang, P.-Q. Tf_2O-Mediated Intermolecular Coupling of Secondary Amides with Enamines/ Ketones: A Versatile, Direct Access to β-Enaminones. *Eur. J. Org. Chem*. **2019**, 7169−7174. (f) Xu, Z.; Wang, X.-G.; Wei, Y.-H.; Ji, K.-L.; Zheng, J.-F.; Ye, J.-L.; Huang, P.-Q. Organocatalytic, Enantioselective Reductive Bis-Functionalization of Secondary Amides: One-Pot Construction of Chiral 2,2-Disubstituted 3-Iminoindoline. *Org. Lett.* **2019**, *21*, 7587−7591. (g) Liu, Y.-C.; Zheng, X.; Huang, P.-Q. Photoredox Catalysis for the Coupling Reaction of Nitrones with Aromatic Tertiary Amines. *Acta Chim. Sinica* **2019**, *77*, 850-855. For a mini-review, see: Huang, P.-Q. Direct Transformations of Amides: Tactics and Recent Progress. *Acta Chim. Sinica* **2018**, *76*, 357-365.

[16] For selected examples, see: (a) Huang, P.-Q.; Huang, S.-Y.; Gao, L.-H.; Mao, Z.-Y.; Chang, Z.; Wang, A.-E. Enantioselective Total Synthesis of (+)-Methoxystemofoline and (+)-Isomethoxystemofoline. *Chem. Commun.* **2015**, *51*, 4576−4578. (b) Yang, Z.-P.; He, Q.; Ye, J.-L.; Huang, P.-Q. Asymmetric Total Synthesis and Absolute Configuration Determination of (−)-Verrupyrroloindoline. *Org. Lett.* **2018**, *20*, 4200−4203. (c) Liu, Z.-J.; Huang, P.-Q. Biomimetic Enantioselective Total Synthesis of (–)-Robustanoids A, B and Analogs, *J. Org. Chem*. **2019**, *84*, 5627−5634. For an account, see: (d) Geng, H.; Huang, P.-Q. Rapid Generation of Molecular Complexity by Chemical Synthesis: Highly Efficient Total Synthesis of Hexacyclic Alkaloid (−)-Chaetominine and Its Biosynthetic Implications. *Chem. Rec.* **2019**, *19*, 523−533.

[17] (a) Huang, P.-Q. Towards Step Economical Synthesis of Alkaloids. The 24th International Society of Heterocyclic Chemistry Congress (*ISHC*-24): Abstract book, pp. 58, 2013, Shanghai. (b) Kawagishi, F.; Yokoshima, S.; Fukuyama, T. Synthetic Studies on Haliclonin A. *ISHC*-24: Abstract book, pp. 95, 2013, Shanghai. (c) Luo, S.-P.; Guo, L.-D.; Gao, L.-H.; Li, S.; Huang, P.-Q. Toward the Total Synthesis of Haliclonin A: Construction of a Tricyclic Substructure. *Chem. Eur. J.* **2013**, *19*, 87−91. (d) Guo, L.-D.; Huang, X.-Z.; Luo, S.-P.; Cao, W.-S.; Ruan, Y.-P.; Ye, J.-L.; Huang, P.-Q. Organocatalytic, Asymmetric Total Synthesis of (–)-Haliclonin A. *Angew. Chem. Int. Ed.* **2016**, *55*, 4064−4068. (e) Guo, L.-D. Ph D dissertation (Huang), Xiamen University, China, **2016**. (f) Orihara, K.; Kawagishi, F.; Yokoshima, S.; Fukuyama, T. Synthetic Studies of Haliclonin A: Construction of the 3-Azabicyclo[3.3.1]nonane Skeleton with a Bridge that Forms the 17-Membered Ring. *Synlett* **2018**, *29*, 769−772. (g) keyama, S.; Ishihara, J. Formal Synthesis of (−)-Haliclonin A: Stereoselective Construction of an Azabicyclo[3.3.1]nonane Ring System by a Tandem Radical Reaction. *Org. Lett.* **2020**, *22*, 5046–5050.

