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Catalytic Asymmetric Claisen Rearrangement of Unactivated Allyl Vinyl Ethers

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Abstract: Nearly a century after their original discovery, catalyzed enantioselective variants of the venerable Claisen rearrangement remain relatively rare. We have discovered a cooperative transition metal−Lewis acid cocatalyst system that affects highly enantio- and diastereoselective examples of archetypical Claisen rearrangements. The catalyzed rearrangements proceed using an easily prepared enantioenriched transition metal catalyst and a commercially available Lewis acid cocatalyst at ambient temperature in common solvents.

Pericyclic reactions, including [3,3] sigmatropic rearrangements, enjoy unparalleled value for the synthesis of complex organic structures.[1] As a result, the growing emphasis on catalytic asymmetric transformations in academic, medicinal, and process chemistry-related synthesis activities has inspired the development of an extensive array of catalyzed enantioselective reaction variants. However, catalyzed variants of the [3,3] sigmatropic rearrangement family of pericyclic reactions proceeding with high enantioselectivity continue to be relatively rare.[2] Among the highly successful catalytic asymmetric [3,3] rearrangements that have been developed, reaction variants successfully harnessing these transformation's potential for establishing vicinal stereocenter relationships are especially unique.[3] As a complementary solution to the development of enantioselective [3,3] sigmatropic rearrangements controlling both absolute and relative stereochemistry, we describe herein the Ru(II)-catalyzed Claisen rearrangement of unactivated allyl vinyl ethers (Figure 1).

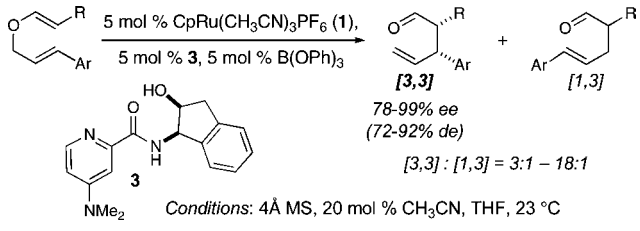
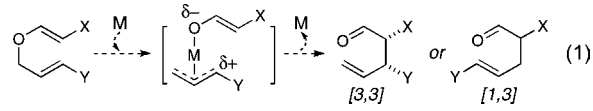


Figure 1. Enatioselective Ru(II)-catalyzed Claisen rearrangements.

The homology existing between concerted, but nonsynchronous, Claisen rearrangements and intramolecular S_N' reactions implicates C−O bond scission and ensuing enolate-allyl cation recombination as one mechanism for Claisen catalyst design (eq 1).[4] However, lacking the intrinsic regiochemical bias present in the concerted processes, rearrangements initiated by C−O bond cleavage require a mechanism for rendering the formal [3,3] sigmatropic process preferred relative to the competing [1,3] rearrangement. The proficiency of [Cp*Ru(2,2′-bipyridine)]$^+$ complexes as catalysts for allylic alkylation reactions exhibiting a strong bias for generating branched substitution products, therefore, provided one model for initial Claisen catalyst designs.[5] Moreover, the activation of allylic ethers toward nucleophilic substitution by the [CpRu(quinaldic acid)]$^+$ complex, ostensibly with assistance by an intramolecular H-bond to the departing ether oxygen, was also instrumental in preliminary catalyst design.[6]



Based on the preceding analysis, the Ru(II) complexes obtained by reacting [CpRu(CH$_3$CN)$_3$]PF$_6$ (**1**) with ligands **2**−**4** were examined as catalysts for the asymmetric Claisen rearrangements of 1,6-disubstituted allyl vinyl ethers (e.g., **5**). The picolinamide ligands **2** and **3** were designed as enantioenriched surrogates for quinaldic acid based on similarities in metal chelate size and pendent H-bond donor shared by these two ligand types (eq 2). As constituted, however, the derived Ru(II) complexes were not competent catalysts, as reacting allyl vinyl ether **5** with varying amounts (5−10 mol %) of Ru(II) salt **1** combined with **2** or **3** (1 equiv relative to **1**) elicited no detectable rearrangement (Table 1).

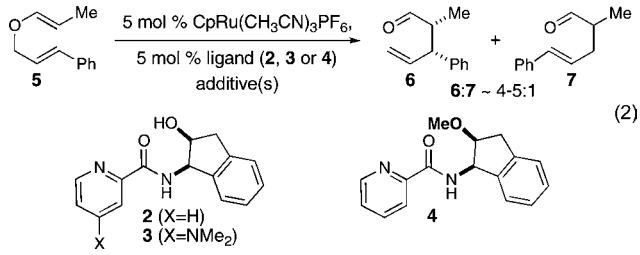


Table 1. Survey of Catalyst Composition and Reaction Conditions (eq 2)

entry	Ligand	Additive(s)	% Conv **5**[a]	% ee **6** (*anti*:*syn*)
a	**2** or **3**	−	0[b]	−
b	**2**	5 mol % B(OPh)$_3$	63	81 (2:1)
c	**3**	5 mol % B(OPh)$_3$	63	89 (10:1)
d	**3**	5 mol % B(OPh)$_3$, 100 wt % 4 Å MS	93	89 (16:1)
e	**3**	5 mol % B(OPh)$_3$, 4 Å MS, 20 mol % CH$_3$CN	100 (91% yield **6**+**7**)	93 (20:1)[c]
f	**4**	5 mol % B(OPh)$_3$, 4 Å MS, 20 mol % CH$_3$CN	45	24 (2:1)

