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Sequential Ru−Pd Catalysis: A Two-Catalyst One-Pot Protocol for the Synthesis of N- and O-Heterocycles

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Abstract: An atom economic, selective, and highly practical two-metal one-pot synthesis of heterocycles has been developed that efficiently affords enantio- and diastereopure N- and O-heterocyclic products. Furthermore, use of a chiral catalyst in the two-metal procedure allows formation of all possible diastereomers, even those that are traditionally difficult to access via cyclization routes due to thermodynamics. Interestingly, the nature of the enantiodiscriminating event differs between the use of amine versus alcohol nucleophiles. The method also affords heterocyclic products that are synthetically useful intermediates. Through the *Z*-vinylsilane a variety of stereodefined trisubstituted olefin products can be accessed including several all-carbon motifs. Finally, the utility of these heterocyclic products in total synthesis is demonstrated through concise syntheses of a kainoid intermediate, a constituent of oil of rose, and the ring B portion of bryostatin, a potent chemotherapeutic.

1. Introduction

Functionalized chiral heterocyclic rings such as tetrahydrofurans, pyrans, pyrrolidines, and piperidines are found in a diverse array of bioactive natural products, ranging in complexity from the simple such as nicotine to the complex such as bryostatin. While several methods are available for the synthesis of these moieties, their formation often involves an intramolecular ring closure of a chiral intermediate, necessitating lengthy syntheses and isolation of the cyclization precursor. Furthermore, methods that offer selective access to all possible diastereomers, especially those that are thermodynamically disfavored, are less common. For example, cyclization methods for the formation of cis-2,6-substituted tetrahydropyrans are prevalent, but very few methods offer direct access to the thermodynamically unfavored trans pyrans in isomerically pure form.[1] With these challenges in mind, we envisioned developing a transition-metal-catalyzed synthesis of heterocyclic products that was (1) efficient, generating multiple bonds in one pot, (2) regio- and stereoselective, allowing for all diastereomeric products to be selectively generated, and (3) practical, being experimentally simple and tolerant of multiple functional groups. The basis for our synthesis centered on the ruthenium-catalyzed ene−yne coupling reaction. Employing $[RuCp(CH_3CN)_3]PF_6$ (**1**) to effect alkene/alkyne cross-coupling is a highly versatile and efficient strategy for diene synthesis.[2] We envisioned utilizing the coupling reaction to set up the necessary juxtaposition of reactive groups to induce an in situ cyclization to form heterocycles (Scheme 1). For example, when the ene partner is a homoallylic group such as **3** and the yne partner contains a pendant nucleophile (**2**), the product of coupling, **4**, will contain a *newly formed* allylic group. Since palladium catalysts are known to promote ionization of allylic groups and induce asymmetry in the cyclization, we surmised that the resulting π-allyl complex could be trapped with the pendant nucleophile to form enantioenriched heterocyclic products (**6**) *without isolation of the 1,4-diene intermediate*.

To realize this tandem process, there were several issues that needed to be addressed. The first was the regioselectivity of the ruthenium-catalyzed coupling reactions. In some instances, two isomeric products are generated—the "linear" product **5** and the "branched" product **4**. While both diene intermediates can undergo ionization, the trans double bond present in **5** precludes cyclization to five- and six-membered heterocyclic rings. Therefore, our initial goal was to control the regioselectivity of coupling for essentially all cases. The answer was found by utilizing silyl-substituted alkynes (**7**) wherein steric interactions within the ruthenacycle intermediates favor reaction through **10** (Scheme 2).[3] An additional feature of this strategy is that the resulting vinyl silane offers a pathway for further structural elaboration and differentiates the two resulting double bonds.[4]

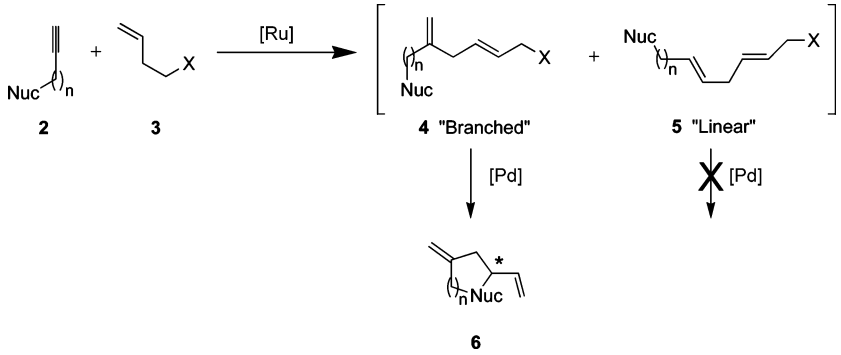
With the first issue addressed, we focused on optimizing the conditions to induce tandem coupling and cyclization. While several metals are known to catalyze nucleophilic trapping of π-allyl species, palladium is one of the most general, forming

(1) Some notable exceptions: (a) Evans, P. A.; Cui, J.; Gharpure, S. J.; Hinkle, R. J. *J. Am. Chem. Soc.* **2003**, *125*, 11456. (b) Marcotte, S.; D'Hooge, F.; Ramadas, S.; Feasson, C.; Pannecoucke, X.; Quirion, J.-C. *Tetrahedron Lett.* **2001**, *42*, 5879. (c) McDonald, F. E.; Singhi, A. D. *Tetrahedron Lett.* **1997**, *38*, 7683. (d) Vares, L.; Rein, T. *J. Org. Chem.* **2002**, *67*, 7226. (e) Williams, D. R.; Clark, M. P.; Berliner, M. A. *Tetrahedron Lett.* **1999**, *40*, 2287. (f) Panek, J. S.; Huang, H. *J. Am. Chem. Soc.* **2000**, *122*, 9836.

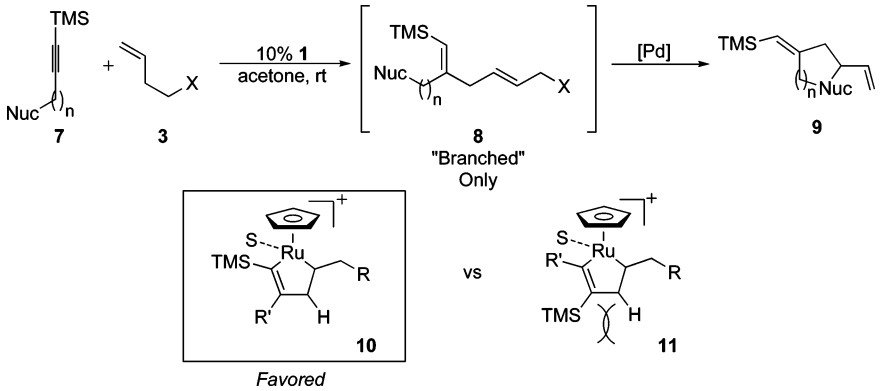
(2) (a) Trost, B. M.; Surivet, J.-P.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 15592. (b) Trost, B. M.; Shen, H. C.; Pinkerton, A. B. *Chem. Eur. J.* **2002**, *8*, 2341. (c) Trost, B. M.; Pinkerton, A. B.; Toste, F. D.; Sperrle, M. *J. Am. Chem. Soc.* **2001**, *123*, 12504. (d) Trost, B. M.; Surivet, J.-P.; Toste, F. D. *J. Am. Chem. Soc.* **2001**, *123*, 2897. (e) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067. (f) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 714. (g) Trost, B. M.; Toste, F. D. *Tetrahedron Lett.* **1999**, *40*, 7739.

(3) Trost, B. M.; Machacek, M. R.; Schnaderback, M. J. *Org. Lett.* **2000**, *2*, 1761.

Scheme 1. Tandem Coupling Cyclization



Scheme 2. Regioisomer Solution



rings that range in size from five-membered to large macrocyclic structures.[5] Furthermore, a diverse set of nucleophiles are tolerated (C, N, S, O), thereby potentiating the type of products that can be formed. Finally, several chiral ligands have been developed for palladium-catalyzed allylic substitution, offering the opportunity to develop an asymmetric process. However, incorporating asymmetric transition-metal catalysis into a one-pot process is a formidable goal.[6] The key issue is compatibility of the two catalyst systems. The reagents or catalysts may interfere with each other by acting as nondissociating ligands that shut down the catalytic cycle or distort the chiral pocket which is crucial for high enantioselectivity. In addition to these general issues, our system poses another challenge. To obtain high enantioselectivity in the cyclization step, it is important that only the chiral palladium catalyst effects ionization and cyclization of **8**. If the achiral ruthenium catalyst participates in this step, the product enantioselectivity would degrade.[7]

To address the issue of selective ionization, we embarked on finding a leaving group (X in **3**) such that ionization only occurred in the presence of the palladium catalyst. Initial studies indicated that allyl carbonates, nitrobenzoates, and acetates were readily ionized in the presence of ruthenium catalyst **1**. Furthermore, both coupling and ionization occurred at similar rates, making them impractical for the one-pot process. Reactions using less activated leaving groups such as phenol[8] were not general and failed with routine nucleophiles, presumably due to the ability of phenol to also act as a nucleophile. Since *p*-nitrophenyl ether can also be ionized by palladium but is less nucleophilic, we chose this functional group as a starting point for our studies. The ease of accessing such aryl ethers by nucleophilic aromatic substitution further enhances the attractiveness of these leaving groups.