[18] Gao, Y.-J.; Luo, S.-P.; Ye, J.-L.; Huang, P.-Q. An Attempted Approach to the Tricyclic Core of Haliclonin A: Structural Elucidation of the Final Product by 2D NMR. *Chin. Chem. Lett.* **2017**, *28*, 1176−1181.

[19] For selected reviews, see: (a) Hillenbrand, J.; Leutzsch, M.; Fürstner, A. Molybdenum Alkylidyne Complexes with Tripodal Silanolate Ligands: The Next Generation of Alkyne Metathesis Catalysts. *Angew. Chem. Int. Ed.* **2019**, *58*, 15690–15696. (b) Ehrhorn, H.; Tamm, M. Well-Defined Alkyne Metathesis Catalysts: Developments and Recent Applications. *Chem. Eur. J.* **2019**, *25*, 3190–3208. (c) Vanderwal, C. D.; Atwood, B. R. Recent Advances in Alkene Metathesis for Natural Product Synthesis-Striking Achievements Resulting from Increased Sophistication in Catalyst Design and Synthesis Strategy. *Aldrichimica Acta* **2017**, *50*, 17–27. (d) Fürstner, A. Alkyne Metathesis on the Rise. *Angew. Chem. Int. Ed.* **2013**, *52*, 2794–2819.

[20] (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. Synthesis and Activity of a New Generation of Ruthenium-Based Olefin Metathesis Catalysts Coordinated with 1,3-Dimesityl-4,5-dihydroimidazol-2-ylidene Ligands. *Org. Lett.* **1999**, *1*, 953−956. (b) Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H. A General Model for Selectivity in Olefin Cross Metathesis. *J. Am. Chem. Soc.* **2003**, *125*, 11360−11370. For reviews on the use of metathesis in total synthesis, see: (c) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. Metathesis Reactions in Total Synthesis. *Angew. Chem. Int. Ed.* **2005**, *44*, 4490–4527. (d) Fürstner, A. Metathesis in total synthesis. *Chem. Comm.* **2011**, *47*, 6505–6511. Macrocycle formation by RCM with Grubbs I under high dilution conditions, see: (e) Fürstner, A.; Langemann, K. Conformationally Unbiased Macrocyclization Reactions by Ring Closing Metathesis. *J. Org. Chem.* **1996**, *61*, 3942−3943. (f) Fürstner, A.; Langemann, K. Total Syntheses of (+)-Ricinelaidic Acid Lactone and of (−)-Gloeosporone

Based on Transition-Metal-Catalyzed C−C Bond Formations. *J. Am. Chem. Soc.* **1997**, *119*, 9130–9136.

[21] For a recent review, see: Cheng-Sánchez, I.; Sarabia, F. Recent Advances in Total Synthesis via Metathesis Reactions. *Synthesis* **2018**, *50*, 3749−3786.

[22] Bachi, M. D.; Balanov, A.; Bar-Ner, N. Thiol Mediated Free Radical Cyclization of Alkenyl and Alkynyl Isocyanides. *J. Org. Chem.* **1994**, *59*, 7752−7758.

[23] For a review, see: Sukhorukov, A. Y.; Sukhanova, A. A.; Zlotin, S. G. Stereoselective Reactions of Nitro Compounds in the Synthesis of Natural Compound Analogs and Active Pharmaceutical Ingredients. *Tetrahedron* **2016**, *72*, 6191–6281.

[24] For recent a review, see: Chen, W.; Zhang, H.-B. Asymmetric Construction of All-carbon Quaternary Stereocenters in the Total Synthesis of Natural Products. *Sci. China Chem.* **2016**, *59*, 1065−1078.

[25] For selected reviews, see: (a) Bella, M.; Gasperi, T. Organocatalytic Formation of Quaternary Stereocenters. *Synthesis* **2009**, 1583−1614. (b) Odagi, M.; Nagasawa, K. Recent Advances in Natural Products Synthesis Using Bifunctional Organocatalysts bearing a Hydrogen-Bonding Donor Moiety. *Asian J. Org. Chem.* **2019**, *8*, 1766−1774.