[a] Reactions performed in THF at 23 °C. [b] Up to 10 mol % each of [CpRu(CH$_3$CN)$_3$]PF$_6$ and ligand (**2** or **3**) were used. [c] 28% ee for compound **7**.

Based on the supposition that the ligand-modified Ru(II) complexes had failed to achieve the necessary C−O oxidative insertion, the capacity of Lewis acid cocatalysts to assist oxidative insertion through Lewis acid−base association with the ether

oxygen was evaluated. The impact of the putative Ru(II)-main group Lewis acid cocatalyst system was dramatically apparent upon reacting allyl vinyl ether **5** with $[CpRu(CH_3CN)_3]PF_6$ and **2** (5 mol % each) and $B(OPh)_3$ (5 mol %, THF, 23 °C). Under these conditions, substrate conversion to a mixture of rearrangement adducts **6** and **7** improved to 63% with good enantioselectivity for the formal [3,3] adduct **6** (86% ee), albeit with only moderate diastereoselectivity ($\mathbf{6}_{anti}$:$\mathbf{6}_{syn}$ = 6:1) (Table 1, entries b, c). The Ru(II) catalyst obtained from the 4-(dimethylamino)pyridine-2-carboxamide ligand **3** delivered the *anti* 2,3-disubstituted pentenal **6** from allyl vinyl ether **5** with similar enantioselectivity and considerably improved diastereoselectivity (89% ee, $\mathbf{6}_{anti}/\mathbf{6}_{syn}$ = 10:1). Supporting control experiments confirmed that $B(OPh)_3$, alone or in combination with the ligands **2** or **3**, elicited no detectable rearrangement.[7]

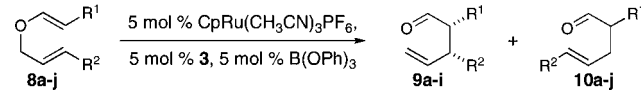
Further improvements in substrate conversion were realized by incorporating 4 Å molecular sieves (MS) to the previously optimized reaction conditions. Catalyzed rearrangement of allyl vinyl ether **5** (5 mol % **1**, 5 mol % **3**, 5 mol % $B(OPh)_3$, THF, 23 °C) in the presence of 4 Å MS (100 wt %) provided 93% conversion with a commensurate, and unanticipated, improvement in both diastereo- and regioselectivity ($\mathbf{6}_{anti}$:$\mathbf{6}_{syn}$ = 16:1, **6**:**7** = 4.6:1).

Added acetonitrile was also found to have a beneficial effect on the catalyzed rearrangements. Control experiments revealed that the Ru(II)-catalyzed Claisen rearrangements were subject to product inhibition; added acetonitrile was expected to disrupt the putative Ru(II)-pentenal chelate emerging from the rearrangement event. Thus, 20 mol % added CH_3CN resulted in full substrate conversion (91% yield **6** + **7**) while simultaneously yielding enhancements in enantio-, diastereo-, and regioselectivity for the [3,3] adduct (93% ee $\mathbf{6}_{anti}$, $\mathbf{6}_{anti}$:$\mathbf{6}_{syn}$ = 20:1, **6**:**7** = 5.3:1) (Table 1, entry e). Similarly high levels of enantioselectivity were not observed in the minor [1,3] product **7** (28% ee).

In accord with our original catalyst design, catalyst competency proved to be critically dependent on the presence of the free alcohol function in the ligand **3**. The CpRu(II) complex obtained from picolinamide ligand **4** in which a methyl ether replaces this alcohol function provided a dramatically inferior catalyst for the rearrangement of ether **5**, affording substantially eroded substrate conversion and stereoselectivity compared to reactions employing catalyst complexes derived from **3** (Table 1, entry f).

