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Authors
Schatz, Devon J
Li, Wenqin
Pronin, Sergey V

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Catalytic enantioselective conjugate addition en route to paxilline indoloterpenoids.

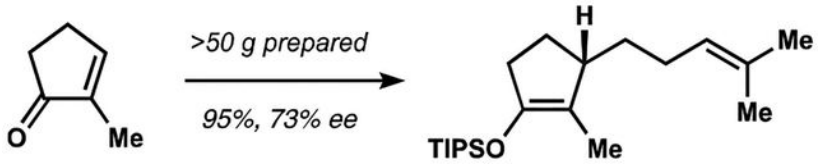
Devon J. Schatz, **Wenqin Li**, **Sergey V. Pronin**

Department of Chemistry, University of California, Irvine, California 92697-2025, United States

Abstract

Development of enantioselective synthesis of precursor en route to paxilline indoloterpenoids is described. Evaluation of 25 diphosphine-based ligands has led to identification of JosiPhos derivative that allows for asymmetric conjugate addition of homoprenyl Grignard reagent to 2-methylcyclopent-2-en-1-one in excellent yield and with appreciable levels of enantioinduction. Application to the conjugate addition of other Grignard reagents is demonstrated.

Graphical abstract



Indoloterpenoids of the paxilline type (e.g., **1**–**4**, Figure 1) belong to a large family of secondary metabolites that exhibit unique molecular architectures and a diverse set of biological activities[1]. More than one hundred congeners identified to date share a common structural motif that contains an indole moiety fused to a rearranged diterpenoid fragment, which results from an unusual polycyclization of a prenylated indole[2]. The representative physiological and cellular effects attributed to this family of natural products include neurological[3] and insecticidal[4] activities, modulation of lipid balance[5], and inhibition of mitosis[6]. The uniting polycyclic motif combined with the diversity of individual structural features of paxilline indoloterpenoids and the broad scope of their biological activities have fascinated organic chemists for the past four decades, leading to the development of numerous syntheses[1,7]. Of particular note are the remarkable efforts by the Smith laboratory that have yielded several strategies for the assembly of the indoloterpenoid motif and have culminated in the syntheses of penitrem D[8] and nodulisporic acids B, C and D[9]. In their contributions, the Johnson group has employed clever desymmetrization tactics to install the vicinal quaternary centers and the tetrahydropyran fragment of paspaline[10]. The recent synthesis of paspaline by the Newhouse group that takes advantage of a biomimetic

intramolecular alkylation of an indole with a pendant tertiary alcohol stands out due to notable brevity of the route[11]. The success of these and other studies notwithstanding, further advances in this area of synthesis are expected to improve access to the members of the paxilline family. We recently demonstrated an entry to these natural products that relies on a new polycyclization to access the common terpenoid core (represented by **5**)[12,13]. Polycyclization-based strategies can dramatically simplify the assembly of structures containing multiple ring systems[14], but find little precedent in studies toward paxilline indoloterpenoids due to the unique and synthetically challenging connectivity pattern found in the shared polycyclic motif[15,16]. The success of our approach was dependent in part on the ability to access scalemic cyclopentanone derivative **6**, which served as a precursor en route to the tricyclic ketone **5**. Here we describe our studies that secured scalable access to **6** with synthetically useful levels of enantioenrichment and enabled a short, enantioselective synthesis of (–)-nodulisporic acid C[13].

