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Transition-Metal-Catalyzed Ring Opening of Hetero-Diels–Alder Adducts

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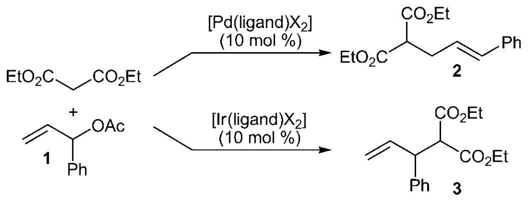
cycloaddition · homogeneous catalysis · ring-opening · selectivity · transition metals

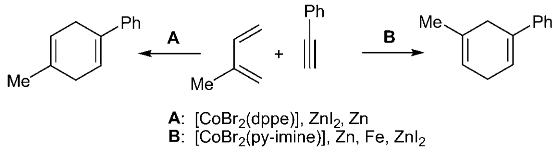
The control of selectivity (whether chemo-, regio-, or stereo-) is of fundamental importance in organic synthesis, especially with regard to the generation of complex target structures. The most successful modern synthetic methodologies deliver the desired products in excellent yields and with efficient control of the diverse selectivities.

A simple thought experiment can effectively demonstrate the fundamental motivation for this overview: The addition of elemental bromine to cyclohexene is a common reaction that has been carried out by countless generations of chemistry students and leads to the generation of *trans*-1,2-dibromocyclohexane. The reaction mechanism dictates the selective *trans* addition of the bromine atoms to the double bond. A far from trivial question is how the diastereomeric *cis*-1,2-dibromocyclohexane can be generated from the same starting materials. The solution to this fundamental problem is still far beyond our reach. As such, processes that permit the selective generation of different products from the same precursors simply by varying the reaction conditions or the catalyst are at the center of academic and synthetic interest.[1] The Tsuji–Trost reaction (Scheme 1) provides a prominent example for regioselective control by variation of the applied transition-metal complex.[2] The reaction of **1** with malonate esters in the presence of a palladium catalyst leads to the attack of the sterically less hindered end of the π-allyl palladium complex to give **2**.[3] If an iridium-based catalyst is used, the branched product **3** is obtained.[4]



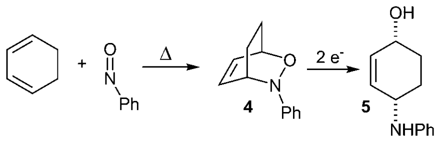
Scheme 1. Regiodivergent palladium- and iridium-catalyzed Tsuji–Trost reactions.

Plietker et al. recently demonstrated a regiospecific approach in an iron-mediated variant of the Tsuji–Trost reaction of malonate esters with either allylic alcohols such as **1** or cinnamate derivatives. In this case substitution occurs without formation of a π-allyl metal intermediate.[5] A further example of a regioselective synthesis is the cobalt-catalyzed Diels–Alder reaction of 1,3-dienes with alkynes. While diphosphine complexes deliver the *para*-substituted product (**A**),[6] the *meta*-substituted regioisomer is generated in excellent yields as the sole product when an imino(pyridine) cobalt complex is utilized (**B**, Scheme 2).[7]



Scheme 2. Regiodivergent cobalt-catalyzed Diels–Alder reaction. dppe = ethane-1,2-diylbis(diphenylphosphane), py-imine = mesityl pyridin-2-ylmethylene amine.

Hetero-Diels–Alder reactions are especially attractive, as the introduction of heteroatoms permits the rapid escalation of complexity. A striking example is the thermal hetero-Diels–Alder reaction of nitroso compounds and 1,3-dienes. Diels–Alder adducts such as **4** can be converted to molecules with a high density of functionalities after reductive workup. One product, the cyclohexene derivative **5**, is a good example, demonstrating the exclusive *cis* relationship of the amino and hydroxy groups in the 1- and 4-positions. The regioselectivity is a consequence of the concerted mechanism of this Diels–Alder reaction (Scheme 3). Unfortunately this is a further example of a transformation where generation of the corresponding *trans* isomer would require multiple additional steps.



Scheme 3. 1,4-Hydroxyamination of 1,3-dienes via a thermal Diels–Alder reactions.

