

Catalytic Asymmetric Claisen Rearrangement of Unactivated Allyl Vinyl Ethers

Marilyn E. Geherty, Robert D. Dura, and Scott G. Nelson*

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

Received May 19, 2010; E-mail: sgnelson@pitt.edu

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).

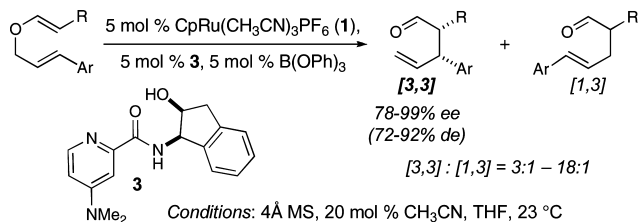
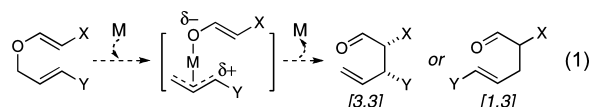


Figure 1. Enantioselective Ru(II)-catalyzed Claisen rearrangements.

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 $[\text{Cp}^*\text{Ru}(2,2'\text{-bipyridine})]^+$ 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 $[\text{CpRu}(\text{quinaldic acid})]^+$ 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 $[\text{CpRu}(\text{CH}_3\text{CN})_3]\text{PF}_6$ (**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).

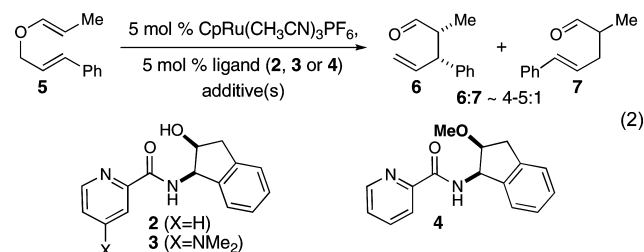


Table 1. Survey of Catalyst Composition and Reaction Conditions (eq 2)

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 $[\text{CpRu}(\text{CH}_3\text{CN})_3]\text{PF}_6$ 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(CH₃CN)₃]PF₆ 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 (**6_{anti}**:**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, **6_{anti}**:**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

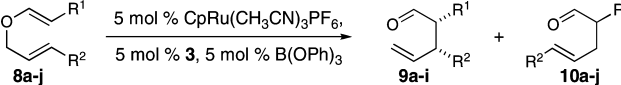
Further improvements in substrate conversion were realized by incorporating 4 Å molecular sieves (MS) to the previously optimized reaction conditions. Catalyzed rearrangement of allyl vinyl ether **5** (5 mol % **1**, 5 mol % **3**, 5 mol % B(OPh)₃, THF, 23 °C) in the presence of 4 Å MS (100 wt %) provided 93% conversion with a commensurate, and unanticipated, improvement in both diastereo- and regioselectivity (**6_{anti}**:**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 CH₃CN 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 **6_{anti}**, **6_{anti}**:**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).

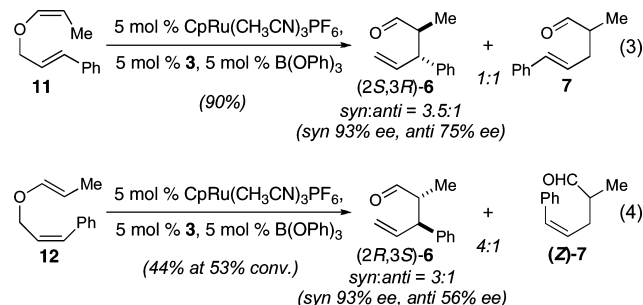
In accord with our original catalyst design, catalyst competency proved to be critically dependent on the presence of the free alcohol function in the ligand **3**. The CpRu(II) complex obtained from picolinamide ligand **4** in which a methyl ether replaces this alcohol function provided a dramatically 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 % CH₃CN, 100 wt % 4 Å MS, THF, 23 °C), various C₆ alkyl-C₆ 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 C₆-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* allyl vinyl ethers.