Our evaluation of existing methods that achieve highly enantioselective synthesis of 2-methylcyclopentanone derivatives carrying a primary alkyl substituent at the C3 position of the five-membered ring quickly revealed that indirect installation of a homoprenyl substituent imposed by these strategies would result in a significant increase in the number of steps required for the assembly of tricyclic ketone **5**, defeating the advantage of brevity associated with our approach to paxilline indoloterpenoids. We therefore turned our attention to catalytic conjugate additions of organometallic reagents, which promised direct installation of the desired substituents as well as the silyl enol ether functionality necessary for the subsequent alkenylation event. Among the plethora of relevant asymmetric transformations, only a few allow for conjugate addition of alkyl nucleophiles to cyclopentenones with high degree of enantioenrichment[17]. Thus, the pioneering efforts by the Pfaltz[18], Hoveyda[19] and Leighton[20] groups identified three classes of ligands (**8**–**10**, Scheme 1) that enabled highly enantioselective copper-catalyzed conjugate addition of dialkylzinc nucleophiles to cyclopent-2-en-1-one. However, examples of application to relevant α-substituted enones were not reported. The Alexakis group demonstrated that application of bifunctional *N*-heterocyclic carbene-based ligands, such as **12**, allowed for highly enantioselective copper-catalyzed conjugate addition of Grignard reagents to α-substituted cycloalkenones, a first of its kind[21]. At the same time, only moderate levels of enantioenrichment were observed in the case of primary alkyl Grignard nucleophiles. The Minnard group recently discovered that ligands from the JosiPhos family, such as **13**, originally introduced by the Feringa group in relevant enantioselective conjugate additions of Grignard reagents[22], could be applied to 2-methylcyclopent-2-en-1-one[23]. Included in this report was the successful addition of the desired homoprenyl substituent in useful levels of enantioenrichment. Inspired by this report, we sought to examine the potential for improving upon the latter result.

Conjugate addition of homoprenylmagnesium bromide (**14**) to 2-methylcyclopent-2-en-1-one in the presence of JosiPhos SL-J004–1 (**13**) produced desired cyclopentanone **15** in 65% ee (entry 1, Table 1), which was comparable with the result reported by the Minnaard group[23] and provided a reference point for subsequent investigations. We also noticed formation of significant amounts (≥15 mol%) of the 1,2-addition product. Evaluation of a

series of JosiPhos ligands revealed a dramatic dependence of the reactivity and stereochemical outcome of the conjugate addition on the change in the phosphine substituents (entries 2–15). Thus, replacement of the diphenylphosphino group in **13** with dialkylphosphine-derived substituents in **16** and **17** resulted in complete loss of enantioinduction (entries 2 and 3). Switching the cyclohexyl substituents for the *tert*-butyl groups of ligand **18** afforded none of the desired 1,4-addition product (entry 4), as did the alternative arrangement of the phosphine moieties in ligand **19** (entry 5) and the corresponding bis(trifluoromethyl) derivative **20** (entry 6). The reactivity could be rescued with *o*-tolyl derivative **21**, but formation of the racemic product was observed (entry 7). Application of diphosphine **22** produced low but measurable levels of enantioenrichment (entry 8) and similar outcome was observed with bis(diarylphosphino) derivative **23** (entry 9). Gratifyingly, switching phenyl substituents of **23** to 2-furyl substituents in ligand **24** secured access to ketone **15** with appreciable levels of enantioenrichment (entry 10). While the improvement on the stereochemical outcome was only marginal when compared with the Minnaard's conditions, application of ligand **24** did result in the improved efficiency of the conjugate additions and none of the 1,2-addition product was observed. Further changes in the aryl substituents of bis(diarylphosphino) JosiPhos derivatives resulted in complete loss of enantioinduction (entries 11–14) or desired reactivity (entry 15). Changes in other reaction parameters, including concentration (entry 16) and solvents (entries 17–20), proved detrimental to the desired outcome and application of ligands from other families of diphosphine derivatives, including JosPoPhos (**30**, entry 21), WalPhos (**31**–**33**, entries 22–24), BINAP (**34**, entry 25), BIPHEP (**35**, entry 26), PhanePhos (**36**, entry 27), DuPhos (**37**, entry 28), Chiraphos (**38**, entry 29), and DIOP (**39**, entry 30) led to formation of the racemic product.

Application of JosiPhos derivative **24** allowed for efficient production of silyl enol ether **6** from 2-methylcyclopent-2-en-1-one with synthetically useful levels of enantioselectivity (Scheme 2)[16]. The reaction was routinely performed on a multigram scale and over 50 g of enantioenriched product **6** has been procured to date. During our studies en route to (–)-nodulisporic acid C, we discovered that the level of enantioenrichment achieved via the catalytic conjugate addition could be significantly improved at the stage of pivalate **40**, which was prepared in six steps from silyl enol ether **6**. Thus, careful single crystallization from hexanes delivered **40** in 97% ee and excellent recovery of 76%, leaving essentially racemic material in the supernatant. Pivalate **40** could be converted in one step to dienoate **41**, which secured access to (–)-nodulisporic acid C in twelve steps from 2-methylcyclopent-2-en-1-one (longest linear sequence).