[26] For selected examples with high enantioselectivity, see: (a) Hanessian, S.; Pham, V. Catalytic Asymmetric Conjugate Addition of Nitroalkanes to Cycloalkenones. *Org. Lett.* **2000**, *2*, 2975−2978. (b) Mitchell, C. E. T.; Brenner, S. E.; Garcia-Fortanet, J.; Ley, S. V. An Efficient, Asymmetric Organocatalyst-mediated Conjugate Addition of Nitroalkanes to Unsaturated Cyclic and Acyclic Ketones. *Org. Biomol. Chem.* **2006**, *4*, 2039–2049. (c) Mitchell, C. E. T.; Brenner, S. E.; Ley, S. V. A Versatile Organocatalyst for the Asymmetric Conjugate Addition of Nitroalkanes to Enones. *Chem. Commun.* **2005**, 5346–5348. (d) Li, P. F.; Wang, Y. C.; Liang, X. M.; Ye, J. X. Asymmetric Multifunctional Organocatalytic Michael Addition of Nitroalkanes to α,β-Unsaturated Ketones. *Chem. Commun*. **2008**, 3302–3304. (e) Mei, K.; Jin, M.; Zhang, S.; Li, P.; Liu, W.; Chen, X.; Xue, F.; Duan, W.; Wang, W. Simple Cyclohexanediamine-Derived Primary Amine Thiourea Catalyzed Highly Enantioselective Conjugate Addition of Nitroalkanes to Enones. *Org. Lett.* **2009**, *11*, 2864–2867. (f) Kwiatkowski, P.; Dudziński, K.; Łyźwa, D. Effect of High Pressure on the Organocatalytic Asymmetric Michael Reaction: Highly Enantioselective Synthesis of *γ*-Nitroketones with Quaternary Stereogenic Centers. *Org. Lett.* **2011**, *13*, 3624–3627.

[27] Nicolaou, K. C.; Montagnon, T.; Baran, P. S. Modulation of the Reactivity Profile of IBX by Ligand Complexation: Ambient Temperature Dehydrogenation of Aldehydes and Ketones to α,β-Unsaturated Carbonyl Compounds. *Angew. Chem. Int. Ed.* **2002**, *41*, 993–996.

[28] Hwu, J. R.; Wetzel, J. M. The Trimethylsilyl Cationic Species as a Bulky Proton. Application to Chemoselective Dioxolanation. *J. Org. Chem.* **1985**, *50*, 3946–3948.

[29] Luche, J. L. Lanthanides in Organic Chemistry. 1. Selective 1,2 Reductions of Conjugated Ketones. *J. Am. Chem. Soc.* **1978**, *100*, 2226–2227.

[30] For selected methods for the construction of 3-azabicyclo[3.3.1]nonane motifs, see: (a) Yi, X.; Tang, H. X.; Chen, J.; Xu, X. L.; Ma, Y. M. Facile One-pot Synthesis of A 3-Azabicyclo[3.3.1]nonane Scaffold by A Tandem Mannich Reaction. *Org. Chem. Front.* **2018**, *5*, 3003–3007. (b) Ko, H. M.; Dong, G.-B. Cooperative Activation of Cyclobutanones and Olefins Leads to Bridged Ring Systems by a Catalytic [4 + 2] Coupling. *Nat. Chem.* **2014**, *6*, 739–744.

[31] (a) Boger, D. L.; Mathvink, J. Acyl radicals: intermolecular and intramolecular alkene addition reactions. *J. Org. Chem.* **1992**, *57*, 1429–1443. (b) Rigby, J. H.; Danca, D. M.; Homer, J. H. Carbamoyl Radicals from Se-Phenylselenocarbamates: Intramolecular Additions to Alkenes. *Tetrahedron Lett.* **1998**, *39*, 8413–8416. (c) Grainger, R. S.; Welsh, E. J. Formal Synthesis of (−)-Aphanorphine Using Sequential Photomediated Radical Reactions of Dithiocarbamates. *Angew. Chem. Int. Ed.* **2007**, *46*, 5377-5380. (d) Trost, B. M.; Waser, J.; Meyer, A. Total Synthesis of (−)-Pseudolaric Acid B. *J. Am. Chem. Soc.* **2008**, *130*, 16424–16434.