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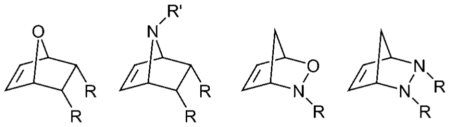
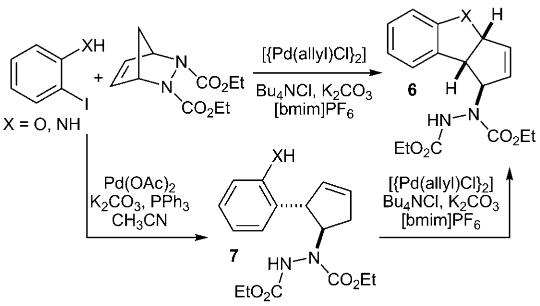
The bicyclic intermediate **4** is amenable to further functionalization through a variety of further methods. Both the oxygen and the nitrogen atom in **4** are in allylic positions with respect to the double bond. This, together with the strained character of the bicyclic system, permits attack by nucleophilic transition-metal complexes to generate a π-allyl metal complex and one of the heteroatoms serves as a leaving group. Scheme 4 depicts the most common adducts, easily accessible by hetero Diels–Alder cycloadditions, which have been used to study this type of reaction.



Scheme 4. Heterobicyclic alkenes.

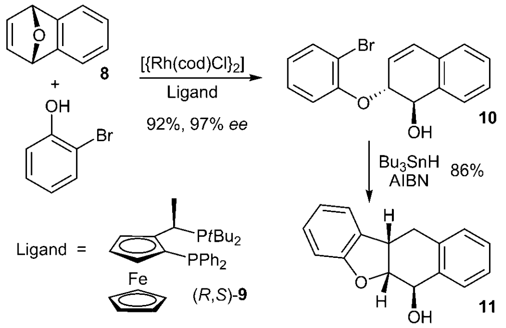
A very promising palladium-catalyzed ring opening of azabicyclic alkenes with subsequent cyclization to give cyclopentene-anellated benzofuran and indole derivatives was recently described by Radhakrishnan et al. (Scheme 5).[8] 2-Iodophenol (X = O) or 2-iodoaniline (X = NH) serves as the twofold (carbon and heteroatom) nucleophile. Product **6** is generated starting from just two distinct molecules in a single transformation with a rapid increase in complexity. Target molecules similar to **6** are generated in good to excellent yields and with high *trans* selectivity. It is worth pointing out that high chemoselectivity is observed in this reaction. If triphenylphosphine is used as the ligand, products of type **7** arise in which only the new carbon–carbon bond has been formed. These products can be isolated in good yield. Isolated derivatives of **7** can be converted to products of type **6** under phosphine-free conditions, strongly suggesting that **7** is an intermediate in the cascade sequence.



Scheme 5. Palladium-catalyzed ring-opening/cyclization cascade. [bmim]PF_6 = 1-butyl-3-methylimidazole hexafluorophosphate.

A possible π-allyl palladium species, which would lead to the formation of the carbon–oxygen bond first does not seem to be realistic. The authors propose a mechanism that involves insertion of the double bond of the bicyclic alkene into the palladium–aryl bond. Only in the next step does the bicycle open to give **7** with concomitant generation of a new double bond. This intermediate is coordinated to palladium, and palladation of the heteroatom leads to a σ-alkyl palladium species which upon reductive elimination and displacement of the double bond gives **6**. Ruthenium- and rhodium-catalyzed ring-opening reactions are, in contrast, generally thought to proceed via π-allyl metal species. The newest developments in this field are presented in the following.

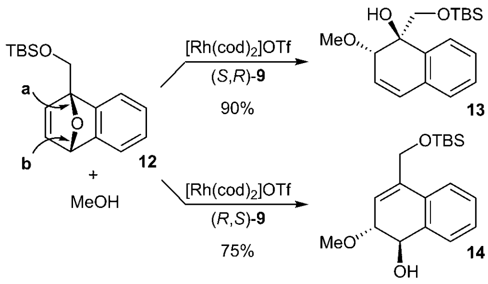
The pioneering work by Lautens et al. concerning ring-opening reactions of oxabenzonorbornadienes (i.e. **8**) utilized rhodium catalysis with chiral ferrocene-based ligands (**9**) and led to products such as **10** after nucleophilic attack by various heteroatom nucleophiles (phenols in Scheme 6). The products were obtained in excellent yields and with high enantioselectivities, permitting complete desymmetrization of the starting material.[9] In subsequent reactions the obtained hydroxydihydronaphthalene derivatives (such as **10**) can be transformed into more complex molecules, for example the tetracyclic target molecule **11**.



Scheme 6. Rhodium-catalyzed desymmetrization of oxabenzonorbornadiene. cod = 1,5-cyclooctadiene, AIBN = 2,2′-azobisisobutyronitrile.