Considering the limited precedent associated with the catalytic asymmetric conjugate addition of Grignard reagents to 2-methylcyclopent-2-en-1-one, we sought to evaluate the performance of JosiPhos derivative **24** in the relevant reactions. We discovered that corresponding 2-phenethyl-, but-1-en-4-yl-, and 1-pentyl-substituted silyl enol ethers could be efficiently prepared from 2-methylcyclopent-2-en-1-one with moderate levels of enantioenrichment (entries 1–3 in Table 2). Addition of isobutyl and isopropyl Grignard reagents delivered racemic products (entries 4 and 5) and attempted application of allyl and phenyl Grignard reagents resulted in preferential 1,2-addition (entries 6 and 7). Thus,

application of ligand **24** offered no apparent advantage in the cases of but-1-en-4-yl and 1-pentyl Grignard reagents over the previously report by the Minnaard group[23].

In summary, we disclose our investigations into catalytic asymmetric conjugate additions of Grignard reagents to 2-methylcyclopent-2-en-1-one that have secured convenient and scalable access to the cyclopentanone-derived precursor en route to the shared polycyclic motif of the paxilline indoloterpenoids and has allowed for short enantioselective synthesis of (−)-nodulisporic acid C. Our studies further highlight the challenges associated with the catalytic asymmetric conjugate addition of organometallic reagents to α-substituted cyclic alkenones and the need for new and improved solutions to these challenges in the context of synthesis of natural products[24].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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References

1. Zou Y, Smith AB III. Total synthesis of architecturally complex indole terpenoids: strategic and tactical evolution. J. Antibiot 2018, 71, 185–204.
2. Minami A, Liu C, Oikawa H Total biosynthesis of fungal indole diterpenes using cell factories. Heterocycles 2016, 92, 397–421.
3. Knaus H-G, et al. Tremorgenic indole alkaloids potently inhibit smooth muscle high-conductance calcium-activated potassium channels. Biochemistry 1994, 33, 5819–5828. [PubMed: 7514038]
4. Meinke PT, et al. Discovery of the development candidate N-tert-butyl nodulisporamide: a safe and efficacious once monthly oral agent for the control of fleas and ticks on companion animals. J. Med. Chem 2009, 52, 3505–3515. [PubMed: 19445514]
5. Huang X-H, Tomoda H, Nishida H, Masuma R, Ōmura S Terpendoles, novel ACAT inhibitors produced by *Albophoma yamanashiensis*. I. Production, isolation and biological properties. J. Antibiot 1995, 48, 1–4.
6. Nakazawa J, et al. A novel action of terpendole E on the motor activity of mitotic kinesin Eg5. Chem. Biol 2003, 10, 131–137. [PubMed: 12618185]
7. Corsello MA, Kim J, Garg NK Indole diterpenoid natural products as the inspiration for new synthetic methods and strategies. Chem. Sci 2017, 8, 5836–5844. [PubMed: 28970940]
8. (a)Smith AB III; Kanoh N; Ishiyama H; Hartz RA Total synthesis of (−)-penitrem D. J. Am. Chem. Soc 2000, 122, 11254–11255.(b)Smith AB III; Kanoh N; Ishiyama H; Minakawa N; Rainier JD; Hartz RA; Cho YS; Cui H; Moser WM Tremorgenic indole alkaloids. The total synthesis of (−)-penitrem D. J. Am. Chem. Soc 2003, 125, 8228–8237. [PubMed: 12837093]
9. (a)Zou Y; Melvin JE; Gonzales SS; Spafford MJ; Smith AB III. Total synthesis of (−)-nodulisporic acid D. J. Am. Chem. Soc 2015, 137, 7095–7098. [PubMed: 26029849] (b)Zou Y; Li X; Yang Y; Berritt S; Melvin J; Gonzales S; Spafford M; Smith AB III. Total synthesis of (−)-nodulisporic acids D, C, and B: Evolution of a unified synthetic strategy. J. Am. Chem. Soc 2018, 140, 9502–9511. [PubMed: 30028603]
10. (a)Sharpe RJ, Johnson JS A global and local desymmetrization approach to the synthesis of steroidal alkaloids: stereocontrolled total synthesis of paspaline J. Am. Chem. Soc 2015, 137,