2. Enantioselective Heterocyclization Reactions

2.1. Enantioselective N-Heterocyclization Reactions. Our initial goal was the formation of N-heterocycles, utilizing *p*-nitrobenzenesulfonamide as the nucleophile. This group was desirable because of its compatibility with the ruthenium catalyst[9] and for the mild conditions under which it can be removed.[10] To induce asymmetry in the cyclization, we employed the diphenylphosphinobenzoic acid based chiral ligands (**L-1**−**L-4**). A first pass application of (*R*,*R*)-**L-1**

(4) (a) Denmark, S. E.; Choi, J. Y. *J. Am. Chem. Soc.* **1999**, *121*, 5821. (b) Hirabayashi, K.; Ando, J.; Mori, A.; Nishihara, Y.; Hiyama, T. *Synlett* **1999**, 99. (c) Shibata, K.; Miyazawa, K.; Goto, Y. *Chem. Commun.* **1997**, 1309. (d) Gouda, K.-I.; Hagiwara, E.; Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1996**, *61*, 7232. (e) Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1989**, *54*, 268. (f) Tamao, K.; Kobayashi, K.; Ito, Y. *Tetrahedron Lett.* **1989**, *30*, 6051. (g) Hosomi, A.; Kohra, S.; Tominaga, T. *Chem. Pharm. Bull.* **1988**, *36*, 4622.

(5) (a) Trost, B. M. *Chem. Pharm. Bull.* **2002**, *50*, 1. (b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921.

(6) Recent examples of dual transition-metal processes: (a) Jeong, N.; Seo, S. D.; Shin, J. Y. *J. Am. Chem. Soc.* **2000**, *122*, 10220. (b) Doi, T.; Kobuko, M.; Yamamoto, K.; Takahashi, T. *Org. Synth.* **1998**, *63*, 428. (c) Lopez, F.; Castedo, L.; Mascarenas, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 4218.

(7) Ru is known to catalyze allylic ionization and allylic substitution reactions: (a) Renaud, J.-L.; Bruneau, C.; Demerseman, B. *Synlett* **2003**, *3*, 408. (b) Trost, B. M.; Fraisse, P. L.; Ball, Z. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1059. (c) Trost, B. M.; Fraisse, P. L. Unpublished results. (d) Onitsuka, K.; Matsushima, Y.; Takahashi, S. *Yuki Gosei Kagaku Kyokaishi* **2002**, *60*, 752. (e) Matsushima, Y.; Onitsuka, K.; Kondo, T.; Mitsudo, T.; Takahashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 10405. (f) Zhang, S.-W.; Mitsudo, T.; Kondo, T.; Watanabe, Y. *J. Organomet. Chem.* **1993**, *450*, 197.

(8) (a) Takahasi, K.; Miyake, A.; Hata, G. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 230. (b) Takahashi, K.; Miyake, A.; Hata, G. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1012. (c) Brady, D. G. *Chem. Commun.* **1970**, 434. (d) Fiaud, J. C.; Hibon de Gournay, A.; Larchevegere, M.; Kagan, H. B. *J. Organomet. Chem.* **1978**, *154*, 175. (e) Tsuji, J.; Kobayashi, Y.; Kataoka, H.; Takahashi, T. *Tetrahedron Lett.* **1980**, *21*, 3393.

(9) Free amines are not compatible with the $CpRu(CH_3CN)_3$ catalyst.

(10) (a) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373. (b) Fukuyama, T.; Cheung, M.; Jow, C.-K.; Hidai, Y.; Kan, T. *Tetrahedron Lett.* **1997**, *38*, 5831. (c) Wuts, P. G. M.; Northuis, J. M. *Tetrahedron Lett.* **1998**, *39*, 3889.

Scheme 3. Catalyst Compatibility

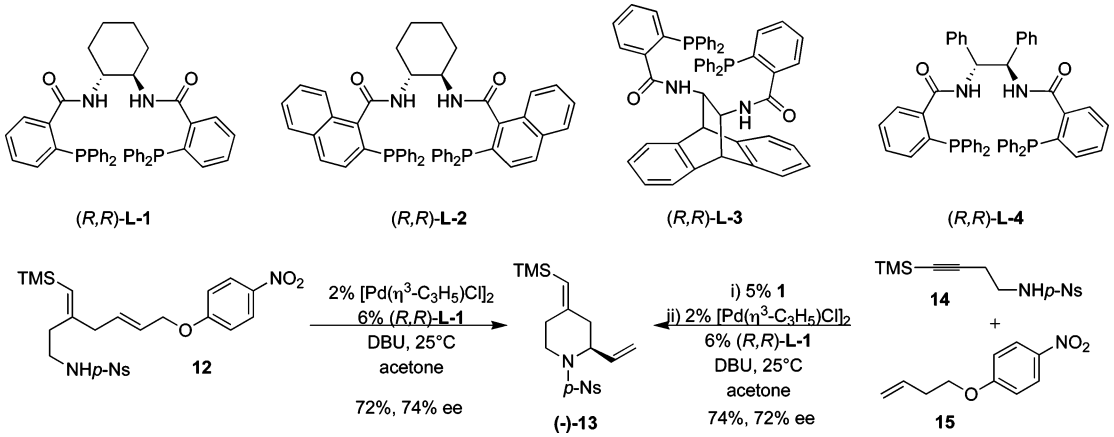
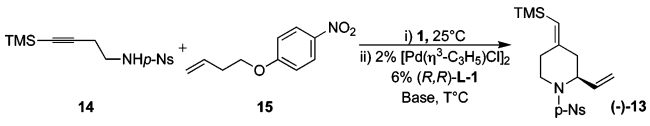


Table 1. Optimization of the N-Heterocyclization Reaction



entry	% **1**	cyclization *T* (°C)	base	cyclization solvent	% yield[a]	% ee[b]
1	10	25	DBU	acetone	74	72
2	5	25	DBU	acetone	80	78
3	5	25	AcOH/NBu_4OAc (2:1)	acetone	14	10
4	5	25	AcOH	acetone	0[c]	
5	5	25	TMG	acetone	74	71
6	5	25	quinuclidine	acetone	77	46
7	5	25	TBAF	acetone	80	54
8	5	60	DBU	acetone	84	68
9	5	0	DBU	acetone	88	70
10	5	25	DBU	DCM	82	89
11	5	25	DBU	dioxane	80	78
12	5	25	DBU	DCE	66	83
13	5	25	DBU	DCM/acetone (3:1)[d]	90	84
14	2	25	DBU	DCM/acetone (10:1)[d,e]	83	88

[a] All reactions run with a 1.7:1 ratio of **15**:**14** with **1** in acetone at 0.2 M for 2 h at room temperature followed by addition of DBU, $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, and (*R*,*R*)-**L-1** in the given solvent to afford 0.08 M and stirring for 2 h at the given temperature. Yields represent isolated yields after chromatography. [b] The ee was determined by HPLC. [c] Only elimination to triene was observed. [d] Ru-catalyzed reaction run in acetone only. Cyclization run in noted solvent mixture. [e] Ruthenium coupling run at 0.5 M in acetone.

afforded piperidine **13** in 72% yield and 74% ee. Even more encouraging was that the enantioselectivity and yield were similar regardless of whether the reaction was performed in two separate operations or in one pot. This similarity implied that the intrinsic reactivity and enantioselectivity of the palladium-catalyzed cyclization were not affected by the presence of the ruthenium catalyst. Furthermore, no background reaction was seen when **12** was subjected to conditions for cyclization without palladium. These results indicate that the dual-catalyst concept is viable (Scheme 3).