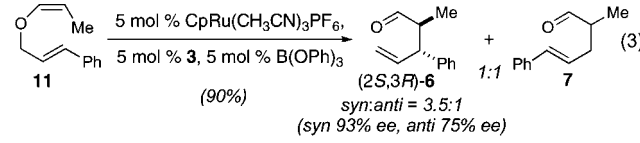
Under these fully optimized reaction conditions (5 mol % **1**, 5 mol % **3**, 5 mol % $B(OPh)_3$, 20 mol % CH_3CN, 100 wt % 4 Å MS, THF, 23 °C), various C_1 alkyl-C_6 aryl or heteroaryl allyl vinyl ethers **8a**−**i** afforded Claisen rearrangement adducts **9a**−**i** possessing generally high enantioselectivity and consistently high *anti* diastereoselectivity, an outcome directly complementary to the *syn* diastereoselection characterizing thermal [3,3] rearrangements of similar *E*,*E*-allyl vinyl ethers (Table 2). Unlike enantio- and diastereoselectivity, however, regioselectivity exhibited considerable variability over the range of C_6-aryl substrates examined (**9**:**10** = 18:1−3:1). Rearrangement stereo- and regioselectivity was also strongly dependent on substrate olefin geometry. As anticipated, inverting the geometry of either olefin present in the Claisen substrate produced a turnover in diastereoselectivity; *Z* vinyl ether **11** (eq 3) and *Z* allyl ether **12** (eq 4) each afforded the *syn* [3,3] adduct **6** as the major rearrangement stereoisomer (93% ee); however, diastereoselectivity and, in the case of **11**, regioselectivity were eroded relative to those obtained from the *E*,*E* ally vinyl ethers.

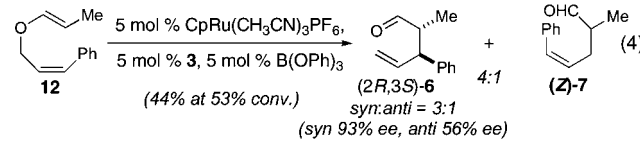
Table 2. Catalyzed [3,3] Rearrangement of C_6-Aryl Allyl Vinyl Ethers



entry	Allyl vinyl ether (**8**)	% ee **9** (*anti*:*syn*)	**9**:**10**	% yield (**9**+**10**)[a,b]
a	R^1 = Et, R^2 = Ph (**8a**)	>99 (6.3:1)	3.6:1	89
b	R^1 = Me, R^2 = 4-$MeOC_6H_4$ (**8b**)	90 (18:1)	14:1	86
c	R^1 = Me, R^2 = 4-MeC_6H_4 (**8c**)	92 (17:1)	7.6:1	90
d	R^1 = Me, R^2 = 4-BrC_6H_4 (**8d**)	92 (25:1)	4.7:1	92
e	R^1 = Me, R^2 = 2-$MeOC_6H_4$ (**8e**)	78 (11:1)	4.4:1	89
f	R^1 = Me, R^2 = 3-$MeOC_6H_4$ (**8f**)	93 (25:1)	6.5:1	80
g	R^1 = Me, R^2 = 3-ClC_6H_4 (**8g**)	96 (17:1)	4.6:1	78
h	R^1 = Me, R^2 = 2-Furyl (**8h**)	96 (10:1)	18:1	63
i	R^1 = Me, R^2 = 1-Naphthyl (**8i**)	96 (10:1)	3:1	90
j[c]	R^1 = Me, R^2 = $^cC_6H_{11}$ (**8j**)	26 (**10j**)	0:100	70

[a] Reaction conditions: CH_3CN (20 mol %), 4 Å MS (100 wt %), THF, 23 °C. [b] Compounds **9** and **10** are inseparable by routine chromatography; methods for separating **9** and **10** are provided in the Supporting Information. [c] $B(O^pC_6H_4F)$ (10 mol %) was used as cocatalyst.





Conditions (eqs 3 & 4): 4Å MS, 20 mol % CH_3CN, THF, 23 °C, 24 h

Using the present catalyst system, the regiochemical bias exhibited by rearrangements of C_6-aryl substrates does not extend to the corresponding C_6-alkyl substrates. Catalyzed rearrangement of the C_6-alkyl substrate **8j** afforded only the [1,3] adduct **10j** with modest enantioselectivity (26% ee) (Table 2, entry j). The attenuated reactivity of these substrates relative to the C_6-aryl derivatives required higher catalyst loadings (10 mol % **1** + **3**) and $B(O^pC_6H_4F)_3$ (10 mol %), in place of $B(OPh)_3$, as the Lewis acid cocatalyst to achieve satisfactory efficiency.

These investigations have identified a unique catalyst system for affecting highly enantio- and diastereoselective Claisen rearrangements. The reactions employ easily obtained catalysts and ligands and proceed in common solvents at ambient temperature. While effective [3,3] rearrangements are currently limited to C_6-aryl substrates, we anticipate that current efforts to elucidate both the reaction mechanism and catalyst structure will expand the structural diversity available from these reactions.

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Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Control experiments confirmed that the individual catalyst components (**1**, **3**, or $B(OPh)_3$) possess no catalytic competency separately or in any combination aside from that described in the text.

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