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Rh(I)-Catalyzed Ring-Opening of Hetaryne–Furan Diels–Alder Adducts: Rapid Access to Stereochemically Defined Heterocyclic Scaffolds

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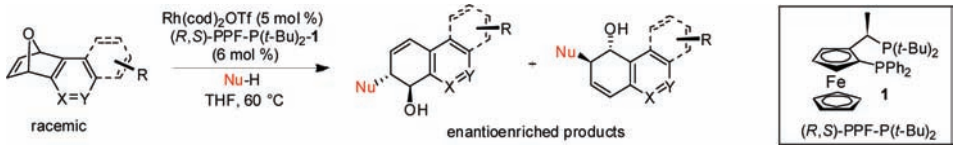
ABSTRACT



Probing the nucleophilic ring-opening of various bicyclic [2.2.1] hetaryne–furan Diels–Alder adducts revealed that efficient reactivity could be observed with heteroatom nucleophiles by using a cationic Rh(I) complex in combination with a chiral Josiphos-type phosphine ligand. Remarkably, this catalyst system was not impeeded by the incorporation of a heteroatom into the substrate. Racemic materials afforded separable mixtures of enantioenriched regioisomers, indicating that strong reagent control is operative.

In the context of modern organic synthesis, benzyne and other arynes are generally considered classic well-studied reactive intermediates.[1] Arynes are highly reactive partners in cycloadditions, and consequently Diels–Alder reactions are commonly used as both traps for the detection of arynes and useful synthetic tools for the construction of polycyclic scaffolds. Reacting arynes with furan affords [2.2.1] benzo-fused oxabicyclic alkenes that have served as highly useful building blocks through transition metal catalyzed asymmetric ring-opening reactions.[2] A number of heterocyclic variants of arynes and their corresponding hetaryne–furan Diels–Alder adducts are known (Figure 1),[3] but until now the behavior of such heterocyclic systems in transition metal catalyzed ring-opening reactions had not been explored.

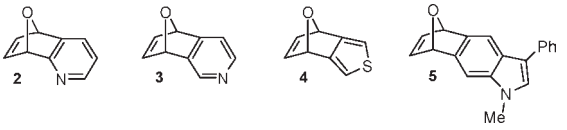


Figure 1. Examples of hetaryne–furan Diels–Alder adducts.

A number of challenges are associated with the incorporation of a heteroatom into the oxabicyclic substrate: the potential for catalyst poisoning is introduced, and substrate electronics may be strongly affected.[4]

(1) For recent reviews on arynes, see: (a) Pelissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701. (b) Wenk, H.; Winkler, M.; Sander, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 502. (c) Dyke, A.; Hester, A.; Lloyd-Jones, G. *Synthesis* **2006**, *24*, 4093. (d) Peña, D.; Pérez, D.; Guitián, E. *Heterocycles* **2007**, *74*, 89. (e) Sanz, R. *Org. Prep. Proceed. Int.* **2008**, *40*, 215.

(2) Ni catalysis: (a) Lautens, M.; Chiu, P.; Ma, S.; Rovis, T. *J. Am. Chem. Soc.* **1995**, *117*, 532. (b) Lautens, M.; Ma, S.; Chiu, P. *J. Am. Chem. Soc.* **1997**, *119*, 6478. bPd catalysis:(c) Lautens, M.; Hiebert, S. *J. Am. Chem. Soc.* **2004**, *126*, 1437. (d) Li, L.; Rayabarapu, D.; Nandi, M.; Cheng, C. *Org. Lett.* **2003**, *5*, 1621. (e) Ogura, T.; Yoshida, K.; Yanagisawa, A.; Imamoto, T. *Org. Lett.* **2009**, *11*, 2245. nCu catalysis:(f) Arrayás, R.; Cabrera, S.; Carretero, J. *Org. Lett.* **2003**, *5*, 1333. (g) Millet, R.; Gremaud, L.; Bernardez, T.; Palais, L.; Alexakis, A. *Synthesis* **2009**, 2101. Ir catalysis:(h) Yang, D.; Hu, P.; Long, Y.; Wu, Y.; Zeng, H.; Wang, H.; Zuo, X. *Beilstein J. Org. Chem.* **2009**, *5*, 53. Rh catalysis: (i) Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res.* **2003**, *36*, 48 and references cited therein.

