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Communication

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A Ruthenium/Phosphoramidite-catalyzed Asymmetric Interrupted Metallo-ene Reaction

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Supporting Information Placeholder

Abstract: Allylic chlorides prepared from commercially available *trans*-1,4-dichloro-2-butene were converted to *trans*-disubstituted 5- and 6-membered ring systems with perfect diastereoselectivity and high enantioselectivity under chiral ruthenium catalysis. These products contain stereodefined secondary and tertiary alcohols that originate from the trapping of an alkylruthenium intermediate with adventitious water. Key to the success of this transformation was the development of a new BINOL-based phosphoramidite ligand containing bulky substitution at its 3- and 3'-positions. As a demonstration of product utility, diastereoselective Friedel-Crafts reactions were performed on the chiral benzylic alcohols in high yield and stereoselectivity.

The interception of allylmetal intermediates with adjoining π-unsaturation, also known as the intramolecular metallo-ene reaction, has made significant contributions to the construction of densely-functionalized cyclic molecules.[1] While the metallo-ene reaction can be seen as mechanistically analogous to a traditional ene reaction, there are significant differences between the two processes (Figure 1a). In the former process, the transient alkylmetal intermediate generated subsequent to carbometallation can either be further functionalized by substitution reactions or undergo β-hydride elimination to form a 1,4-diene. This divergence in mechanism gives the metallo-ene reaction a versatility that a traditional ene reaction lacks.

In contrast to the first metallo-ene reactions which relied on the stoichiometric generation of allylmetal intermediates from allylic halides, transition metal π-allyl chemistry has allowed for the possibility of a catalytic, enantioselective process to be realized, though to date few examples have been described.[2] Makino and coworkers have reported a palladium-catalyzed metallo-ene reaction of allylic acetates in moderate enantioselectivity (Figure 1b).[2b] Carreira and coworkers have shown that chiral iridium complexes can promote asymmetric polyene reactions from racemic secondary alcohols (Figure 1c).[2c] In either case, there is ambiguity whether the mechanism is truly ene-like or involves carbocationic intermediates. In this study, we disclose a process that is consistent with a metallo-ene reaction whose intermediate is captured by an external nucleophile concomitant with C-C bond formation.

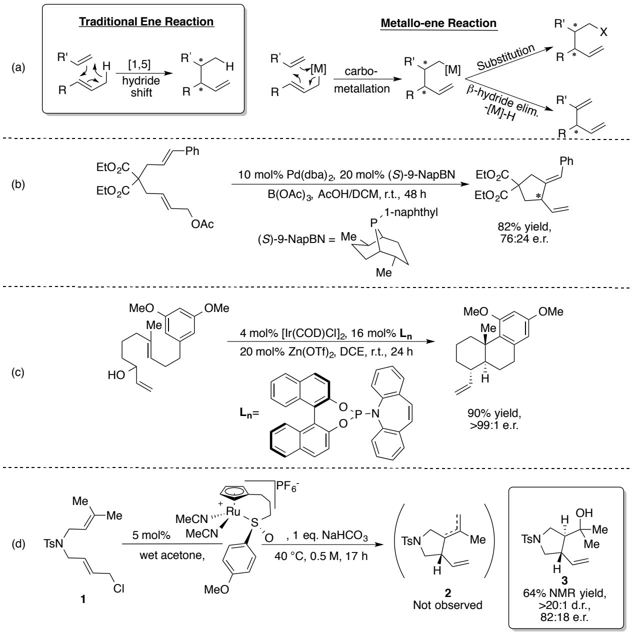
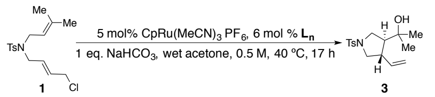
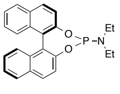
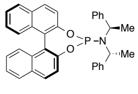
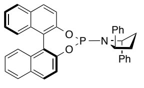
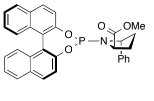
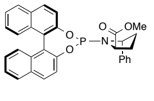
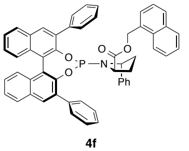


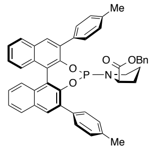
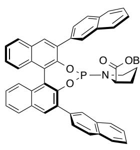
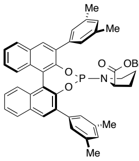
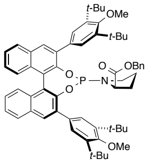
Figure 1 (a) The traditional ene reaction and the metallo-ene reaction (b) Palladium-catalyzed asymmetric metallo-ene reaction reported by Makino. (c) Iridium-catalyzed polyene cyclization reported by Carreira. (d) Initial attempt at an asymmetric ruthenium-catalyzed asymmetric metallo-ene reaction.