4968–4971. [PubMed: 25856767] (b)Sharpe RJ; Johnson JS Asymmetric total synthesis of the indole diterpene alkaloid paspaline. J. Org. Chem 2015, 80, 9740–9766 [PubMed: 26398568]

11. Kim DE; Zweig JE; Newhouse TR Total synthesis of paspaline A and emindole PB by computational augmentation of a transform-guided retrosynthetic strategy. J. Am. Chem. Soc 2019, 141, 1479–1483. [PubMed: 30626183]
12. George DT; Kuenstner EJ; Pronin SV A concise approach to paxilline indole diterpenes. J. Am. Chem. Soc 2015, 137, 15410–15413. [PubMed: 26593869]
13. Godfrey NA; Schatz DJ; Pronin SV Twelve-step asymmetric synthesis of (−)-nodulisporic acid C. J. Am. Chem. Soc 2018, 140, 12770–12774. [PubMed: 30261724]
14. Nicolaou KC, Edmonds DJ, Bulger PG Cascade reactions in total synthesis. Angew. Chem. Int. Ed 2006, 45, 7134–7186.
15. Rainier JD, Smith AB III. Polyene cyclizations to indole diterpenes. The first synthesis of (+)-emindole SA using a biomimetic approach. Tetrahedron Lett. 2000, 41, 9419–9423.
16. Clark JS, Myatt J, Wilson C, Roberts L, Walshe N Exploration of the biomimetic synthesis of indole-diterpene mycotoxins: an unexpected cascade reaction during the attempted synthesis of emindole SB. Chem. Commun 2003, 39, 1546–1547.
17. For reviews, see:(a)Alexakis A; Benheim C Enantioselective Copper-Catalysed Conjugate Addition. Eur. J. Org. Chem 2002, 3221–3236.(b)Hayashi T; Yamasaki K Rhodium-Catalyzed Asymmetric 1,4-Addition and Its Related Asymmetric Reactions. Chem. Rev 2003, 103, 2829–2844. [PubMed: 12914482] (c)López F; Minnaard AJ; Feringa BL Catalytic Enantioselective Conjugate Addition with Grignard Reagents. Acc. Chem. Res 2007, 40, 179–188. [PubMed: 17370989] (d)Alexakis A; Bäckvall JE; Krause N; Pàmies O; Diéguez M Enantioselective Copper-Catalyzed Conjugate Addition and Allylic Substitution Reactions. Chem. Rev 2008, 108, 2796–2823. [PubMed: 18671436] (e)Harutyunyan SR; den Hartog T; Geurts K; Minnaard AJ; Feringa BL Catalytic Asymmetric Conjugate Addition and Allylic Alkylation with Grignard Reagents. Chem. Rev 2008, 108, 2824–2852. [PubMed: 18698733] (f)Gutnov A Palladium-Catalyzed Asymmetric Conjugate Addition of Aryl-Metal Species. Eur. J. Org. Chem 2008, 4547–4554. (g)Alexakis A, Krause N, Woodward S, Eds. Copper-Catalyzed Asymmetric Synthesis; Wiley-VCH: Weinheim, 2014.(h)Maksymowicz RM; Bissette AJ; Fletcher SP Asymmetric Conjugate Additions and Allylic Alkylations Using Nucleophiles Generated by Hydro- or Carbometallation. Chem. Eur. J 2015, 21, 5668–5678. [PubMed: 25603764]
18. Escher IE; Pfaltz A New chiral oxazoline-phosphite ligands for the enantioselective copper-catalyzed 1,4-addition of organozinc reagents to enones. Tetrahedron 2000, 56, 2879–2888.
19. Degrado SJ; Mizutani H; Hoveyda AH Modular Peptide-Based Phosphine Ligands in Asymmetric Catalysis: Efficient and Enantioselective Cu-Catalyzed Conjugate Additions to Five-, Six-, and Seven-Membered Cyclic Enones. J. Am. Chem. Soc 2001, 123, 755–756. [PubMed: 11456598]
20. Krauss IJ; Leighton JL Highly practical and enantioselective Cu-catalyzed conjugate addition of alkylzinc reagents to cyclic enones at ambient temperature. Org. Lett 2003, 5, 3201–3203. [PubMed: 12943387]
21. (a)Germain N; Guénée L; Mauduit M; Alexakis A Asymmetric Conjugate Addition to α-Substituted Enones/Enolate Trapping. Org. Lett 2014, 16, 118–121. [PubMed: 24320076] (b)Germain N; Alexakis A Formation of Contiguous Quaternary and Tertiary Stereocenters by Sequential Asymmetric Conjugate Addition of Grignard Reagents to 2-Substituted Enones and Mg-Enolate Trapping. Chem. Eur. J 2015, 21, 8597–8606. [PubMed: 25916571] (c)Homs A; Muratore ME; Echavarren AE Enantioselective Total Synthesis of (–)-Nardoaristolone B via a Gold(I)-Catalyzed Oxidative Cyclization. Org. Lett 2015, 17, 461–463. [PubMed: 25563976]
22. Feringa BL; Badorrey R; Peña D; Harutyunyan SR; Minnaard AJ Copper-catalyzed asymmetric conjugate addition of Grignard reagents to cyclic enones. Proc. Natl. Acad. Sci. USA 2004, 101, 5834–5838. [PubMed: 15075388]
23. Calvo BC; Madduri AVR; Harutyunyan SR; Minnaard AJ Copper-Catalysed Conjugate Addition of Grignard Reagents to 2-Methylcyclopentenone and Sequential Enolate Alkylation. Adv. Synth. Catal 2014, 356, 2061–2069.
24. Ting CP; Maimone TJ Total Synthesis of Hyperforin. J. Am. Chem. Soc 2015, 137, 10516–10519. [PubMed: 26252484]