(3) 2,3-Pyridyne: (a) Walters, M.; Shay, J. *Synth. Commun.* **1997**, *27*, 3573. 3,4-Pyridyne:(b) Tsukazaki, M.; Snieckus, V. *Heterocycles* **1992**, *33*, 533. Thiophyne:(c) Ye, X.; Li, W.; Wong, H. *J. Am. Chem. Soc.* **1996**, *118*, 2511. 5,6-Indolyne:(d) Buszek, K.; Luo, D.; Kondrashov, M.; Brown, N.; VanderVelde, D. *Org. Lett.* **2007**, *9*, 4135.

(4) Our previous work indicates that substrate electronics can have a profound effect on reactivity and selectivity: (a) Lautens, M.; Schmid, G. A.; Chau, A. *J. Org. Chem.* **2002**, *67*, 8043. (b) Lautens, M.; Fagnou, K. *Proc. Nat. Acad. Sci. U.S.A.* **2004**, *101*, 5455.

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Furthermore, although many unsymmetrical hetaryne−furan Diels−Alder cycloadducts can be easily prepared as racemates, no method for their synthesis in enantiomerically pure form currently exists in the literature. We did not see this as a major limitation however, since we previously demonstrated that racemic unsymmetrical oxabenzonorbornenes can be ring-opened with a chiral catalyst to give a regiodivergent resolution,[5] wherein each enantiomer of the substrate reacts in parallel to afford a mixture of enantioenriched regioisomers.[6]

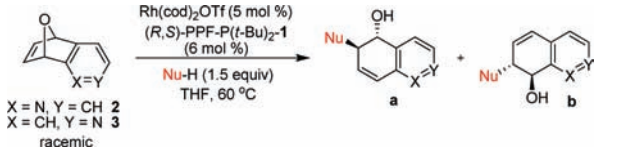
Table 1. Initial Screen of Catalyst Conditions

entry	catalyst	ligand	additive	yield [%] **6a**	(% ee)[a] **6b**
1[b]	$[Rh(cod)Cl]_2$	none	none	n.r.	n.r.
2	$[Rh(cod)Cl]_2$	dppf	none	n.r.	n.r.
3[c]	$[Rh(cod)Cl]_2$	dppf	NH_4Cl	n.r.	n.r.
4	$Rh(cod)_2OTf$	none	none	–[d]	–[d]
5	$Rh(cod)_2OTf$	dppf	none	n.r.	n.r.
6[e]	$Rh(cod)_2OTf$	**1**	TBAI	n.r.	n.r.
7[f]	$Rh(cod)_2OTf$	**1**	NH_4BF_4	n.r.	n.r.
8[g]	**$Rh(cod)_2OTf$**	**1**	**none**	**29 (>99)**	**34 (>99)**

[a] Yield determined following column chromatography, % ee in parentheses determined by chiral HPLC. [b] Reaction performed using 2,2,2-TFE as the solvent. [c] NH_4Cl (1 equiv) was added to the catalyst prior to the addition of substrate. [d] Complete decomposition to an intractable mixture was observed. [e] TBAI (20 mol %) was added to the catalyst prior to the addition of substrate. [f] NH_4BF_4 (1 equiv) was added to the catalyst prior to the addition of substrate. [g] Reaction performed at 60 °C.

We initiated our study by attempting the Rh(I)-catalyzed methanolysis of 1,4-dihydroepoxyquinoline **2** (Table 1). It was found to be recalcitrant toward most standard Rh-catalyzed ring-opening conditions, failing to react using $[Rh(cod)Cl]_2$ with or without dppf or protic additives (Table 1, entries 1−3). Changing to ligand-free conditions with the cationic species $[Rh(cod)_2OTf]$ consumed the substrate **2**, but this proved too reactive and led only to decomposition (Table 1, entry 4). Using a Rh−I species (generated *in situ* from $[Rh(cod)_2OTf]$ and TBAI) in combination with *t*-Bu-Josiphos that previously demonstrated an excellent reactivity profile in our earlier work also failed to give any conversion (Table 1, entry 6).[7] We were pleased to discover however that employing the $[Rh(cod)_2OTf]$ catalyst with *t*-Bu-Josiphos in the absence of any additive gave efficient ring-opening, yielding methanolysis products **6a** and **6b** that were separable by flash chromatography, each in >99% ee (Table 1, entry 8).