Our laboratory has developed chiral cyclopentadienylruthenium (CpRu) complexes that are excellent catalysts for intermolecular asymmetric allylic substitution reactions, particularly with allylic chlorides.[3] To achieve high enantioselectivities required use of substituents on the Cp ring to create the chiral space and maintain reactivity. We hypothesized that these complexes would be competent at performing an intramolecular metallo-ene reaction. Our initial attempts at performing this reaction on allylic chloride **1**, readily obtainable from commercial starting materials in only two steps, with a chiral CpRu-sulfoxide complex produced a surprising result when performed in untreated acetone (Figure 1d). Rather than observing the expected cyclic diene **2**, we obtained tertiary alcohol **3** in a 64% NMR yield, >20:1 d.r., and 82:18 e.r.[4] Presumably, **3** originates from trapping of an alkylruthenium intermediate by adventitious water following cyclization but prior to the β-hydride

Table 1. Effect of Ligand Structure on Asymmetric Interrupted Metallo-ene Reaction

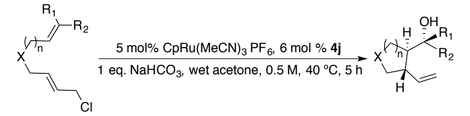


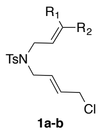
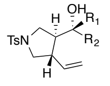
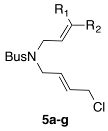
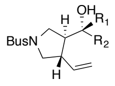
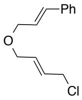
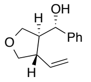
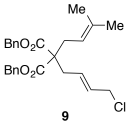
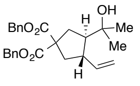
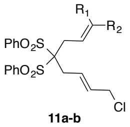
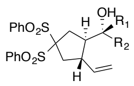
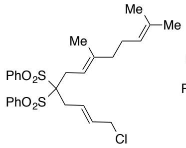
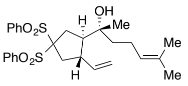
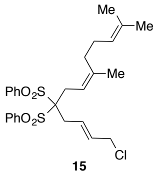
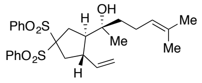
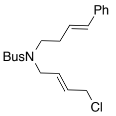
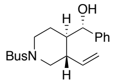
		
4a 97% yield, 24:76 e.r.	**4b** 77% yield, 65:35 e.r.	**4c** 74% yield, 78:22 e.r.
		
4d 67% yield, 67:33 e.r.	**4e** 56% yield, 39:61 e.r.	**4f** 67% yield, 85:15 e.r.

			
4g 76% yield, 92:8 e.r.	**4h** 55% yield, 90:10 e.r.	**4i** 71% yield, 90:10 e.r.	**4j** **82% yield (78% isolated), 94:6 e.r.**

Yields determined by NMR integration relative to an internal standard (1,1,2,2-tetrachloroethane). Enantiomeric ratios (e.r.) determined by chiral HPLC. All observed diastereomeric ratios (d.r.) were >20:1 as determined by NMR integration

Table 2. Substrate Scope



Substrate[a]	Product	Result[b]
 **1a-b**	 **3a-b**	R_1=Me, R_2=Me, 78% yield, 94:6 e.r. R_1=H, R_2=Ph, 55% yield, 95:5 e.r.
 **5a-g**	 **6a-g**	R_1=H, R_2=Ph, 87% yield, 95:5 e.r. R_1=H, R_2=4-ClPh, 64% yield, 98:2 e.r. R_1=H, R_2=4-BrPh, 42% yield, 98:2 e.r. R_1=H, R_2=4-MeOPh, 85% yield, 94:6 e.r.[c] R_1=H, R_2=2-MePh, 85% yield, 94:6 e.r. R_1=Me, R_2=Ph, 71% yield, 96:4 e.r. R_1=Me, R_2=3-MeOPh, 60% yield, 97:3 e.r.
 **7**	 **8**	73% yield, >95:5 e.r.[d]
 **9**	 **10**	52% yield, 94:6 e.r.[e]
 **11a-b**	 **12a-b**	R_1=Me, R_2=Me, 74% yield, 94:6 e.r.[c] R_1=H, R_2=Ph, 76% yield, 94:6 e.r
 **13**	 **14**	60% yield, 99:1 e.r.[c]
 **15**	 **16**	56% yield, 96:4 e.r.[c]
 **17**	 **18**	50% yield, 93:7 e.r.