[32] For a review on Heck reaction, see: Beletskaya, I. P.; Cheprakov, A. V. The Heck Reaction as a Sharpening Stone of Palladium Catalysis. *Chem. Rev.* **2000**, *100*, 3009–3066.

[33] (a) Koreeda, M.; Rima, D. J.; Luengo, J. Palladium-Catalyzed Procedures for [3+2] Annulation via Intramolecular Alkenylpalladation and Arylpalladation. *J. Org. Chem.* **1988**, *53*, 5588–5590. (b) Friestad, G. K.; Branchaud, B. P. A New Approach to the Pancratistatin C-Ring from D-Glucose: Ferrier Rearrangement, Pseudoinversion and Pd-Catalyzed Cyclizations. *Tetrahedron Lett.* **1997**, *38*, 5933–5936.

[34] (a) Hande, S. M.; Nakajima, M.; Kamisaki, H.; Tsukano, C.; Takemoto, Y. Flexible Strategy for Syntheses of Spirooxindoles using Palladium Catalyzed Carbosilylation and Sakurai Type Cyclization. *Org*. *Lett.* **2011**, *13*, 1828–1831. (b) Fielding, M. R.; Grigg, R.; Urch, C. J. Novel Synthesis of Oxindoles from Carbamoyl Chlorides via Palladium Catalysed Cyclisation–anion Capture. *Chem. Comm.* **2000**, 2239–2240.

[35] Jiao, L.; Liang, Y.; Zhang, Q.-F.; Zhang, S.-W.; Xu, J.-X. Catalyst-free, High-yield, and Stereospecific Synthesis of 3-Phenylthio β-Lactam Derivatives. *Synthesis* **2006**, 659–665.

[36] For a review, see: Kraus, G. A.; Hon, Y. S.; Thomas, P. J.; Laramay, S.; Liras, S.; Hanson, J. Organic Synthesis Using Bridgehead Carbocations and Bridgehead Enones. *Chem. Rev.* **1989**, *89*, 1591–1598.

[37] Y. M. A. Yamada, S. Ikegami, Efficient Baylis–Hillman reactions promoted by mild cooperative catalysts and their application to catalytic asymmetric synthesis. *Tetrahedron Lett.* **2000**, *41*, 2165–2169.

[38] Zhang, J. Y.; Yan, Y. T.; Hu, R.; Li, T.; Bai, W. J.; Yang, Y. Enantioselective Total Syntheses of Lyconadins A–E through a Palladium-Catalyzed Heck-Type Reaction. *Angew. Chem. Int. Ed*. **2020**, *59*, 2860–2866.

[39] Sidera, M.; Roth, P. M. C.; Maksymowicz, R. M.; Fletcher, S. P. Formation of Quaternary Centers by Copper-Catalyzed Asymmetric Conjugate Addition of Alkylzirconium Reagents. *Angew. Chem. Int. Ed.* **2013**, *52*, 7995–7999.

[40] After we had established the method for the catalytic asymmetric addition of nitromethane to cyclohexanone **10**, and turned to the total synthesis of haliclonin A, the following method appeared: Gu, X.-D.; Dai, Y.-Y.; Guo, T.-T.; Franchino, A.; Dixon, D. J.; Ye, J.-X. A General, Scalable, Organocatalytic Nitro-Michael Addition to Enones: Enantioselective Access to All-Carbon Quaternary Stereocenters. *Org. Lett.* **2015**, *17*, 1505–1508.

[41] For a recent review, see: Chauhan, P.; Mahajan, S.; Kaya, U.; Hack, D.; Dieter Enders, D. Bifunctional Amine-Squaramides: Powerful Hydrogen-Bonding Organocatalysts for Asymmetric Domino/Cascade Reactions. *Adv. Synth. Catal.* **2015**, *357*, 253–281.