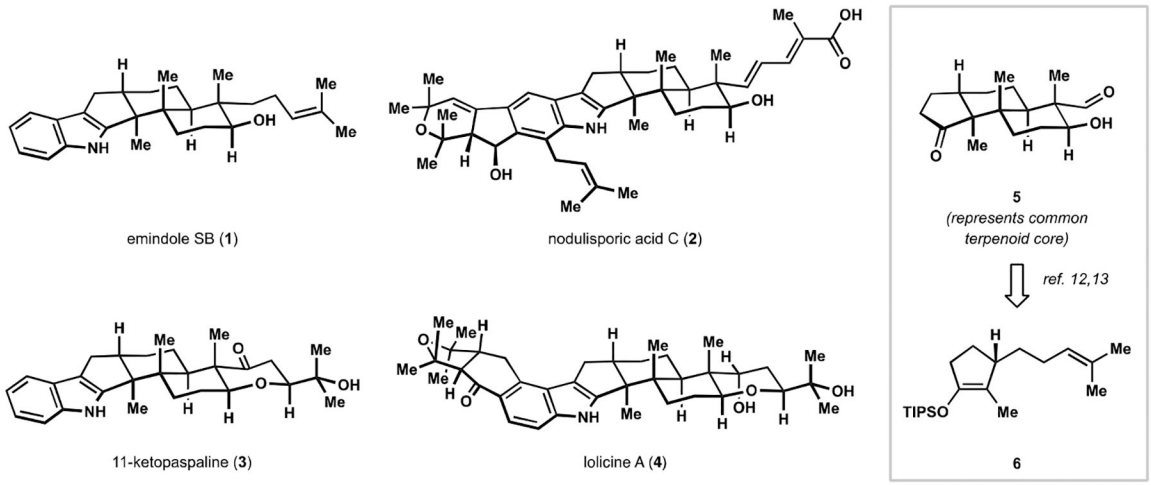
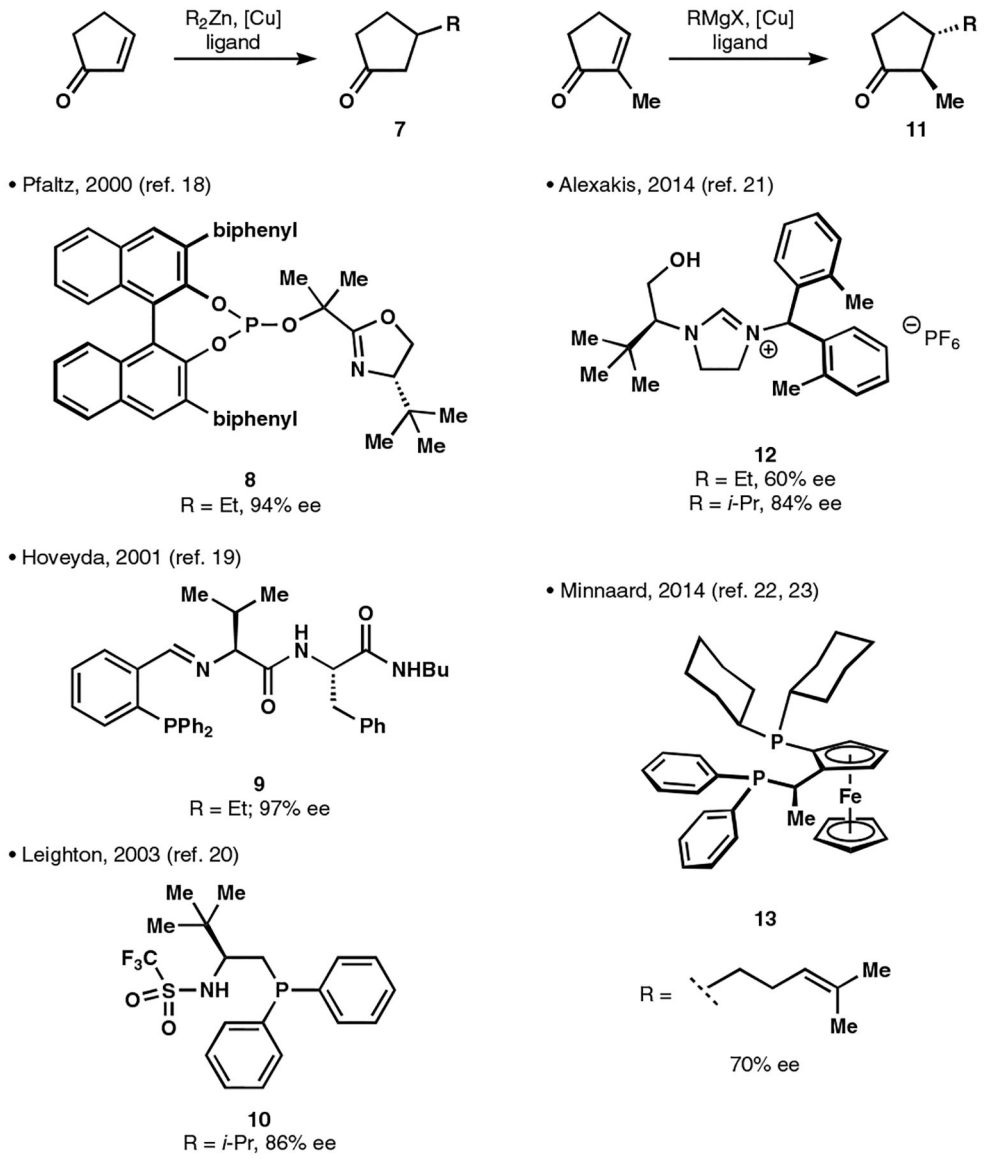