[a] Bus= *tert*-butylsulfonyl
[b] Isolated yield. d.r. is >20:1 in all cases. e.r. determined by chiral HPLC, unless otherwise indicated.
[c] 5 vol% H_2O added.
[d] *ee* determined by conversion of the alcohol to the *O*-methylmandelate ester.
[e] 7.5 mol% CpRu(MeCN)$_3$PF$_6$ and 9 mol% **4j** used.

elimination necessary for the generation of 2. Interestingly, no direct π-allyl hydration was observed, indicating that the intramolecular cyclization of the π-allyl intermediate is faster than intermolecular attack by water.[5]

Unfortunately, neither modifying the sulfoxide on the chiral CpRu complex nor varying the choice of base led to a significant improvement in enantioselectivity. While looking for viable alternatives to these chiral ruthenium complexes, our attention shifted to the possibility of using a chiral phosphoramidite ligand in conjunction with a much more conveniently available pre-catalyst, CpRu(MeCN)$_3$PF$_6$. Chiral phosphoramidites have attracted considerable attention in the chemical community due to their highly modular nature, ease of synthesis, and broad applicability to a range of asymmetric transformations.[6] While there have been many examples of enantioselective iridium-, palladium-, and copper-catalyzed allylic substitution reactions[7-9] which have benefited from the application of these ligands, there are no known examples of ruthenium-phosphoramidite allylic substitution, as far as we are aware. In general, asymmetric ruthenium-phosphoramidite catalysis has been underexplored,[10] and more specifically, there are no known examples of asymmetric CpRu-phosphoramidite catalysis to date.

We were delighted to discover that this interrupted metallo-ene reaction could be performed in excellent yield and modest enantioselectivity with 5 mol% of CpRu(MeCN)$_3$PF$_6$ and 6 mol% of BINOL-based 4a (Table 1).[11] Ligands 4b and 4c, which both incorporate chiral C$_2$-symmetric amines, displayed no enhanced selectivity. At this point, we theorized that reducing the number of symmetry elements on the ligand would lead to an enhancement in enantioselectivity. In fact, pyroglutamic acid-derived C$_1$-symmetric ligands related to 4d-e have been shown to be effective ligands for oxidative allylic alkylation reactions.[12] While 4d and 4e themselves proved to be only moderately selective and displayed a negligible matched-mismatched effect, a significant increase in selectivity was observed when 3,3'-substitution on the BINOL was included on the basic ligand structure, as seen for ligand 4f. Switching out the *trans*-2,6-

disubstituted pyrrolidine for the easier to synthesize benzyl ester of proline further improved the e.r. to 92:8. A screen of various substitution patterns at the 3,3'-position of the BINOL backbone revealed that the bulky, BHT-like aryl groups on 4j offered the highest levels of enantioselectivity.

With the optimum ligand in hand, we began exploring the scope of the interrupted metallo-ene reaction (Table 2). Styrenyl substrate 1b was converted into secondary alcohol 3b in high diastereo- and enantioselectivity (>20:1 d.r. and 95:5 e.r.), but in a somewhat lower yield due to a competing reaction. The major observed side product for this reaction was (E)-N-tosylcinnamylamine, implying that the allylsulfonamide fragment was being ionized to a significant extent during the reaction. Gratifyingly, simply switching to a less electron withdrawing *tert*-buylsulfonyl (Bus) protecting group[13] minimized the amount of sulfonamide cleavage and provided secondary alcohol 5a in an improved 87% yield without sacrificing selectivity. The reaction tolerates both *para*-(5b-d) and *ortho*-substitution (5e) on the aromatic ring in good to excellent yields and similarly high levels of enantioselectivity. Stereodefined trisubstituted styrenyl olefins 5f and *meta*-substituted 5g can be converted into tertiary alcohols 6f and 6g as single diastereomers and in high enantioselectivity.