Table 2. Catalyzed [3,3] Rearrangement of C₆-Aryl Allyl Vinyl Ethers

				
entry	Allyl vinyl ether (8)	% ee 9 (<i>anti:syn</i>)	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 ₆ H ₄ (8b)	90 (18:1)	14:1	86
c	R ¹ = Me, R ² = 4-MeC ₆ H ₄ (8c)	92 (17:1)	7.6:1	90
d	R ¹ = Me, R ² = 4-BrC ₆ H ₄ (8d)	92 (25:1)	4.7:1	92
e	R ¹ = Me, R ² = 2-MeOC ₆ H ₄ (8e)	78 (11:1)	4.4:1	89
f	R ¹ = Me, R ² = 3-MeOC ₆ H ₄ (8f)	93 (25:1)	6.5:1	80
g	R ¹ = Me, R ² = 3-ClC ₆ H 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 = ^c C ₆ H ₁₁ (8j)	26 (10j)	0:100	70

^a Reaction conditions: CH₃CN (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^cC₆H₄F) (10 mol %) was used as cocatalyst.



Conditions (eqs 3 & 4): 4 Å MS, 20 mol % CH₃CN, THF, 23 °C, 24 h

Using the present catalyst system, the regiochemical bias exhibited by rearrangements of C₆-aryl substrates does not extend to the corresponding C₆-alkyl substrates. Catalyzed rearrangement of the C₆-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 C₆-aryl derivatives required higher catalyst loadings (10 mol % **1** + **3**) and B(O^cC₆H₄F)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 C₆-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.

Acknowledgment. Support from the National Science Foundation (CHE 0718467) is gratefully acknowledged.

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

References

- (1) (a) Ziegler, F. E. *Chem. Rev.* **1988**, 88, 1423. (b) Martín Castro, A. M. *Chem. Rev.* **2004**, 104, 2939.
- (2) (a) Maruoka, K.; Saito, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1995**, 117, 1165. (b) Tayama, E.; Saito, A.; Ooi, T.; Maruoka, K. *Tetrahedron* **2002**, 58, 8307. (c) Yoon, T. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, 123, 2911. (d) Anderson, C. E.; Overman, L. E. *J. Am. Chem. Soc.* **2003**, 125, 12412. (e) Burger, E. C.; Tunge, J. A. *Org. Lett.* **2004**, 6, 4113. (f) Burger, E. C.; Tunge, J. A. *Chem. Commun.* **2005**, 2835. (g) Tunge, J. A.; Burger, E. C. *Eur. J. Org. Chem.* **2005**, 1715. (h) Constant, S.; Tortoioli, S.; Muller, J.; Lacour, J. *Angew. Chem., Int. Ed.* **2007**, 46, 2082. (i) Linder, D.; Buron, F.; Constant, S.; Lacour, J. *Eur. J. Org. Chem.* **2008**, 5778. (j) Linton, E. C.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2008**, 130, 16162.
- (3) (a) Abraham, L.; Czerwonka, R.; Hiersemann, M. *Angew. Chem., Int. Ed.* **2001**, 40, 4700. (b) Abraham, L.; Körner, M.; Schwab, P.; Hiersemann, M. *Adv. Synth. Catal.* **2004**, 346, 1281. (c) Akiyama, K.; Mikami, K. *Tetrahedron Lett.* **2004**, 45, 7217. (d) Uyeda, C.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, 130, 9228.
- (4) Schenck, T. G.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, 107, 2058.
- (5) (a) Kondo, T.; Ono, H.; Satake, N.; Mitsudo, T.; Watanabe, Y. *Organometallics* **1995**, 14, 1945. (b) Mbaye, M. D.; Demerseman, B.; Renaud, J.-L.; Toupet, L.; Bruneau, C. *Angew. Chem., Int. Ed.* **2003**, 42, 5066.
- (6) Tanaka, S.; Saburi, H.; Ishibashi, Y.; Kitamura, M. *Org. Lett.* **2004**, 6, 1873.
- (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.

JA1039314