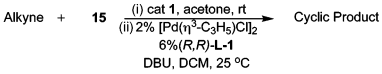
A screen of chiral ligands **L-1**−**L-4** showed that **L-1** reliably afforded product with higher enantioselectivity. Catalyst loading had mild effects on yield with either 2% or 5% **1** and 2% $(Pd(\eta^3\text{-}C_3H_5)Cl)_2$ being ideal. Choice of reaction pH was crucial for the success of the cyclization. Reactions conducted under acidic or buffered conditions (Table 1, entry 3 and 4) led to significant amounts of triene products formed by elimination from the allyl intermediate. The type of base also had a dramatic impact with amine bases such as DBU and TMG showing the best yield and selectivity profiles. Fluoride bases such as TBAF afforded excellent yield but poor enantioselectivity (entry 7). Temperature also had an impact on the selectivity, with both increases and decreases from ambient temperature being deleterious. Clearly, the enantioselectivity is a delicate balance between the rate of ionization, π-allyl complex isomerization, and nucleophilic attack. While all three of these variables are affected by temperature, they may not all be cooperative. Finally, the effect of solvent was investigated. Though the preferred solvent for the ene−yne coupling is acetone, chlorinated solvents such as methylene chloride afforded the highest selectivities for the cyclization step (89% ee). While running the cross-coupling reaction in chlorinated solvents led to significantly reduced conversion, cyclization in a mixed solvent system (entry 13) maintained high enantioselectivity—thereby allowing for a simple injection of methylene chloride, base, and palladium catalyst to the reaction mixture after ene−yne coupling was complete. Lowering the ruthenium loading and accordingly the fraction of acetone present in the cyclization afforded nearly ideal selectivity, while slightly decreasing the yield (entry 14). On the basis of these results, the two mixed solvent systems were adopted as ideal.

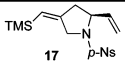
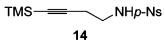
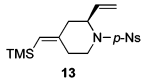
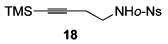
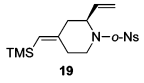
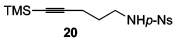
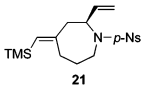
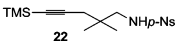
Given our optimized conditions, we investigated the scope of the asymmetric one-pot reaction sequence (Table 2). Both pyrrolidines (**17**) and piperidines (**13**) are formed with good yield and enantioselectivity under the optimized conditions. Seven-membered rings (**21**) are formed with lower efficiency accompanied by significant amounts of elimination to the triene product. Since cyclization to seven-membered rings is kinetically slower, elimination becomes competitive. Interestingly, the enantioselectivity for formation of **21** also drops significantly. Alkyne **22** was synthesized to increase the cyclization rate; however, no ene−yne coupling was observed even under extended reaction times.

The absolute configuration of these heterocyclic products is assigned based upon correlation to a product of known absolute configuration (vide supra). On the basis of our working model,[11] ionization constitutes the enantiodiscriminating event. The predictions are based on literature precedent as well as experimental results. For example, chloride ion is known to

(11) (a) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545. (b) Trost, B. M. *Acc. Chem. Res.* **1996**, *29*, 355.

Table 2. Enantioselective Cyclization Reactions: Nitrogen Nucleophiles



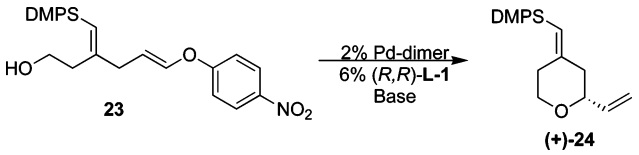
Entry	Alkyne	Condition[a]	Cyclic Product	% Yield[b]	% ee[c]
1	 **16**	A	 **17**	90	91
2	**16**	B	**17**	78	92
3	 **14**	A	 **13**	90	84
4	**14**	B	**13**	83	88
5	 **18**	A	 **19**	90	88
6	 **20**	C	 **21**	37[d]	13
7	 **22**	C	---	No Rxn	---

[a] All reactions run with a 1.7:1 ratio of **15** to alkyne under inert atmosphere under the conditions listed below. Condition A, for a 0.2 mmol scale: (i) 5% **1**, 1.0 mL of acetone, room temperature, 2 h; (ii) 2% [[Pd(η^3-C_3H_5)Cl]$_2$, 6% (*R*,*R*)-**L-1**, 1 equiv of DBU, 3.0 mL of DCM, room temperature, 2 h. Condition B, for a 0.2 mmol scale: (i) 2% **1**, 0.4 mL of acetone, room temperature, 2 h; (ii) 2% [Pd(η^3-C_3H_5)Cl]$_2$, 6% (*R*,*R*)-**L-1**, 1 equiv of DBU, 3.6 mL of DCM, room temperature, 2 h. Condition C, for a 0.2 mmol scale: (i) 10% **1**, 1.0 mL of acetone, room temperature, 2 h; (ii) 2% [Pd(η^3-C_3H_5)Cl]$_2$, 6% (*R*,*R*)-**L-1**, 1 equiv of DBU, 3.0 mL of DCM, room temperature, 2 h. [b] Isolated yields after chromatography. [c] Percent ee was measured by chiral HPLC. [d] Thirty-six percent of triene elimination product was also observed.

increase the rate of isomerization of the palladium π-allyl intermediate, which should decrease the selectivity if ionization is the enantiodiscrimination event. In support of this, addition of tetrabutylammonium chloride to the cyclization reaction causes a precipitous drop in the selectivity.

2.2. Enantioselective O-Heterocyclization Reactions. Since many complex natural products contain chiral pyrans and furans, we were interested in extending the enantioselective mixed-metal process to oxygen-containing heterocycles. However, in contrast to their phenolic and carboxylate counterparts, simple alkyl alcohols are known to be poor nucleophiles for enantioselective palladium π-allyl substitutions.[12] The poor nucleophilicity is attributed to the mismatch between the "hard" alcohol nucleophile and "soft" palladium π-allyl complex. To overcome the inherent mismatch presented by alkoxy nucleophiles, previous solutions have relied on intramolecular closures,[13] large excesses of alcohol, or using tin,[14] boron,[15] silyl,[16] or zinc[17] ethers to "soften" the nucleophile. Furthermore, to our knowledge there were no reports of an *asymmetric* allylic substitution using simple alcohol nucleophiles without boron cocatalysis.[18,19] Despite this significant challenge, we began a search for

Table 3. Optimizing Pyran Formation



entry	Pd source	solvent	base	*T* (°C)	% yield[a]	% ee[b]
1	[Pd(η^3-C_3H_5)Cl]$_2$	DCM	TBAF	25	42	NA[c]
2	[Pd(η^3-C_3H_5)Cl]$_2$	DCM	TMG	25	61	NA[c]
3	$Pd_2(dba)_3$·$CHCl_3$	THF	NEt_3	60	73	72
4	$Pd_2(dba)_3$·$CHCl_3$	THF	NEt_3	25	86	77
5	$Pd_2(dba)_3$·$CHCl_3$	THF	NEt_3	0	83	81
6	$Pd_2(dba)_3$·$CHCl_3$	THF	NEt_3	−35	27	89
7	$Pd_2(dba)_3$·$CHCl_3$	DCM	NEt_3	0	80	94
8	[Pd(η^3-C_3H_5)Cl]$_2$	DCM	NEt_3	0	71	92
9	$Pd_2(dba)_3$·$CHCl_3$	DCM	0.2 equiv NEt_3	0	85	86

[a] All reactions run in degassed solvent under argon with 1 equiv of base for 2 h at 0.08 M at the given temperature. Yields represent isolated yields after chromatography. [b] The ee was determined by HPLC. [c] Racemic dppp ligand used.

conditions that would yield an enantioselective cyclization of 1,4-diene intermediate **23** (Table 3).

Gratifyingly, the palladium-catalyzed cyclization proceeds smoothly under several conditions. Similar to the sulfonamide cases, methylene chloride was found to be the optimum solvent both in terms of yield and selectivity. It was also apparent that $Pd_2(dba)_3$·$CHCl_3$ afforded better yield and selectivity than the π-allyl chloride dimer. Furthermore, of all the bases tested, triethylamine gave the best yield and selectivity. Interesting temperature effects were also noticed, with the enantioselectivity displaying a prominent inverse dependence on temperature. As the temperature of the cyclization was lowered from 60 to 0 °C, there was a continuous increase in the selectivity of (+)-**24**. Temperatures below zero led to poor conversions, and as such 0 °C was chosen as optimal, affording product in 94% ee.

With our optimized conditions in hand, we again tested the one-pot process for scope (Table 4). Furans and pyrans both form in good yield, with pyrans affording the highest selectivities. Attempted seven-membered ring formation was unsuccessful affording only the triene elimination product. The absolute configuration of these heterocyclic products was assigned to be opposite of that found in the sulfonamide cases, based upon subsequent correlation in one case to a known stereochemistry (vide infra). On the basis of our working model,[11] now the nucleophilic addition constitutes the enantiodiscriminating event. This prediction is supported by the fact

(12) (a) Takahashi, K.; Miyaki, A.; Hata, G. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 230. (b) Stork, G.; Poirier, J. M. *J. Am. Chem. Soc.* **1983**, *105*, 1073. (c) Keinan, E.; Roth, Z. *J. Org. Chem.* **1983**, *48*, 1769. (d) Stanton, S. A.; Felman, S. W.; Parkhurst, C. S.; Godleski, S. A. *J. Am. Chem. Soc.* **1983**, *105*, 1964. (e) Keinan, E.; Sahai, M.; Poth, Z.; Nudelman, A.; Herzig, J. *J. Org. Chem.* **1985**, *50*, 3558.