Table 2. Effect of Nitrogen Position



entry	substrate	nucleophile		yield [%] (% ee)[a] **a**	**b**
1	**2**	MeOH	**6**	29 (>99)	34 (>99)
2	**2**	Bn_2NH	**7**	32 (67)	30 (>99)
3	**2**	$PhNHCH_3$	**8**	43 (75)	43 (>99)
4	**2**		**9**	37 (60)	38 (>99)
5	**3**	MeOH	**10**	25 (>99)[b]	25 (>99)[b]
6	**3**	Bn_2NH	**11**	30 (94)	29 (>99)
7	**3**	$PhNHCH_3$	**12**	40 (94)	41 (>99)
8	**3**		**13**	48 (91)	45 (>99)

[a] Yield determined following column chromatography, % ee in parentheses determined by chiral HPLC. [b] Isolated as an inseparable mixture of regioisomers (ratio determined by ^1H NMR).

We then examined the ring-opening of oxabicycle **2** with nitrogen nucleophiles (Table 2, entries 2−4). The products were obtained in good combined yield as near 1:1 mixtures of separable regioisomers. In general, ring-opening of oxabicycle **2** with amines proceeded to give one regioisomer (product type **a**) in moderate ee (60−75%) and the other regioisomer (product type **b**) as virtually a single enantiomer (>99% ee).[8] In contrast, the ring-opening of 1,4-dihydroepoxyisoquinoline **3** was also investigated and found to proceed with high efficiency to give both regioisomeric dihydroisoquinoline products in excellent ee (Table 2, entries 5−8).

The intricacy of substrate electronics was further probed by examining the reactivity of substituted 1,4-dihydroepoxyquinolines **14** and **15** (Table 3).[9] Ethoxy-substituted oxabicycle **14** reacted efficiently, giving regioisomeric pairs of products in good yield (Table 3, entries 1−4). A strong

(5) (a) Webster, R.; Böing, C.; Lautens, M. *J. Am. Chem. Soc.* **2009**, *131*, 444. (b) Webster, R.; Boyer, A.; Fleming, M.; Lautens, M. *Org. Lett.* **2010**, *12*, 5418.

(6) For reviews on regiodivergent/parallel kinetic resolutions, see: Kumar, R. R.; Kagan, H. B. *Adv. Synth. Catal.* **2010**, *352*, 231. Dehli, J. R.; Gotor, V. *Chem. Soc. Rev.* **2002**, *31*, 365. For selected reports, see: Wu, B.; Parquette, J. R.; RajanBabu, T. V. *Science* **2009**, *326*, 1662. Jana, C. K.; Studer, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 6542. Gansäuer, A.; Fan, C. A.; Keller, F.; Keil, J. *J. Am. Chem. Soc.* **2007**, *129*, 3484. Gansäuer, A.; Fan, C. A.; Keller, F.; Karbaum, P. *Chem.—Eur. J.* **2007**, *13*, 8084. Pineschi, M.; Del Moro, F.; Crotti, P.; Di Bussolo, V.; Macchia, F. *J. Org. Chem.* **2004**, *69*, 2099. Tanaka, K.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 8078. Chen, Y. G.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 11302. Vedejs, E.; Chen, X. H. *J. Am. Chem. Soc.* **1997**, *119*, 2584. Doyle, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Ruppar, D. A.; Martin, S. F.; Spaller, M. R.; Liras, S. *J. Am. Chem. Soc.* **1995**, *117*, 11021. Bolm, C.; Schlingloff, G. *J. Chem. Soc., Chem. Commun.* **1995**, 1247.

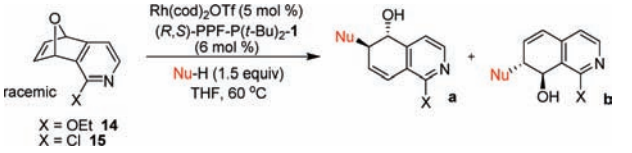
(7) (a) Lautens, M.; Fagnou, K. *J. Am. Chem. Soc.* **2001**, *123*, 7170. (b) Fagnou, K.; Lautens, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 26.

(8) This difference in enantioselectivity is likely because oxabicycle **2** possesses a strong inherent substrate reactivity bias, leading to the erosion of the ee for one product; however this cannot be verified since we have not successfully ring-opened oxabicycle **2** using an achiral catalyst in order to observe the substrate's inherent mode of reactivity (see ref 5a for a more thorough discussion).

(9) Prepared according to literature procedures. For ethoxy-substituted oxabicycle **14**, see: (a) Connon, S.; Hegarty, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1245. For chloro-substituted oxabicycle **15**, see:(b) Guitián, E. *Eur. J. Org. Chem.* **2001**, 4543.

electronic effect appears to be operative, since one of the two regioisomers (product type **a**) was produced in only modest ee (58−89%), while the other (product type **b**) was universally formed in very high ee (>99%). Conversly, chloro-substituted oxabicycle **15** exhibited excellent ee for each regioisomeric product, and good yields were maintained for both regioisomers (Table 3, entries 5−8).