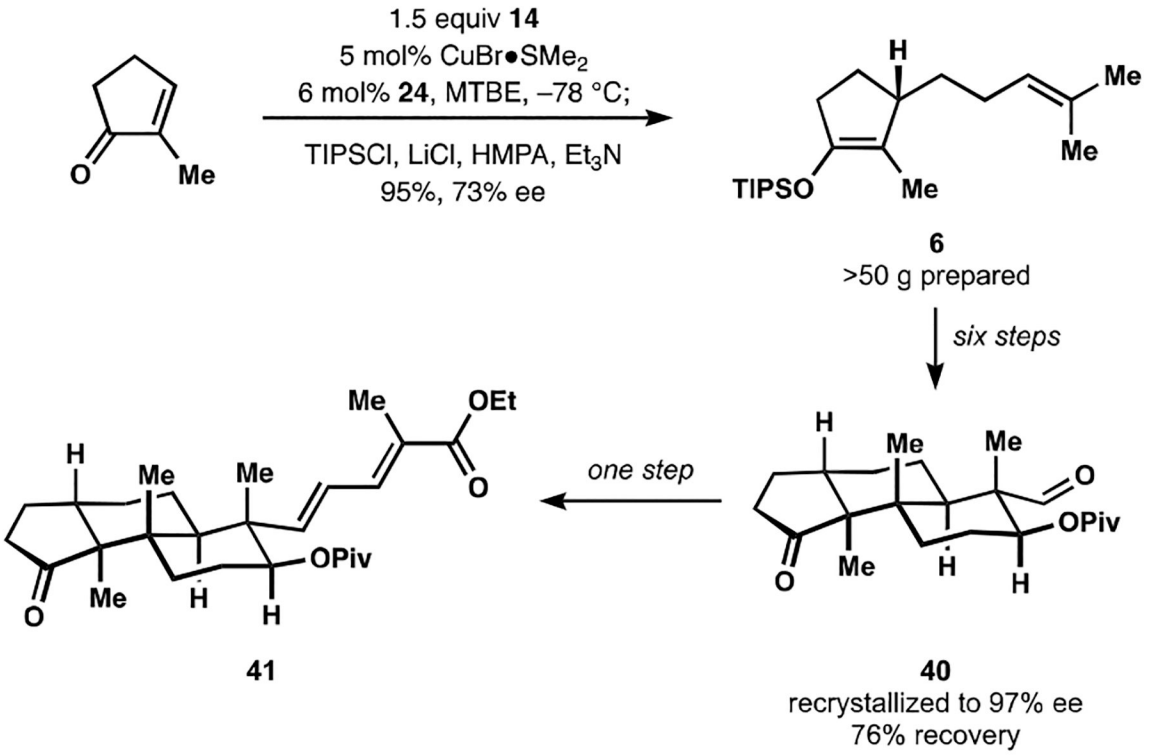
Figure 1.