(13) (a) Trost, B. M.; Tenaglia, A. *Tetrahedron Lett.* **1988**, *29*, 2927. (b) Lakhmiri, R.; Lhoste, P.; Sinou, D. *Tetrahedron Lett.* **1989**, *30*, 4669. (c) Thorey, C.; Wilken, J.; Henin, F.; Martens, J.; Mehler, T.; Muzart, J. *Tetrahedron Lett.* **1995**, *36*, 5527. (d) Fournier-Nguefack, C.; Lhoste, P.; Sinou, D. *Tetrahedron* **1997**, *53*, 4353. (e) Hamada, Y.; Seto, N.; Takayanagi, Y.; Nakano, T.; Hara, O. *Tetrahedron Lett.* **1999**, *40*, 7791. (f) Lautens, M.; Fagnou, K.; Rovis, T. *J. Am. Chem. Soc.* **2000**, *122*, 5650.

(14) (a) Trost, B. M.; Bonk, P. J. *J. Am. Chem. Soc.* **1985**, *107*, 8277. (b) Trost, B. M.; Tenaglia, A. *Tetrahedron Lett.* **1988**, *29*, 2931.

(15) (a) Trost, B. M.; McEachern, E. J.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 12702. (b) Trost, B. M.; McEachern, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 8649. (c) Trost, B. M.; Brown, B. S.; McEachern, E. J.; Kuhn, O. *Chem. Eur. J.* **2003**, *9*, 4442.

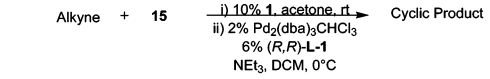
(16) Suzuki, T.; Sato, O.; Hirama, M. *Tetrahedron Lett.* **1990**, *31*, 4747.

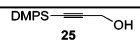
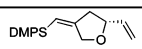
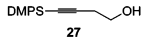
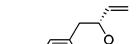
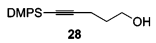
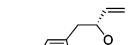
(17) Kim, H.; Lee, C. *Org. Lett.* **2002**, *4*, 4369.

(18) Enantioselective cyclization using boron cocatalysis has been achieved, see ref 15.

(19) Low enantioselectivity has been reported: (a) Fournier-Nguefack, C.; Lhoste, P.; Sinou, D. *J. Chem. Res.* **1988**, 105A. Enantioselective allylic cyclizations of alkoxy nucleophiles were developed independently and concurrently with this work: (b) Jiang, L.; Burke, S. D. *Org. Lett.* **2001**, *3*, 1953. (c) Jiang, L.; Burke, S. D. *Org. Lett.* **2002**, *4*, 3411.

Table 4. Enantioselective O-Heterocyclization Reactions



Entry	Alkyne	Condition[a]	Cyclic Product	% Yield[b]	% ee[c]
1	 **25**	D	 **26**	84	76
2	**25**	D[d]	**26**	85	79
3	 **27**	D	 **24**	80	94
4	 **28**	D	 **29**	0	---

[a] All reactions run with a 6:1 ratio of **15** to alkyne under inert atmosphere under the conditions listed below. Condition D, for a 0.2 mmol scale: (i) 10% **1**, 1.0 mL of acetone, room temperature, 2 h; (ii) concentrate in vacuo, then add 2% $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 6% (*R*,*R*)-**L-1**, 1 equiv of DBU, 4.0 mL of DCM, 0 °C, 2 h. [b] Isolated yields after chromatography. [c] Percent ee was measured by chiral HPLC. [d] Thirty percent NBu_4Cl was added.

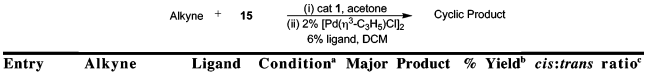
that addition of tetrabutylammonium chloride as a cocatalyst slightly increases the selectivity for furan formation (entry 2) and has no effect on the selectivity of pyran formation.

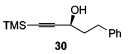
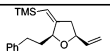
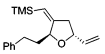
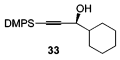
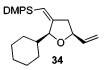
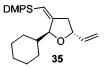
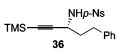
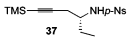
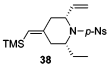
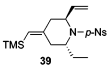
3. Diastereoselective Heterocyclization Reactions

Palladium catalysis allows for diastereo- as well as enantiocontrol. Given chiral starting materials, we investigated whether the chiral catalyst could control the diastereoselectivity in the cyclization, either by enhancing or overcoming the intrinsic substrate-controlled preference. Gratifyingly, good diastereocontrol is exhibited by the catalyst (Table 5). With matched ligand/substrate pairs,[20] the selectivity is universally excellent. Furthermore, in every mismatched case, the nonnatural diastereomer predominates indicating that the catalyst is able to override and control the geometry of cyclization. For example, utilizing an achiral ligand affords **38** as a 2:1 cis/trans diastereomeric ratio (entry 8). Employing the matched chiral ligand leads to exclusive formation of the cis isomer (entry 10), whereas when the mismatched ligand is used, the trans isomer predominates (entry 9). The advantage of catalyst control is clear as both diastereomers can be accessed from a single enantiomer of starting material simply by switching the ligand. Similar levels of control are seen for furan formation (entries 1−3). Increasing the steric demands of the substrate leads to increased selectivity in both the matched (23:1) and mismatched cases (1:4.5) (entries 4−6). Interestingly, the achiral dppp ligand consistently affords lower conversions than its chiral counterpart regardless of whether the chiral reaction involved a "matched" or "mismatched" stereochemical event indicating that the DPPBA-based ligand plays a dual role in the reaction—imparting selectivity and organizing the substrate such that cyclization is facilitated. Finally, entry 7 indicates that biaryl alkynes afford little to no conversion in the ene−yne coupling, potentially due to deactivation of the catalyst from bidentate coordination.

Dramatically, for pyran formation the selectivity is complete—the cis isomer is formed exclusively in matched cases and, more importantly, the trans isomer is formed exclusively in the mismatched cases (Table 6).[21] This is significant because while cyclization methods for the formation of cis 2,6-tetrahydropyrans are prevalent, very few methods offer direct access to the thermodynamically unfavorable trans pyran in isomerically pure form.[1] For this class of substrates the ability of the chiral ligands to control the relative stereochemistry is impressive and indicates the potential of this catalyst system.[22] For example, several prominent and bioactive natural products such as the phorboxazoles, salinomycin, and swinholide A contain a trans-2,6-disubstituted pyran and illustrate the possible utility of this method. Furthermore, we have successfully performed the two-metal one-pot procedure on large scale (as high as 20 mmol) indicating its practical nature and potential easy incorporation into total synthesis.[23]

Table 5. Diastereoselective Furan and Piperidine Synthesis



Entry	Alkyne	Ligand	Condition[a]	Major Product	% Yield[b]	*cis*:*trans* ratio[c]
1	 **30**	dppp	D	 **31**	47	4:1
2	**30**	(*R*,*R*)-**L-1**	D	 **32**	87	1:3.5
3	**30**	(*S*,*S*)-**L-1**	D	**31**	80	10:1
4	 **33**	dppp	D	 **34**	45	5:1
5	**33**	(*R*,*R*)-**L-1**	D	 **35**	53[d]	1:4.5
6	**33**	(*S*,*S*)-**L-1**	D	**34**	57[d]	23:1
7	 **36**	(*R*,*R*)-**L-1**	C	—	No Rxn	—
8	 **37**	dppp	A	 **38**	37	2:1[e]
9	**37**	(*R*,*R*)-**L-1**	A	 **39**	73	1:2[e]
10	**37**	(*S*,*S*)-**L-1**	A	**38**	68	99:1[e]

[a] All reactions run with a 1.7:1 ratio of **15** to alkyne under inert atmosphere under the conditions listed below. Condition A, for a 0.2 mmol scale: (i) 5% **1**, 1.0 mL of acetone, room temperature, 2 h; (ii) 2% $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 6% ligand, 1 equiv of DBU, 3.0 mL of DCM, room temperature, 2 h. Condition B, for a 0.2 mmol scale: (i) 2% **1**, 0.4 mL of acetone, room temperature, 2 h; (ii) 2% $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 6% ligand, 1 equiv of DBU, 3.6 mL of DCM, room temperature, 2 h. Condition C, for a 0.2 mmol scale: (i) 10% **1**, 1.0 mL of acetone, room temperature, 2 h; (ii) 2% $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 6% ligand, 1 equiv of DBU, 3.0 mL of DCM, room temperature, 2 h. Condition D: use a 6:1 ratio of **15**/alkyne. For a 0.2 mmol scale: (i) 10% **1**, 1.0 mL of acetone, room temperature, 2 h; (ii) concentrate in vacuo, add 2% $Pd_2(dba)_3{\cdot}CHCl_3$, 6% ligand, 1 equiv of NEt_3, 4.0 mL of DCM, 0 °C, 2 h. [b] Isolated yields. [c] The dr was measured by ^1H NMR. [d] Yield based on recovered starting material is 80%. [e] The dr was measured by HPLC.