[42] For a recent example, see: Kozma, V.; Fülöp, F.; Szőllősi, G. 1,2-

Diamine-Derived (Thio)phosphoramide Organocatalysts in Asymmetric Michael Additions. *Adv. Synth. Catal.* **2020**, *362*, 2444-2458..

[43] Berkessel, A.; Seelig, B. A Simplified Synthesis of Takemoto's Catalyst. *Synthesis* **2009**, *41,* 2113–2115.

[44] Nicolaou, K. C.; Montagnon, T.; Baran, P. S. Oxidation of Silyl Enol Ethers by Using IBX and IBX·*N*-Oxide Complexes: A Mild and Selective Reaction for the Synthesis of Enones. *Angew. Chem. Int. Ed.* **2002**, *41*, 996–1000.

[45] Ito, Y.; Hirao, T.; Saegusa, T. Synthesis of α,β-Unsaturated Carbonyl Compounds by Palladium(II)-Catalyzed Dehydrosilylation of Silyl Enol Ethers *J. Org. Chem.* **1978**, *43*, 1011–1013.

[46] (a) Mahrwald, R. Diastereoselection in Lewis-Acid-Mediated Aldol Additions. *Chem. Rev.* **1999**, *99*, 1095–1120. (b) Gao, P.; Cook, S. P. A Reductive-Heck Approach to the Hydroazulene Ring System: A Formal Synthesis of the Englerin. *Org. Lett*. **2012**, *14*, 3340–3343.

[47] Nyasse, B.; Grehn, L.; Ragnarsson, U. Mild, Efficient Cleavage of Arenesulfonamides by Magnesium Reduction. *Chem. Commun.* **1997**, 1017–1018.

[48] Bian, M.; Wang, Z.; Xiong, X.-C.; Sun, Y.; Matera, C.; Nicolaou, K. C.; Li, A. Total Syntheses of Anominine and Tubingensin A. *J. Am. Chem. Soc.* **2012**, *134*, 8078–8081.

[49] Kobayashi, S. Rare Earth Metal Trifluoromethanesulfonates as Water-Tolerant Lewis Acid Catalysts in Organic Synthesis. *Synlett* **1994**, 689–701.

[50] (a) Girard, P.; Namy, J. L.; Kagan, H. B. Divalent Lanthanide Derivatives in Organic Synthesis. 1. Mild Preparation of Samarium Iodide and Ytterbium Iodide and Their Use as Reducing or Coupling Agents. *J. Am. Chem. Soc.* **1980**, *102*, 2693–2698. For excellent recent reviews, see: (b) Szostak, M.; Fazakerley, N. J.; Parmar, D.; Procter, D. J. Cross-Coupling Reactions Using Samarium(II) Iodide. *Chem. Rev.* **2014**, *114*, 5959–6039. (c) Benedetti, E.; Bressy, C.; Smietana, M.; Arseniyadis, S. Recent Applications of Kagan's Reagent (SmI_2) in Natural Product Synthesis, in *Efficiency in Natural Product Total Synthesis*. Huang, P.-Q.; Yao, Z.-J.; Richard, P. H. Eds. pp 273-296. John Wiley & Sons, Inc.: Hoboken, USA, **2018**.

[51] For examples of enol in total synthesis, see: (a) Hara, R.; Furukawa, T.; Kashima, H.; Kusama, H.; Horiguchi, Y.; Kuwajima, I. Enantioselective Total Synthesis of (+)-Taxusin. *J. Am. Chem. Soc.* **1999,** *121,* 3072–3082. (b) Kusama, H.; Hara, R.; Kawahara, S.; Nishimori, T.; Kashima, H.; Nakamura, N.; Morihira, K.; Kuwajima, I. Enantioselective Total Synthesis of (−)-Taxol. *J. Am. Chem. Soc.* **2000**, *122,* 3811–3820.

[52] Hickmann, V.; Kondoh, A.; Gabor, B.; Alcarazo, M.; Fürstner, A. Catalysis-Based and Protecting-Group-Free Total Syntheses of the Marine Oxylipins Hybridalactone and the Ecklonialactones A, B, and C. *J. Am. Chem. Soc.* **2011**, *133*, 13471–13480.