Representative members of the paxilline family and our approach to the common terpenoid core.



Scheme 1.

Examples of enantioselective conjugate addition of alkyl organometallic reagents to cyclopentenones.

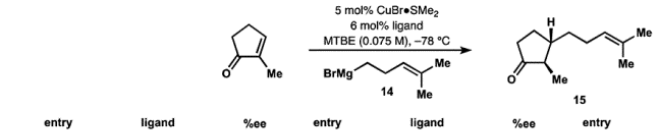


Scheme 2.

Application of enantioselective conjugate addition to the synthesis of the dienoate fragment of nodulisporic acids.

Table 1.

Optimization of the catalytic system en route to **15**.



entry	ligand	%ee	entry	ligand	%ee	entry	ligand	%ee
1	SL-J004-1 (**13**)	65	11	**25**	0	21	SL-J618-1 (**30**)	0
2	SL-J003-1 (**16**)	0	12	SL-J452-1 (**26**)	0	22	SL-W001-1 (**31**)	0
3	SL-J009-1 (**17**)	0	13	SL-J425-1 (**27**)	0	23	SL-W002-1 (**32**)	0
4	SL-J502-1 (**18**)	-[a]	14	SL-J008-1 (**28**)	0	24	SL-W008-1 (**33**)	0
5	SL-J002-1 (**19**)	-[a]	15	SL-J418-1 (**29**)	-[a]	25	(*R*)-BINAP (**34**)	0
6	SL-J011-1 (**20**)	-[a]	16	SL-J015-1 (**24**)	50[b]	26	(*S*)-MeOBIPHEP (**35**)	0
7	SL-J505-1 (**21**)	0	17	SL-J015-1 (**24**)	15[c]	27	(*S*)-Phanephos (**36**)	0
8	SL-J007-1 (**22**)	37	18	SL-J015-1 (**24**)	10[d]	28	(*R,R*)-Me-Duphos (**37**)	0
9	SL-J005-1 (**23**)	30	19	SL-J015-1 (**24**)	50[e]	29	(*S,S*)-Chiraphos (**38**)	0
10	SL-J015-1 (**24**)	73	20	SL-J015-1 (**24**)	63[f]	30	(*S,S*)-DIOP (**39**)	0

[a]No 1,4 addition product observed. [b]Reaction at 0.2 M. [c]Reaction in Et_2O. [d]Reaction in *i*-Pr_2O. [e]Reaction in CH_2Cl_2. [f]Reaction in toluene.