(20) Matched implies that the catalyst reinforces the natural diastereoselectivity of the substrate, and mismatched implies that the catalyst contradicts the natural diastereoselectivity.

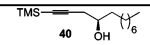
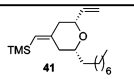
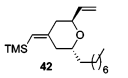
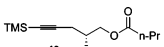
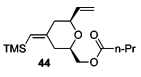
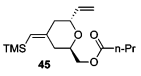
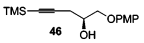
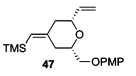
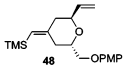
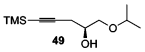
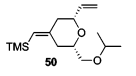
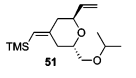
(21) For all substrates in Tables 5 and 6, the relative stereochemistry was determined by ^1H NMR techniques. In particular, the presence of a strong NOE (generally between 5% and 10%) for cis 2,6- and 2,5-disubstituted compounds was observed between protons adjacent to the heteroatom. The corresponding absence of this NOE confirmed the trans stereochemical assignment of the opposite diastereomer. Furthermore, since the absolute stereochemistry of the starting substrate is known, the absolute configuration of the newly created allylic stereogenic center is also known.

(22) For a preliminary account of this work: Trost, B. M.; Machacek, M. R. *Angew. Chem., Int. Ed.* **2002**, *41*, 4693.

(23) See compound **85** in the Supporting Information.

Table 6. Diastereoselective THP Synthesis

Alkyne + **15** → (i) cat **1**, acetone; (ii) 2% $Pd_2(dba)_3$·$CHCl_3$, 6% ligand, DCM → Cyclic Product

Entry	Alkyne	Ligand	Condition[a]	Major Product	% Yield[b]	*cis:trans* ratio[c]
1	 **40**	*rac*-**L-1**	D	 **41**	46	1.4:1
2	**40**	(*R,R*)-**L-1**	D	**41**	80	>97:3
3	**40**	(*S,S*)-**L-1**	D	 **42**	80	<3:>97
4	 **43**	*rac*-**L-1**	D	 **44**	54	3.6:1
5	**43**	(*R,R*)-**L-1**	D	 **45**	60	<3:>97
6	**43**	(*S,S*)-**L-1**	D	**44**	58	>97:3
7	 **46**	*rac*-**L-1**	D	 **47**	45	2.4:1
8	**46**	(*R,R*)-**L-1**	D	**47**	58	>97:3
9	**46**	(*S,S*)-**L-1**	D	 **48**	58	<3:>97
10	 **49**	*rac*-**L-1**	D	 **50**	38	4:1
11	**49**	(*R,R*)-**L-1**	D	**50**	58	>97:3
12	**49**	(*S,S*)-**L-1**	D	 **51**	74	<3:>97

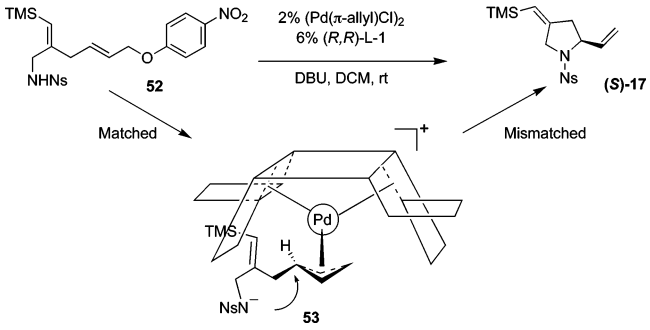
[a] All reactions run under inert atmosphere under the conditions listed. Condition D: use a 6:1 ratio of **15**/alkyne. For a 0.2 mmol scale: (i) 10% **1**, 1.0 mL of acetone, room temperature, 2 h; (ii) concentrate in vacuo, add 2% $Pd_2(dba)_3$·$CHCl_3$, 6% ligand, 1 equiv of NEt_3, 4.0 mL of DCM, 0 °C, 2 h. [b] Isolated yields after chromatography. [c] The dr was measured by ^1H NMR.

4. Absolute Stereochemical Analysis: Prediction and Proof

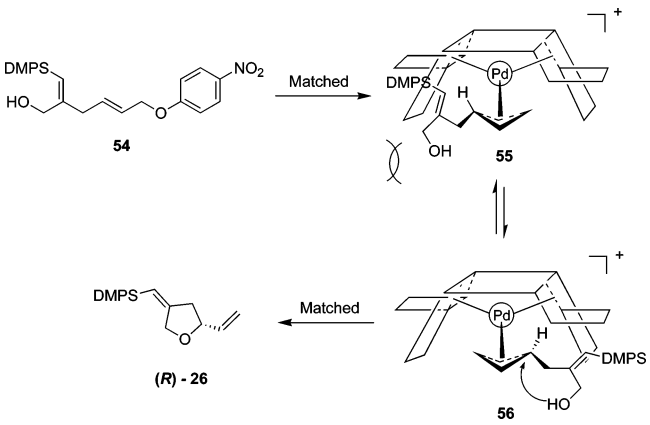
Given the mechanism of palladium-catalyzed allylic alkylation, there are multiple steps that can be considered enantiodetermining. Both the substrate and the reaction conditions define which step or steps will be operating. Applying literature precedent to the sulfonamide substrates, ionization is expected to be enantiodetermining.[24] Matched ionization[25] to form syn complex **53** is followed by fast intramolecular mismatched nucleophilic addition (Scheme 4). By tethering the nucleophile, and using conditions where the sulfonamide is fully deprotonated, the rate of mismatched attack becomes faster than equilibration and the (*S*)-stereochemistry is predicted from the (*R,R*)-ligand even though ring closure involves a "mismatched" event.

Further support for this interpretation comes from both optimization studies and substrate scope. If ionization is enantiodetermining, reactions in which the cyclization of the heteroatom onto the allylpalladium intermediate is kinetically fast should give the highest selectivity. Indeed, pyrrolidine formation occurs

Scheme 4. Sulfonamides: Ionization Is Enantiodetermining



Scheme 5. Oxygen Nucleophiles: Nucleophilic Addition as Enantiodetermining



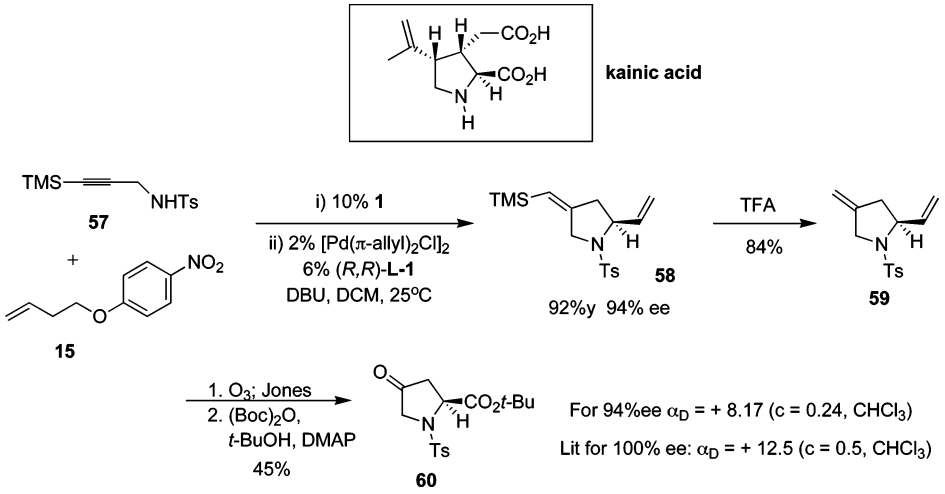
with 92% ee, while the enantioselectivity drops to 88% and 17% for closure to six- and seven-membered rings, respectively. Moreover, addition of 30% tetrabutylammonium chloride to the cyclization of **52** causes a precipitous drop in the enantioselectivity. Since chloride ion is known to increase the rate of equilibration of the intermediate π-allyl species, the rate of equilibration can become competitive with nucleophilic trapping, causing a decrease in the selectivity. Finally, if ionization is enantiodetermining, conditions in which the sulfonamide is fully deprotonated should show the highest selectivity. Experimentally, DBU afforded the best selectivity, whereas weakly basic amines or buffered conditions resulted in poor selectivity.