Table 3. Effect of Aryl Substitution



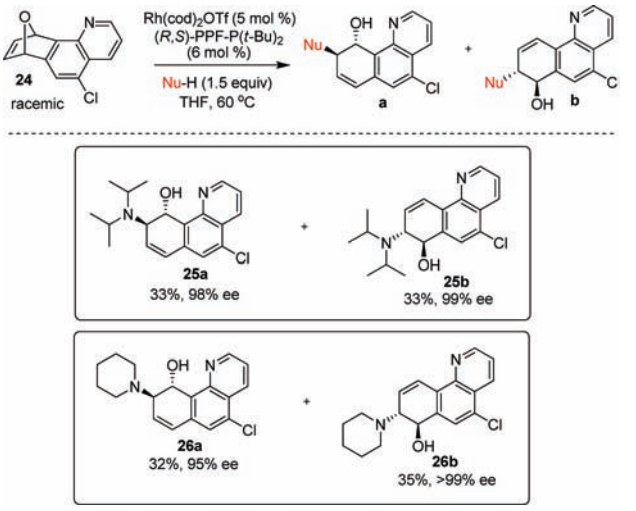
entry	substrate	nucleophile		yield [%] (% ee)[a] a	b
1	**14**	MeOH	**16**	49 (58)	25 (>99)
2	**14**	PhOH	**17**	37 (89)	30 (>99)
3	**14**	$TsNH_2$	**18**	36 (74)[b]	29 (>99)[b]
4	**14**		**19**	48 (75)	41 (>99)
5	**15**	MeOH	**20**	40 (94)	39 (>99)
6	**15**	$PhNHCH_3$	**21**	38 (98)	38 (>99)
7	**15**		**22**	34 (>99)	32 (>99)
8	**15**		**23**	38 (97)	34 (97)

[a] Yield determined following column chromatography, % ee in parentheses determined by chiral HPLC. [b] Absolute configuration established using X-ray analysis.

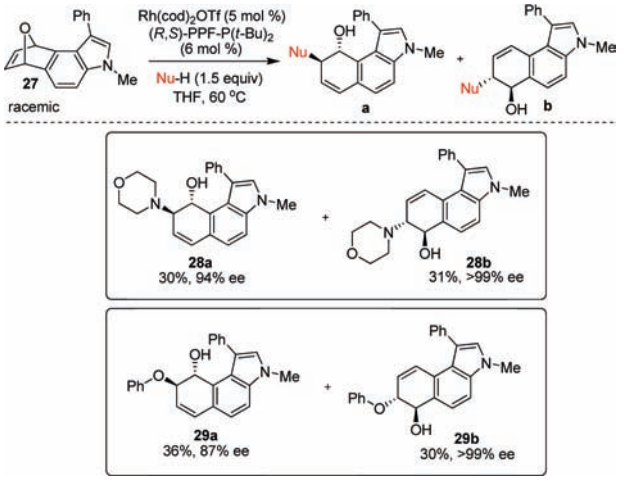
Our success prompted us to investigate more complex heterocycle-fused [2.2.1] oxabicyclic systems. We were drawn to quinoline-fused oxabicycles, such as **24** (Scheme 1), that were conveniently accessible in high yield using a protocol developed by Knochel and co-workers.[10] Subjecting quinoline-fused oxabicycle **24** to the cationic Rh-OTf/*t*-Bu-Josiphos catalyst system resulted in nucleophilic ring-opening with both diisopropylamine and piperidine to give separable regiosiomeric products with exceptional enantioselectivity (>95% ee).

Indolynes have recently garnered significant interest from the synthetic community and have been the subject of several theoretical studies.[11] We found that indolyne−furan cycloadduct **27** reacted smoothly under our optimized conditions to furnish good combined yields of ring-opened regiosomers in excellent ee (Scheme 2).

Scheme 1. Regiodivergent Ring-Opening of a Quinolyne−Furan Diels−Alder Adduct



Scheme 2. Regiodivergent Ring-Opening of an Indolyne−Furan Diels−Alder Adduct



A proposed catalytic cycle that corroborates our previous work in this area is depicted below (Scheme 3).[12] The key event in the cycle is the enantioselective ionization of the substrate **IIa**/**IIb** C−O bond by the cationic active catalyst **I** to give an activated complex **IIIa**/**IIIb** represented as a Rh-σ-enyl species. Protonation of the active complex **IIIa**/**IIIb** by the nucleophile is believed to precede nucleophilic addition[13] to give **IVa**/**IVb** that is subsequently intercepted by the resulting anionic nucleophile

(10) Sapountzis, I.; Lin, W.; Fischer, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 4364.