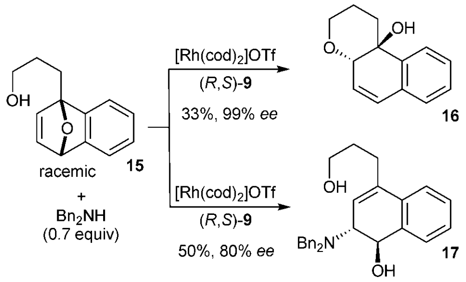
An improvement on this chemistry by use of chiral starting materials such as **12** was recently reported by the Lautens group (Scheme 7).[10] The authors determined that for this class of starting material rhodium triflate complexes were required. At the same time strong substrate control was observed, leading to selective cleavage of the more substituted carbon–oxygen bond (**a**) and exclusive formation of **14**. When a chiral ligand such as **9** was used, double stereodifferentiation was observed, and the catalyst was the dominant factor in determining the ultimate selectivity observed.

The enantiomerically enriched starting material **12** was smoothly converted to either **13** or **14**, depending on which enantiomer of **9** was used, in good yields and enantioselectivities



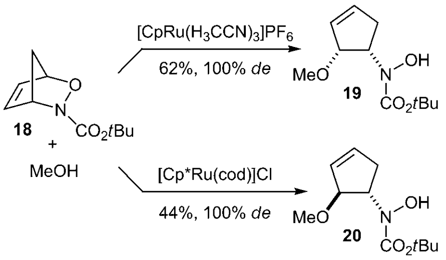
Scheme 7. Regiodivergent ring opening of oxabenzonorbornadienes. TBS = *tert*-butyldimethylsilyl, OTf = trifluoromethanesulfonate.

tivity. The catalyst can clearly differentiate bond **a** from bond **b**. This interesting behavior can be used for the kinetic resolution of racemic oxabenzonorbornadienes. When starting material **15** was subjected to the rhodium-catalyzed reaction, intramolecular trapping resulted in product **16**. In this "matched" scenario very high enantiomeric excess was observed along with exclusive cleavage of bond **b**, while for the "mismatched" scenario bond **a** is cleaved and the intermediate is susceptible to only intermolecular trapping, here by a secondary amine, to give **17** with good enantiomeric excess (Scheme 8).



Scheme 8. Rhodium-catalyzed kinetic resolution of an oxabenzonorbornadiene. Bn = benzyl.

A new aspect of ring-opening reactions was demonstrated with the opening of 3-aza-2-oxabicyclo[2.2.1]hept-5-ene catalyzed by ruthenium complexes (Scheme 9). Two different heteroatoms are present in the bridge, thus leading to the possibility of two distinct products upon ring opening. In a recent publication Tam et al. describe the ruthenium-catalyzed ring-opening reaction of hetero-Diels–Alder adducts such as **18**.[11] Extremely high regio- and stereoselectivities are obtained in the formation of the ring-opened products. Starting from **18** the choice of the ruthenium catalyst permits the exclusive generation of either the *cis* or the *trans* product. While other transition-metal-catalyzed ring-opening reactions predominately give 1,4-cyclopentenes,[12] the ruthenium catalyst leads to the regiochemically homogeneous 1,2-cyclopentene derivatives **19** and **20**. The authors postulate that the first step in the ring opening is the coordination of the cationic complex [CpRu(H_3CCN)$_3$]PF_6 to the double bond of the starting material. Assuming the metal fragment preferentially coordinates on the *exo* side of the bicycle, the nucleophilic attack should proceed from the *endo* side giving the *cis*-configured **19**.



Scheme 9. Stereoselective ruthenium-catalyzed ring-opening reactions. Cp = C_5H_5, Cp* = C_5Me_5.

When the neutral complex [Cp*Ru(cod)]Cl is used, the authors postulate coordination of the complex with the oxygen atom in the ring, followed by insertion into the carbon–oxygen bond with formation of a σ-bound allyl–ruthenium intermediate. S_N2'-type attack by methanol proceeds from the *exo* side thus generating the *trans*-configured stereochemistry in the final product **20**. Various alcohols can serve as nucleophiles, although methanol and ethanol deliver the best results. Even though the yields are not yet optimal there is no "cross-talk" between the distinct pathways, giving an either/or response with respect to the stereochemistry. It remains to be seen if the authors can develop a chiral ruthenium complex capable of achieving kinetic resolution.