Interestingly, cyclizations involving alcohol nucleophiles display the opposite selectivity pattern. For example, improved selectivity is obtained for pyrans over furans. Furthermore, the addition of exogenous chloride has a small but measurable positive effect on the overall selectivity. And finally, strong amine bases such as DBU afford lower selectivity than does the weakly basic triethylamine. This experimental evidence indicates that the nature of the nucleophile is crucial in defining the enantiodetermining step in asymmetric intramolecular cyclization reactions. Simple alcohols are notoriously poor nucleophiles for palladium-catalyzed allylic substitutions. Therefore, the rate of addition is slower than equilibration of the palladium−allyl diastereomers and nucleophilic addition becomes enantiodetermining. Applying this model to 1,4-diene **54**, a matched ionization is followed by rapid equilibration of **55** and **56**. Matched nucleophilic attack through **56** leads to (*R*)-**26** when utilizing (*R,R*)-ligand (Scheme 5).

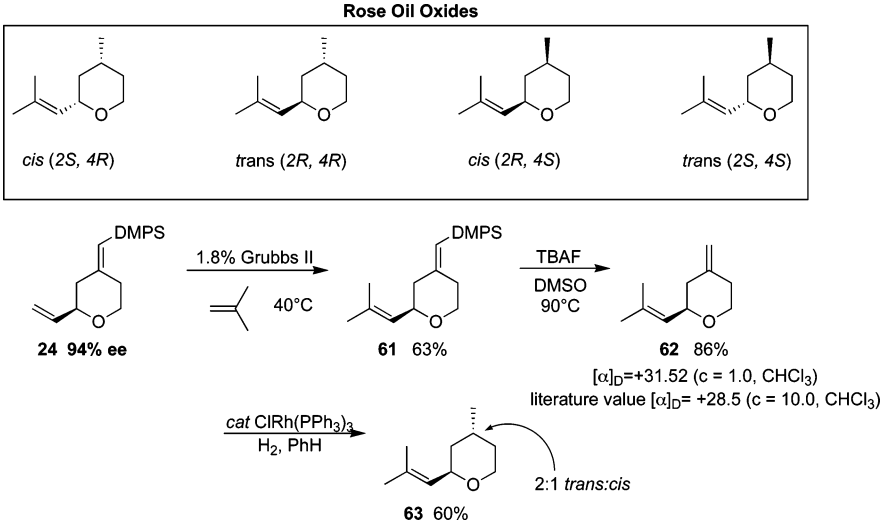
Unambiguous stereochemical proof was achieved through analogue synthesis. Several proline derivatives have been used

(24) (a) Trost, B. M.; Patterson, D. E. *J. Org. Chem.* **1998**, *63*, 1339. (b) Trost, B. M.; Patterson, D. E. *Chem. Eur. J.* **1999**, *5*, 3279.
(25) For definitions of matched and mismatched with respect to the working model see ref 11.

Scheme 6. Synthesis of the 4-Oxyproline Derivative



Scheme 7. Completion of Rose Oil Oxide



as building blocks for total synthesis. We envisioned intersecting a synthesis of the kainoids, a class of nonproteinogenic amino acids with activity as glutamate agonists,[26] through a concise synthesis of the known 4-oxoproline derivative **60**[27] (Scheme 6). The one-pot heterocyclization process using (*R*,*R*)-**L-1** proceeds very smoothly to afford pyrrolidine **58** in 94% ee. Desilylation and oxidation of both olefins through ozonolysis followed by an oxidative workup yielded the keto-acid with complete retention of stereochemistry at the 2-position. The crude acid was then directly capped as a *tert*-butyl ester. Comparison of the optical rotation unambiguously determined the stereochemistry to be (*S*),[28] which matches the predictions made by our working model for ionization being the enantiodiscriminating event.

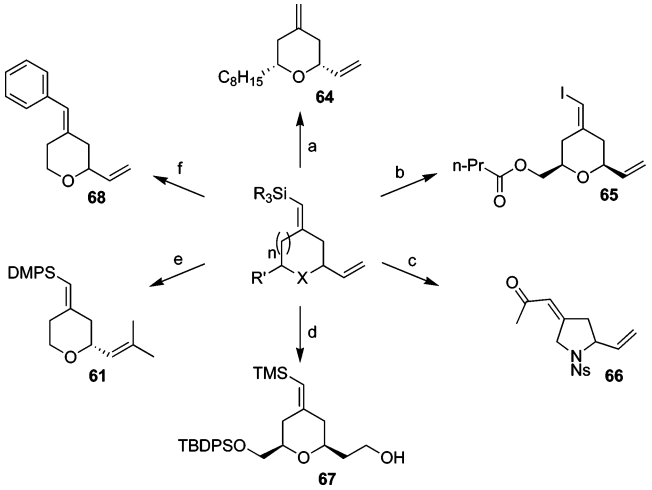
To establish the absolute stereochemistry of the products wherein an alcohol is involved in the nucleophilic addition, we turned to a synthesis of the important fragrance materials, the rose oil oxides.[29] Our synthesis began with a highly chemoselective cross-metathesis of **24** with 2-methylpropene[30] to afford **61**. Subsequent desilylation[31] (Scheme 7) provided **62**, whose optical rotation unambiguously confirmed our predictions.[32] Finally, chemoselective hydrogenation with Wilkinson's catalyst completed the simple three-step approach to rose oil oxide. Thus, the nucleophilic addition is confirmed as the enantiodiscriminating event.

5. Synthetic Utility: A Concise Synthesis of Ring B of Bryostatin

The two-metal, one-pot ene-cyclization method described above provides a unique entry into enantio- and diastereopure substituted heterocycles. There are several key structural features associated with the products of this methodology that make them convenient building blocks for complex total synthesis including: a stereodefined trisubstituted exocyclic vinyl silane, two sterically differentiated olefins, and differentiated substituents on either side of the heteroatom. Given these features, a host of further synthetic transformations can be performed after the

(26) *Kainic Acid as a Tool in Neurobiology*; McGreer, E. G., Olney, J. W., McGreer, D. L., Eds.; Raven Press: New York, 1978 and references therein.
(27) Barraclough, P.; Hudhomme, P.; Spray, C. A.; Young, D. W. *Tetrahedron* **1995**, *51*, 4195.
(28) We are very grateful to Douglas W. Young for sending a copy of his original spectra.
(29) Seidel, F.; Stoll, M. *Helv. Chim. Acta* **1959**, *42*, 1830.
(30) Chatterjee, A. K.; Sanders, D. P.; Grubbs, R. H. *Org. Lett.* **2002**, *4*, 1939.
(31) Oda, H.; Sato, M.; Morizawa, Y.; Oshima, K.; Nozaki, H. *Tetrahderon Lett.* **1983**, *24*, 2877.
(32) Ohloff, G.; Giersch, W.; Schulte, E.; Karl, H.; Enggist, P.; Demoule, E. *Helv. Chim. Acta* **1980**, *63*, 1582.

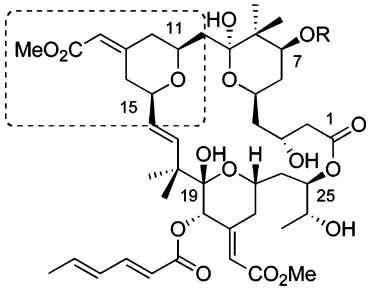
Scheme 8. Representative Further Synthetic Transformations[a–f]



[a] SiR_3 = TMS, n = 1; TFA, DCM, 92%. [b] SiR_3 = TMS, n = 1; NIS, 96%. [c] SiR_3 = TMS, n = 0; AcCl, $AlCl_3$, 50%. [d] SiR_3 = TMS, n = 1; 3% $RhCl(PPh_3)_3$, catecholborane, $NaBO_3$, 78%. [e] SiR_3 = DMPS, n = 1; 2% Grubbs II, isobutylene, 63%. [f] SiR_3 = $Bn(Me)_2Si$, n = 1; 2% $Pd_2(dba)_3 \cdot CHCl_3$, TBAF, PhI, 85%.

cyclization to afford highly functionalized compounds (Scheme 8). Several transformations can be envisioned that take advantage of the stereodefined trisubstituted exocyclic vinyl silane—the most powerful feature of these heterocyclic products. Ipso-substitution reactions such as Freidel–Crafts acylation[33] (path c) and iodination[34] (path b) proceed smoothly to afford products as single geometrical isomers. The stereodefined vinyliodide products are useful intermediates for metal-catalyzed cross-coupling reactions;[35] however, the starting vinylsilane can also be used as a cross-coupling partner.[36] When vinylbenzyldimethylsilane is utilized as the activated silane partner, smooth cross-coupling to form all-carbon trisubstituted olefins is achieved (path f).[37] Furthermore, the exocyclic vinylsilane differentiates the two olefins such that chemoselective transformations can be achieved. For example, both cross-metathesis with isobutylene (path e) and a hydroboration (path d)[38] are highly selective for the monosubstituted alkene (path e). In contrast, oxidizing reagents such as *m*CPBA and osmium tetroxide preferentially oxidize the silyl-substituted olefin with osmium tetroxide affording mixtures of hydroxy and aldehyde products. Finally, the vinyl silane can ultimately be converted to the parent methylene by protodesilylation without olefin isomerization (path a).[39]

