Application of Transition Metal Catalysis to Small Molecule Synthesis

Thesis by

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Acknowledgement.

It is absolutely amazing that five years have passed since I came to Caltech. It is even more amazing that this thesis is now in its final hours. I can honestly say that these five years have been the absolute best of my life thus far. The environment for learning here is amazing, primarily because of the large number of talented people that fill it, from whom I have gotten countless ideas, advice, and inspiration.

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and provided me with countless advice and new ideas. He is one of the smartest, most creative, and enthusiastic chemists that I have ever met. His attitude was contagious, and it helped me to become more excited about my project. Greg became my number one person to talk to about things, in part because he was so helpful, and in part because I had a crush on him. Those were very fun days, and, so far, they have ended well, because Greg eventually asked me out, and things have been spectacular ever since. During my thesis-writing process, Greg has provided a lot of support, including proofreading my entire thesis, making me dinner *every* night, and being patient when I freaked out because I thought it was never going to be done, which happened on a regular basis. Greg has been a wonderful addition to my life.

Abstract

Over the past decade, transition metal catalysis has developed into a new field in organic synthesis, enabling numerous synthetic transformations that were previously not feasible. This thesis describes the application of both ruthenium and rhenium catalysis to the synthesis of several classes of small molecules. Ruthenium-catalyzed ring-opening cross-metathesis of five- through eight-membered ring cycloolefins was investigated for the synthesis of functionalized dienes (Chapter 1). Unsubstituted, trisubstituted, and allyl-substituted cycloolefins were studied. Regioselective reactions could be achieved with the use of unsymmetrical cycloolefins. Ruthenium-catalyzed cross-metathesis was explored for the synthesis of both di- and trisubstituted vinyl boronates (Chapter 2). These reactions proceeded efficiently for a wide variety of functionalized alkenes and generally exhibited high *E*-stereoselectivity. The resultant vinyl boronate products were stereoselectively converted into both *Z*-vinyl bromides and *E*-vinyl iodides. The rhenium-catalyzed 1,3-isomerization of allylic alcohols was employed in the synthesis of various allylic alcohols (Chapter 3). Two different strategies were developed to promote high product selectivity in these reactions: conjugated product synthesis and N,O-bis(trimethylsilyl)acetamide-promoted product trapping. These reactions enabled the synthesis of allylic alcohols with conjugated or non-conjugated, di- or trisubstituted, and electron-rich or electron-deficient alkene components. Partial chirality transfer was observed during the 1,3-isomerization of certain enantioenriched allylic alcohols. The fundamental reaction properties observed during these studies were all consistent with the operation of a mechanism involving a chair-like transition state, which contains a partially cationic allyl moiety, as the primary reaction pathway.

General Experimental Section

NMR spectra were recorded on an Oxford NMR spectrometer running Varian VNMR software. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) with reference to the internal solvent. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), multiplet (m), and broad (br). The reported ^{1}H NMR and ^{13}C NMR data refer to the major alkene isomer (which is identified) except when otherwise noted. Assignment of the *E*/*Z* stereochemistry for the disubstituted alkenes was based upon the coupling constants of their vinylic protons, and that for the trisubstituted alkenes was based upon NOE experiments. High-resolution mass spectra (EI, CI, or FAB) were provided by the California Institute of Technology Mass Spectrometry Facility. Molecular mass calculations were performed with ChemDraw Ultra 9.0.1 (Cambridge Scientific).

GC and HPLC data were obtained using an Agilent 6850 Series GC system and an Agilent 1100 Series HPLC, respectively. Optical rotations were measured using a Jasco P-1010 Polarimeter. Low reaction temperatures (–10 °C to –50 °C) were obtained using a Neslab CC-100 Cryotrol. Analytical thin-layer chromatography (TLC) was performed on silica gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. Visualization was performed using a standard potassium permanganate stain. Flash column chromatography employed silica gel 60 (230-400 mesh) from EM Science. Ether, CH_2Cl_2, benzene, and THF were purified and dried by passage through a solvent column.[i] All other chemicals were used as purchased, unless otherwise noted.

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[i] The solvent columns were composed of activated alumina (A-2) and supported copper redox catalyst (Q-5 reactant). See: Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518-1520.

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