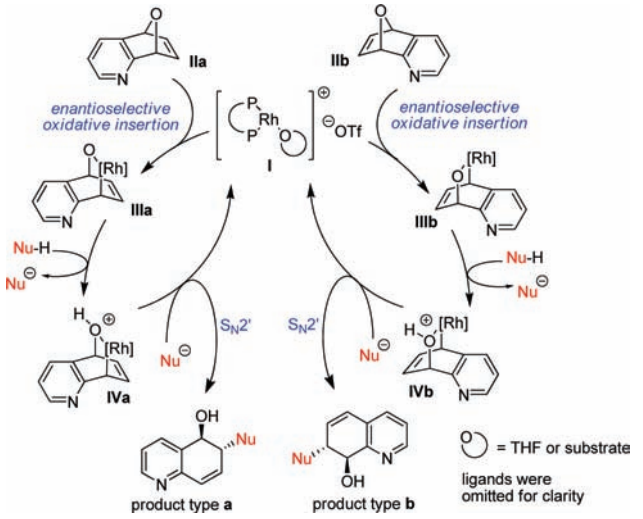
(11) (a) Buszek, K.; Brown, N.; Luo, D. *Org. Lett.* **2009**, *11*, 201. (b) Bronner, S.; Bahnck, K.; Garg, N. *Org. Lett.* **2009**, *11*, 1007. (c) Tian, X.; Huters, A.; Douglas, C.; Garg, N. *Org. Lett.* **2009**, *11*, 2349. (d) Brown, N.; Luo, D.; Decapo, J.; Buszek, K. *Tetrahedron Lett.* **2009**, *50*, 7113. (e) Cheong, P.; Paton, R.; Bronner, S.; G-Yoon, J.; Garg, N.; Houk, K. *J. Am. Chem. Soc.* **2009**, *132*, 1267. (f) Garr, A.; Luo, D.; Brown, N.; Cramer, C.; Buszek, K.; VanderVelde, D. *Org. Lett.* **2010**, *12*, 96.

(12) Fleming, M. J.; Lautens, M. In *Catalyzed Carbon-Heteroatom Bond Formation*; Yudin, A. K., Ed.; John Wiley & Sons Ltd.: Chichester, 2010.

(13) This is based on the following observations: the reaction rate increases with decreasing nucleophile pK_a; no productive reaction is observed using anionic nucleophiles; protic additives generally accelerate the reaction.

in an S_N2' fashion to deliver the product and regenerate the active catalyst.

Scheme 3. Proposed Catalytic Cycle



In summary, the regiodivergent nucleophilic ring-opening of various racemic hetaryne–furan Diels–Alder adducts was achieved using a chiral cationic Rh(I) catalyst. A number of polycyclic heterocycles were prepared in enantiomerically pure form over a short sequence of steps. The products of this chemistry are mostly novel heterocyclic analogues of a bioactive class of compounds (2-aminotetralins),[14] making this methodology geared toward diversity-oriented synthesis and potentially very useful for medicinal chemists. Studies directed at the synthesis of enantiomerically pure hetaryne–furan Diels–Alder adducts to better exploit the utility of this method are ongoing in our laboratories and will be reported in due course.

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Supporting Information Available. Experimental procedures, characterization data for new compounds, additional data tables. This material is available free of charge via the Internet at http://pubs.acs.org.

(14) (a) Koe, B.; Weissman, A.; Welch, W.; Browne, R. *J. Pharmacol. Exp. Ther.* **1983**, *226*, 686. (b) Freeman, J.; Michalson, E.; D'andrea, S.; Baczynskyj, L.; Von Voigtlander, P.; Lahti, R.; Smith, M.; Lawson, C.; Scahill, T.; Mizsak, S.; Szmuszkovicz, J. *J. Med. Chem.* **1991**, *34*, 1891. (c) Zhang, Y.; Tropsha, A.; McPhail, A.; Lee, K. *J. Med. Chem.* **1994**, *37*, 1460. (d) Necas, M.; Dostal, J.; Kejnovska, I.; Vorlickova, M.; Slavik, J. *J. Mol. Struct.* **2005**, *734*, 1.