Scheme 9. Bryostatin 1 and 2



R = Ac; Bryostatin 1
R = H; Bryostatin 2

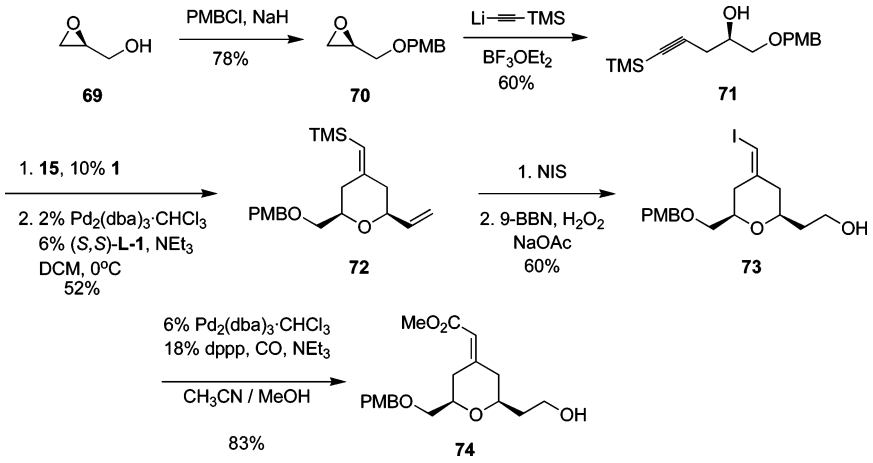
The last feature of our heterocyclic products is the 2,4,6-substitution pattern, a motif that is found in a variety of complex natural products. Of these natural products, the bryostatin family was of particular interest to us given the importance of these compounds in both the biological and chemical community (Scheme 9).[40] The bryostatins are potent antitumor agents against leukemia, B-cell lymphoma, ovarian carcinoma, and melanoma cell lines. In addition, they show interesting stimulatory effects on the immune and hematopoetic systems. Therefore, the bryostatins are attractive targets for total synthesis, and three total syntheses as well as several fragment syntheses have been accomplished.[41] Most striking from the standpoint of the one-pot cross-coupling and cyclization reaction we developed was the B ring portion (C10–C16). This highly conserved feature in the bryostatin family consists of a 2,6-disubstituted pyran ring with a stereodefined exocyclic olefin at the 4-position. Though a small portion of the molecule, this ring embodies two of the major synthetic challenges present in the molecule: the stereoselective installation of the trisubstituted exocyclic olefin and the enantioselective synthesis of pyran rings. Our method nicely addresses both of these issues, and as such we saw this ring as an excellent testing ground to explore its generality.

Our synthesis began with protection of commercially available (*S*)-glycidol as the *p*-methoxybenzyl ether (Scheme 10). The epoxide was then opened with lithium trimethylsilylacetylide to yield the alkyne coupling partner **71** for the ruthenium-catalyzed ene–yne cross-coupling reaction. The diene intermediate was cyclized to pyran **72** with complete syn selectivity in 52% yield over two steps. In this sequence, we opted to isolate the 1,4-diene intermediate because of purification issues as **72** coeluted with the excess **15**.

Stereospecific transformation of the vinylsilane into the desired enoate was accomplished through iodination and subsequent palladium-catalyzed carbonylation. Functionalization of the exocyclic vinyl group was accomplished through a hydroboration–oxidation sequence.[42] This route afforded the fully functionalized ring B portion of bryostatin (**74**) in a short seven-step sequence with 12% overall yield. More importantly, the stereochemical integrity of the trisubstituted olefin created

(33) (a) Pillot, J.-P. *Bull. Soc. Chim. Fr.* **1975**, 2143. (b) Colvin, E. W. *J. Chem. Soc. Rev.* **1978**, *7*, 15. (c) Pillot, J.-P. *Synth. Commun.* **1979**, *9*, 395.
(34) (a) Miller, R. B.; Reichenbach, T. *Tetrahedron Lett.* **1974**, *15*, 543. (b) Piscopio, A. D.; Minowa, N.; Chakraborty, T. K.; Koide, K.; Bertinato, P.; Nicolaou, K. C. *J. Chem. Soc., Chem. Commun.* **1993**, *7*, 617.
(35) *Metal Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinhein, Germany, 1998.
(36) (a) Colvin, E. W. *Silicon in Organic Synthesis*; Buttherworths: London, 1981. (b) Weber, W. P. *Silicon Reagents for Organic Synthesis*; Springer-Verlag: Berlin, 1983.
(37) Vinyl BDMS cross-coupling: Trost, B. M.; Machacek, M. R.; Ball, Z. T. *Org. Lett.* **2003**, *5*, 1895. Other activated vinyl silanes are not compatible with the $CpRu(CH_3CN)_3PF_6$ catalyst and thus are incompatible with our mixed-metal methodology.
(38) Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1992**, *114*, 6671.
(39) (a) O'Neil, S. V.; Quickley, C. A.; Snider, B. B. *J. Org. Chem.* **1997**, *62*, 1970. (b) Kano, S.; Yuasa, Y.; Mochizuki, N.; Shibuya, S. *Heterocycles* **1990**, *30*, 263. (c) Wenkert, E.; Bookser, B. C.; Arrhenius, T. S. *J. Am. Chem. Soc.* **1992**, *114*, 644. (d) Honda, T.; Hoshi, M.; Tsubuki, M. *Heterocycles* **1992**, *34*, 1515. (e) Keusenkothen, P. F.; Smith, M. B. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2485. (f) Wang, C.; Gu, X.; Yu, M. S.; Curran, D. P. *Tetrahedron* **1998**, *54*, 8355.
(40) (a) Petit, G. R.; Day, J. P.; Hartwell, J. L.; Wood, H. B. *Nature* **1970**, *227*, 962. (b) Petit, G. R.; Herald, C. L.; Doubek, D. L.; Herald, D. L.; Arnold, E.; Clardy, J. *J. Am. Chem. Soc.* **1982**, *104*, 6846.
(41) Total syntheses: (a) Kageyama, M.; Tamura, T.; Nantz, M. H.; Roberts, J. C.; Somfai, P.; Whritenour, D. C.; Masamune, S. *J. Am. Chem. Soc.* **1990**, *112*, 7407. (b) Evans, D. A.; Carter, P. H.; Carreira, E. M.; Prunet, J. A.; Charette, A. B.; Lautens, M. *J. Am. Chem. Soc.* **1999**, *121*, 7540. (c) Ohmori, K.; Ogawa, Y.; Obitsu, T.; Ishikawa, Y.; Nishiyama, S.; Yamamura, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 2290.
(42) Higher overall yields were obtained when the hydroboration was performed before carbonylation.

Scheme 10. Synthesis of Ring B



during the ene−yne cross-coupling reaction was completely transferred to the stereochemistry of the exocyclic enoate. This synthesis represents the shortest route to the B ring of bryostatin[43] and introduces a novel approach to the stereospecific installation of the vinyl ester.

6. Conclusion

An atom economic, selective, and highly practical one-pot synthesis of heterocycles has been developed that efficiently affords enantio and diastereopure N- and O-heterocyclic products. Furthermore, use of a chiral palladium catalyst allows formation of all possible diastereomers, even those that are thermodynamically disfavored. This two-metal procedure also affords heterocyclic products that are synthetically useful intermediates. Through the *Z*-vinylsilane a variety of trisubstituted olefin substitution products can be accessed. Finally, the utility of these heterocyclic products was demonstrated through a concise synthesis of the ring B portion of bryostatin, a potent chemotherapeutic. In addition, through a combination of experimental evidence, application of the working model for palladium-catalyzed AAA, and stereochemical proof, we demonstrated that the nature of the nucleophile is important for defining the enantiodetermining step of the asymmetric allylic cyclization reaction. Kinetic trapping of the initially generated π-allyl complex determines the stereochemistry for "soft" nucleophiles such as sulfonamides. In contrast, slow trapping of equilibrating π-allyl diastereomers, determines the selectivity for "hard" nucleophiles such as nonstabilized alcohols.

7. Experimental Section

General procedures for the mixed-metal synthesis of heterocycles are as follows.

Condition A. [CpRu(CH_3CN)$_3$]PF_6 (4.3 mg, 0.01 mmol) was added to a flame-dried test tube under argon. A solution of alkyne (0.20 mmol) and alkene (0.35 mmol) in degassed acetone (1.0 mL) was added to the catalyst via cannula. The reaction was stirred at room temperature under argon for 3 h at which time it was diluted with 2.5 mL of *degassed* DCM. DBU (32 mg, 0.21 mmol) was added followed by a solution of (Pd(π-allyl)Cl)$_2$ (1.5 mg, 0.004 mmol) and (*R*,*R*)-**L-1** (8 mg, 0.012 mmol) in 0.5 mL of DCM. The resulting yellow solution was stirred for 1 h at room temperature at which point the mixture was concentrated in vacuo. The resulting oily residue was purified via flash chromatography (silica, ether/petroleum ether, gradient).