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[1] a) J. Dehli, V. Gotor, *Chem. Soc. Rev.* **2002**, *31*, 365; b) C. Jana, A. Studer, *Angew. Chem.* **2007**, *119*, 6662; *Angew. Chem. Int. Ed.* **2007**, *46*, 6542; c) M. Pineschi, F. Moro, P. Crotti, V. Di Bussolo, F. Macchia, *J. Org. Chem.* **2004**, *69*, 2099; d) K. Tanaka, G. Fu, *J. Am. Chem. Soc.* **2003**, *125*, 8078; e) Y. Chen, L. Deng, *J. Am. Chem. Soc.* **2001**, *123*, 11302; f) E. Vedejs, X. Chen, *J. Am. Chem. Soc.* **1997**, *119*, 2584; g) E. Vedejs, X. Chen, *J. Am. Chem. Soc.* **1997**, *119*, 2584; h) H. Kagan, *Croat. Chem. Acta* **1996**, *69*, 669; i) C. Bolm, G. Schlingloff, *J. Chem. Soc. Chem. Commun.* **1995**, 1247; j) M. P. Doyle, A. B. Dyatkin, A. V. Kalinin, D. A. Ruppar, S. F. Martin, M. R. Spaller, S. Liras, *J. Am. Chem. Soc.* **1995**, *117*, 11021; k) M. Visser, A. Hoveyda, *Tetrahedron* **1995**, *51*, 4383; l) S. F. Martin, M. R. Spaller, S. Liras, B. Hartmann, *J. Am. Chem. Soc.* **1994**, *116*, 4493.

[2] a) Z. Lu, S. Ma, *Angew. Chem.* **2008**, *120*, 264; *Angew. Chem. Int. Ed.* **2008**, *47*, 258; b) T. Graening, H.-G. Schmalz, *Angew. Chem.* **2003**, *115*, 2684; *Angew. Chem. Int. Ed.* **2003**, *42*, 2580; c) B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921; d) B. M. Trost, C. B. Lee in *Catalytic Asymmetric Synthesis II* (Ed.: I. Ojima), Wiley-VCH, Weinheim, **2000**, p. 593; e) A. Pfaltz, M. Lautens in *Comprehensive Asymmetric Catalysis, Vol. 2* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Heidelberg, **1999**, p. 833; f) G. Helmchen, *J. Organomet. Chem.* **1999**, *576*, 203; g) M. Johannsen, K. A. Jørgensen, *Chem. Rev.* **1998**, *98*, 1689; h) B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395; i) C. G. Frost, J. Howarth, J. M. J. Williams, *Tetrahedron: Asymmetry* **1992**, *3*, 1089.

[3] a) J. Tsuji, *Tetrahedron* **1986**, *42*, 4361; b) B. M. Trost, *Tetrahedron* **1977**, *33*, 2615; c) M. F. Semmelhack, *Org. React.* **1972**, *19*, 115.

[4] a) G. Helmchen, A. Dahnz, P. Dübon, M. Schelwies, R. Weihofen, *Chem. Commun.* **2007**, 675; b) R. Takeuchi, S. Kezuka, *Synthesis* **2006**, 3349.

[5] a) B. Plietker, A. Dieskau, K. Moews, A. Jatsch, *Angew. Chem.* **2008**, *120*, 204; *Angew. Chem. Int. Ed.* **2008**, *47*, 198; b) B. Plietker, *Angew. Chem.* **2006**, *118*, 1497; *Angew. Chem. Int. Ed.* **2006**, *45*, 1469.

[6] a) G. Hilt, M. Danz, *Synthesis* **2008**, 2257; b) G. Hilt, T. J. Korn, *Tetrahedron Lett.* **2001**, *42*, 2783.

[7] a) G. Hilt, J. Janikowski, *Org. Lett.* **2009**, *11*, 773; b) P. Mörschel, J. Janikowski, G. Hilt, G. Frenking, *J. Am. Chem. Soc.* **2008**, *130*, 8952; c) G. Hilt, J. Janikowski, W. Hess, *Angew. Chem.* **2006**, *118*, 5328; *Angew. Chem. Int. Ed.* **2006**, *45*, 5204.

[8] J. John, U. Indu, E. Suresh, K. V. Radhakrishnan, *J. Am. Chem. Soc.* **2009**, *131*, 5042.

[9] Leading references: a) M. Lautens, K. Fagnou, T. Rovis, *J. Am. Chem. Soc.* **2000**, *122*, 5650; b) M. Lautens, K. Fagnou, M. Taylor, *Org. Lett.* **2000**, *2*, 1677.

[10] R. Webster, C. Böing, M. Lautens, *J. Am. Chem. Soc.* **2009**, *131*, 444.

[11] B. P. Machin, J. Howell, J. Mandel, N. Blanchard, W. Tam, *Org. Lett.* **2009**, *11*, 2077.

[12] a) W. Lee, K.-H. Kim, M. D. Surman, M. J. Miller, *J. Org. Chem.* **2003**, *68*, 139; b) M. D. Surman, M. J. Mulvihill, M. J. Miller, *Org. Lett.* **2002**, *4*, 139; c) M. D. Surman, M. J. Miller, *J. Org. Chem.* **2001**, *66*, 2466; d) M. D. Surman, M. J. Miller, *Org. Lett.* **2001**, *3*, 519; e) M. J. Mulvihill, M. D. Surman, M. J. Miller, *J. Org. Chem.* **1998**, *63*, 4874.