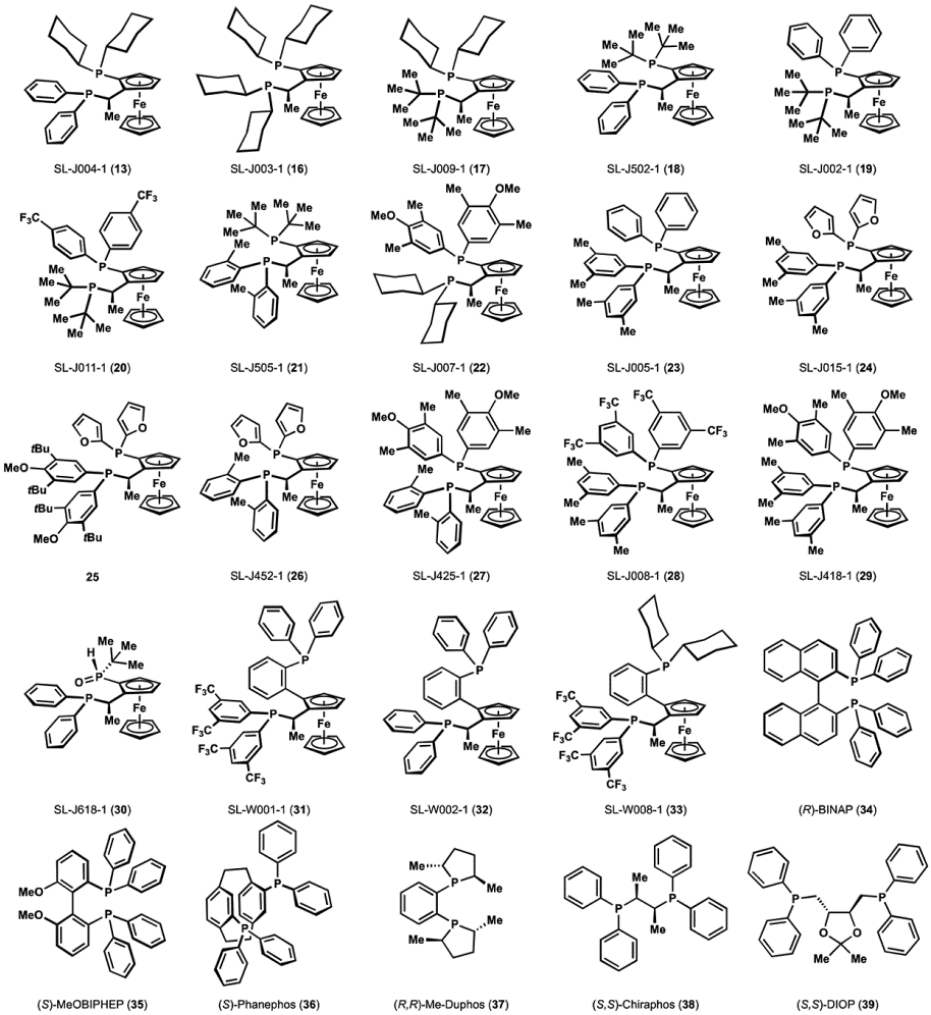
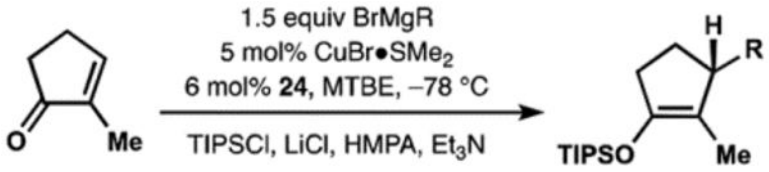
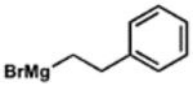
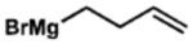
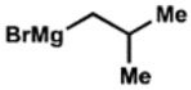
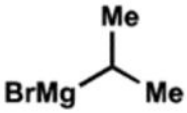
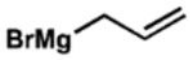
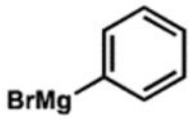


Table 2.

Evaluation of Grignard reagents with JosiPhos Ligand **24** and 2-methylcyclopent-2-en-1-one.



entry	Grignard reagent	yield	% ee[a]
1		80	59
2		80	52
3		84	64
4		75	0
5		80	0
6		1,2 addition	-
7		1,2 addition	-

[a]Determined for the major diastereomer of the corresponding ketones resulting from acid hydrolysis of the isolated silyl enol ethers.