Condition B. [CpRu(CH_3CN)$_3$]PF_6 (1.7 mg, 0.004 mmol) was added to a flame-dried test tube under argon. A solution of alkyne (0.20 mmol) and alkene (0.35 mmol) in degassed acetone (0.4 mL) was added to the catalyst via cannula. The reaction was stirred at room temperature under argon for 3 h at which time it was diluted with 3.6 mL of *degassed* DCM. DBU (32 mg, 0.21 mmol) was added followed by a solution of (Pd(π-allyl)Cl)$_2$ (1.5 mg, 0.004 mmol) and (*R*,*R*)-**L-1** (8 mg, 0.012 mmol) in 0.5 mL of DCM. The resulting yellow solution was stirred for 1 h at room temperature at which point the mixture was concentrated in vacuo. The resulting oily residue was purified via flash chromatography (silica, ether/petroleum ether, gradient).

Condition C. [CpRu(CH_3CN)$_3$]PF_6 (5 mg, 0.012 mmol) was added to a flame-dried test tube under argon. A solution of alkyne (0.12 mmol) and alkene (0.19 mmol) in degassed acetone (0.6 mL) was added to the catalyst via cannula. The reaction was stirred at room temperature under argon for 3 h at which time it was diluted with 1.3 mL of *degassed* DCM. DBU (18 mg, 0.12 mmol) was added followed by a solution of (Pd(π-allyl)Cl)$_2$ (0.9 mg, 0.0024 mmol) and (*R*,*R*)-**L-1** (5 mg, 0.007 mmol) in 0.5 mL of DCM. The resulting yellow solution was stirred for 1 h at room temperature at which point the mixture was concentrated in vacuo. The resulting oily residue was purified via flash chromatography (silica, 0−75% ether/petroleum ether, gradient).

Condition D. [CpRu(CH_3CN)$_3$]PF_6 (8 mg, 0.02 mmol) was added to a flame-dried test tube under argon. A solution of alkyne (0.20 mmol) and alkene (1.2 mmol) in degassed acetone (1.0 mL) was added to the catalyst via cannula. The reaction was stirred at room temperature under argon for 3 h at which time it was directly concentrated in vacuo. The resulting oily residue was purged with argon and dissolved in 1.3 mL of *degassed* DCM. NEt_3 (0.22 mmol) was added followed by a solution of $Pd_2(dba)_3$•$CHCl_3$ (0.004 mmol) and (*R*,*R*)-**L-1** (0.012 mmol) in 0.5 mL of *degassed* DCM. The resulting red solution was stirred for 2 h at 0 °C at which point the mixture was concentrated in vacuo. The resulting oily residue was purified via flash chromatography (silica, 0−75% ether/petroleum ether, gradient).

Compound 58. [CpRu(CH_3CN)$_3$]PF_6 (9 mg, 0.02 mmol) was added to a flame-dried test tube under argon. A solution of **57** (56 mg, 0.20 mmol) and **15** (67 mg, 0.35 mmol) in degassed acetone (1.0 mL) was added to the catalyst via cannula. The reaction was stirred at room temperature for 4 h at which time it was directly concentrated in vacuo. The resulting oily residue was purged with argon and dissolved in 3.0 mL of degassed dichloromethane. DBU (0.032 mL, 0.21 mmol) was added followed by a solution of (Pd(π-allyl)Cl)$_2$ (1.5 mg, 0.004 mmol) and (*R*,*R*)-**L-1** (8.3 mg, 0.012 mmol) in 1.0 mL of DCM. The resulting yellow solution was stirred for 1 h at room temperature at which point the mixture was concentrated in vacuo. The resulting oily residue was

(43) Other routes have accomplished syntheses of similar pieces with the exocyclic olefin stereochemistry installed in 14 steps: (a) Vakalopoulos, A.; Lampe, T. F. J.; Hoffmann, H. M. R. *Org. Lett.* **2001**, *3*, 929. In 18 steps: (b) Hale, K. J.; Hummersome, M. G.; Bhatia, G. S. *Org. Lett.* **2000**, *2*, 2189. In 8 steps: (c) Munt, S. P.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1989**, *8*, 480.

purified via flash chromatography (silica, 0−60% ether/petroleum ether, gradient) to yield 65 mg (92%) of **58** as a light yellow oil. The enantiomeric excess was determined to be 94% by chiral HPLC analysis (Chiralcel AD column, 99:1 heptane/^{i}PrOH, flow rate = 0.5 mL/min, 254 nm, t_r: 39.31 (major), 48.46 (minor)). $[\alpha]_D$ +99.46 (c = 0.81, $CHCl_3$). R_f = 0.61 in 25% diethyl ether/petroleum ether. IR (neat): 2955, 1639, 1351, 1163, 840 cm^{-1}. ^{1}H NMR (300 MHz $CDCl_3$) δ 7.70 (d, J = 8.1 Hz, 2 H), 7.32 (d, J = 8.1 Hz, 2 H), 5.76 (ddd, J = 6.9, 10.2, 17.1 Hz, 1 H), 5.40 (br s, 1 H), 5.21 (d, J = 17.1 Hz, 1 H), 5.09 (d, J = 10.2 Hz, 1 H), 4.11 (m, 1 H), 3.93 (m, 2 H), 2.43 (m, 2 H), 2.44 (s, 3 H), 0.05 (s, 9 H). HRMS Calcd for $C_{17}H_{25}NO_2SSi$: 335.1375. Found: 335.1380.

Compound 72. $CpRu(CH_3CN)_3PF_6$ (0.15 g, 0.34 mmol) was added to a cooled (0 °C) solution of **71** (0.99 g, 3.4 mmol) and **15** (3.6 g, 18.6 mmol) in 17 mL of acetone. The resulting solution was stirred at 0 °C for 5 min and then at room temperature for 3 h. The reaction was directly concentrated in vacuo and purified via flash chromatography (silica, ether/petroleum ether gradient) to yield 0.98 g of 1,4-diene coupling product. The 1,4-diene (0.99 g, 2.14 mmol) was dissolved in 42 mL of *degassed* DCM and cooled to 0 °C. Triethylamine (0.24 g, 2.4 mmol) was added followed by a solution of $Pd_2dba_3{\cdot}CHCl_3$ (44 mg, 0.04 mmol) and (*S*,*S*)-**L-1** (88 mg, 0.13 mmol) in 5 mL of *degassed* DCM. The resulting solution was stirred for 2 h at 0 °C at which time it was directly concentrated in vacuo. The resulting oily residue was purified via flash chromatography (silica, ether/petroleum ether gradient) to yield 0.64 g (86%) of **72** as a colorless oil. The diastereoselectivity was determined to be >97:3 cis by ^{1}H NMR analysis. R_f = 0.8 in 25% ether/petroleum ether. $[\alpha]_D$ +5.35 (c = 6.90, CH_2Cl_2). IR (film from CH_2Cl_2): 2953, 2895, 1622, 1514, 1248, 1100, 1038, 878 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, J = 8.5 Hz, 2 H), 6.91 (d, J = 9.0 Hz, 2 H), 5.93 (ddd, J = 17.0, 10.5, 5.5 Hz, 1 H), 5.32 (s, 1 H), 5.29 (d, J = 17.0 Hz, 1 H), 5.15 (d, J = 10.5 Hz, 1 H), 4.58 (d, J = 12.0 Hz, 1 H), 4.55 (d, J = 12.0 Hz, 1 H), 3.90 (m, 1 H), 3.83 (s, 3 H), 3.55 (m, 3 H), 2.48 (d, J = 13.5 Hz, 1 H), 2.24 (m, 2 H), 2.02 (t, J = 12.0 Hz, 1 H), 0.14 (s, 9 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.09, 152.68, 138.54, 130.37, 129.22 (2 C), 123.64, 115.21, 113.68 (2 C), 79.31, 77.29, 72.98, 72.80, 55.20, 45.19, 36.59, 0.26 (3 H). Anal. Calcd for $C_{20}H_{30}OSi$: C, 69.32%; H, 8.73%. Found: C, 69.15%; H, 8.55%.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health (GM33049) for their generous support of our programs. Mass spectra were provided by the Mass Spectrometry Regional Center for the University of California, San Francisco, supported by the NIH Division of Research Resources. We thank Bristol-Meyers Squibb and Eli-Lilly for predoctoral support of M.R.M. We are indebted to Johnson-Matthey who generously provided palladium salts.

Supporting Information Available: Detailed procedures and full characterization of all synthetic intermediates and products, along with spectral comparison of natural and synthetic analogues. This material is available free of charge via the Internet at http://pubs.acs.org.

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