[53] (a) Heppekausen, J.; Stade, R.; Goddard, R.; Fürstner, A. Practical New Silyloxy-Based Alkyne Metathesis Catalysts with Optimized Activity and Selectivity Profiles. *J. Am. Chem. Soc.* **2010**, *132*, 11045–11057. (b) Heppekausen, J.; Stade, R.; Kondoh, A.; Seidel, G.; Goddard, R.; Fürstner, A. Optimized Synthesis, Structural Investigations, Ligand Tuning and Synthetic Evaluation of Silyloxy‐Based Alkyne Metathesis Catalysts. *Chem. Eur. J.* **2012**, *18*, 10281–10299. (c) Neuhaus, C. M.; Liniger, M.; Stieger, M.; Altmann, K. Total Synthesis of the Tubulin Inhibitor WF-1360F Based on Macrocycle Formation through Ring-Closing Alkyne Metathesis. *Angew. Chem. Int. Ed.* **2013**, *52*, 5866–5870.

[54] For formation of Z-alkenes by alkyne metathesis/Lindlar reduction, see: Fürstner, A. Teaching Metathesis "Simple" Stereochemistry. *Science* **2013**, *341*, 1229713.

[55] Diao, T.; Stahl, S. S. Synthesis of Cyclic Enones via Direct Palladium-Catalyzed Aerobic Dehydrogenation of Ketones. *J. Am. Chem. Soc.* **2011**, *133*, 14566–14569.

[56] Miller, R. D.; McKean, D. R. The Facile Silylation of Aldehydes and Ketones using Trimethylsilyl Iodide: An Exceptionally Simple Procedure for the Generation of Thermodynamically Equilibrated Trimethylsilylenol Ethers. *Synthesis* **1979**, 730–732.

[57] (a) Hayashi, M.; Shibuya, M.; Iwabuchi, Y. Oxidative Conversion of Silyl Enol Ethers to α,β-Unsaturated Ketones Employing Oxoammonium Salts. *Org. Lett.* **2012**, *14*, 154–157. For an accounts, see: (b) Iwabuchi, Y. Discovery and Exploitation of AZADO: The Highly Active Catalyst for Alcohol Oxidation. *Chem. Pharm. Bull.* **2013**, *61*, 1197-1213. (c) Iwabuchi, Y. Recent Progress in Oxidative Organic Transformations Employing Nitroxyl Radical. *J. Synth. Org. Chem. Jpn.* **2019**, *77,* 424-432.

[58] Scheidt, K. A.; Chen, H.; Follows, B. C.; Chemler, S. R.; Coffey, D. S.; Roush, W. R. Tris(dimethylamino)sulfonium Difluorotrimethylsilicate, a Mild Reagent for the Removal of Silicon Protecting Groups. *J. Org. Chem.* **1998**, *63*, 6436–6437.

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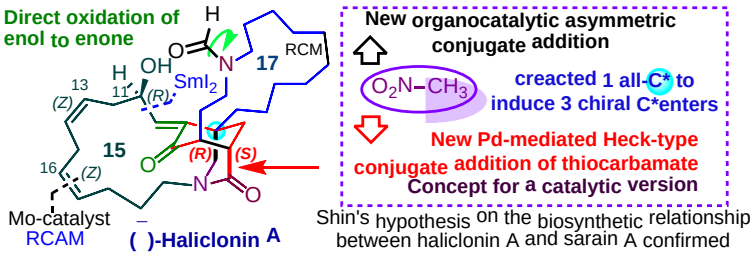

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A crucial synergism of organo- and metal catalysis: The campaign of the catalytic asymmetric total synthesis of (–)-haliclonin A started from an organocatalytic asymmetric conjugate addition, and ended with the oxidation of an enol to the final enone with Iwabuchi's oxoammonium salts. The total synthesis is also highly reliant on metal catalysis: e.g., Pd-mediated Heck-type conjugate addition, RCM with Grubbs' Ru-catalyst, RCAM with Fürstner's Mo-catalyst, and enone-aldehyde reductive cross-coupling with Kagan's reagent (SmI_2).