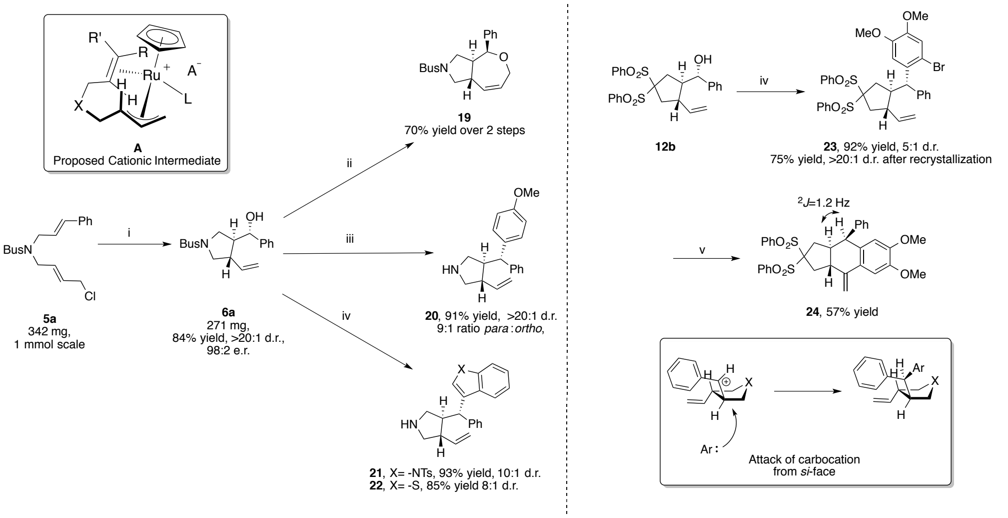
The chemistry can be extended beyond the synthesis of pyrrolidines as ether, benzyl malonate, and bis(phenylsulfonyl) backbones 7, 9, and 11a-b give high levels of diastereo- and enantioselectivity. To test the effect of olefin geometry on the diastereoselectivity of the reaction, geranyl- and neryl-based allylic chlorides 13 and 15 were synthesized and subjected to the reaction conditions. The stereochemical configuration of the tertiary alcohols in carbocycles 14 and 16 is ultimately dictated by the initial geometry of the starting olefin, providing each in high distereoselectivity. The observed lack of diastereomeric mixtures in these cases implies that a mechanism involving carbocation intermediates on the vinyl carbon is not likely. However, this reaction is sensitive to the substrate's ability to stabilize partial positive charge, as pendant non-styrenyl 1,2-disubstituted olefins cannot be cyclized under the reaction conditions. Finally, a *trans*-3,4-disubsituted piperidinyl alcohol 18 could be obtained in modest yield and good enantioselectivity from the corresponding 1,7-diene 17.

The absolute configuration of these products was assigned by analogy to secondary alcohol 8, whose configuration was determined by derivitization to the *O*-methylmandelate ester (see Supporting Information).[14] The assignment of this alcohol as (*S*) supports an outer sphere attack on cationic intermediate A by water rather than an assisted delivery of water by ruthenium to the substrate (Scheme 1).[15]

As a testament to the robustness of the process, the metallo-ene reaction can be performed on a 1 mmol scale without any detriment to yield or selectivity. An extra equivalent of sodium bicarbonate was added to prevent unwanted side reactions at this scale (Scheme 1).[5]

To showcase the utility of the asymmetric metallo-ene reaction, the products were derivatized in a number of ways. First, 6a can be alkylated with allyl bromide and subjected to ring-closing metathesis to deliver a *trans*-fused [5.3.0] bicyclic skeleton 19 in 70 percent yield over two steps. The relative stereochemistry of 19 was determined by 1D NOE (see Supporting information). An interesting tandem Bus deprotection/stereoselective Friedel-Crafts alkylation

Scheme 1. Millimole Scale Ruthenium-catalyzed Interrupted Metallo-ene Reaction and Product Derivatizations



Conditions: i) 5 mol% $CpRu(MeCN)_3PF_6$, 6 mol % **4j,** 2 eq. $NaHCO_3$, wet acetone, 0.5 M, 40 ºC, 5 h; ii) (a) NaH, THF, r.t., 15 min then allyl bromide, 70 ºC, 1 h (b) 10 mol% HGII, DCM, 40 ºC, 3 h; iii) TfOH, 5 eq. anisole, DCM,-78 ºC to r.t., 1 h; iv) $HBF_4 \cdot OEt_2$, 5-10 eq. arene or heteroaromatic, DCM, -78 ºC to r.t., 1 h; v) 5 mol% $Pd_2(dba)_3 \cdot CHCl_3$, 20 mol% $[(tBu)_3PH]BF_4$, Cy_2NMe, 1,4-dioxane, 85 ºC, 5 h reaction can be performed on **6a** in the presence of triflic acid and anisole to deliver pyrrolidine **20** in a 91% yield, >20:1 d.r., and a 9:1 mixture of *para*- to *ortho*-regioisomers. Using a milder Brønsted acid, tetrafluoroboric acid, this tandem sequence can also introduce heteroaromatics such as protected indole or benzothiophene on the carbon skeleton in excellent to good stereoselectivity. In addition, carbocycle **12b** was shown to be an excellent substrate for the Friedel-Crafts alkylation of 4-bromoveratrole, delivering diarylmethane **23** in a 75% yield and >20:1 d.r. after recrystallization. Intramolecular Heck coupling[16] furnished tricycle **24** in 57% yield. The 1.2 Hz coupling constant observed between the benzylic proton and its neighbor establishes their *cis* relationship, which indicates the Friedel-Crafts alkylation proceeded with net retention. This diastereoselectivity is observed by Bach in a somewhat related system.[17] In his proposed model, the conformation of the benzylic carbocation is fixed in order to maximize hyperconjugative effects and to minimize $A^{1,3}$ strain (Scheme 1). The nucleophile attacks the carbocation from the *si*-face leading to the observed stereochemistry.

In conclusion, we have developed a highly diastero- and enantioselective intramolecular interrupted metallo-ene reaction using a readily available precatalyst ligated to a chiral phosphoramidite. We have shown that the reaction is broadly applicable to a wide variety of substrate classes and that the products are valuable scaffolds for further chemical functionalization. A mechanism consistent with our observations invokes outer sphere attack of water on the cationic intermediate **A** (Scheme 1). This new family of simply available chiral CpRu complexes looks very promising to many applications considering the broad utility of CpRu complexes in catalysis. Current work includes expanding the scope of this chemistry to other nucleophiles.

ASSOCIATED CONTENT

Supporting Information. Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

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ACKNOWLEDGMENT

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(2) (a) Oppolzer, W.; Kuo, D. L.; Hutzinger, M. W.; Léger, R.; Durand, J.-O.; Leslie, C. *Tetrahedron Lett.* **1997**, *38*, 6213. (b) Hamada, Y.; Hara, O.; Fujino, H.; Makino, K. *Heterocycles* **2008**, *76*, 197. (c) Schafroth, M. A.; Sarlah, D.; Krautwald, S.; Carreira, E. M. *J. Am. Chem. Soc.* **2012**, *134*, 20276.

(3) (a) Trost, B. M.; Rao, M.; Dieskau, A. P. *J. Am. Chem. Soc.* **2013**, *135*, 18697. (b) Trost, B. M.; Ryan, M. C.; Rao, M.; Markovic, T. Z. *J. Am. Chem. Soc.* **2014**, *136*, 17422.

(4) Similar products to **3** have been synthesized by Toste and coworkers *via* a gold-catalyzed cyclization of allenenes: González, A. Z.; Benitez, D.; Tkatchouk, E.; Goddard, W. A.; Toste, F. D. *J. Am. Chem. Soc.* **2011**, *133*, 5500.

(5) The remaining mass balance consisted of elimination to the (*E*)-1,3-dienamide. While no direct hydration of the π-allyl was seen in this case, typically adding >5 vol% of water will result in this process competing with cyclization at a 0.1 mmol scale. 1 vol% of water can be added to the reaction at a 1 mmol scale without any detriment to yield and selectivity.

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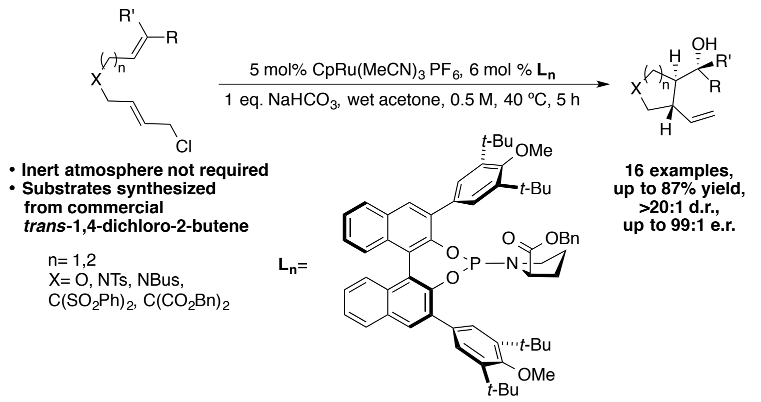
R'
R
n
X
Cl
5 mol% CpRu(MeCN)3 PF6, 6 mol % Ln
1 eq. NaHCO3, wet acetone, 0.5 M, 40 ºC, 5 h
OH
H
R'
R
X
n
H
• Inert atmosphere not required
• Substrates synthesized from commercial trans-1,4-dichloro-2-butene
n= 1,2
X= O, NTs, NBus, C(SO2Ph)2, C(CO2Bn)2
Ln=
t-Bu
OMe
t-Bu
O
O
P
N
O
OBn
t-Bu
OMe
t-Bu
16 examples,
up to 87% yield,
>20:1 d.r.,
up to 99:1 e.r.