# TRANSITION METAL CATALYZED APPROACHES TO THE ASYMMETRIC CONSTRUCTION OF ALL-CARBON QUATERNARY CENTERS

Thesis by

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*To my dear mother*

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Mom…I was questioning whether or not to even write anything here, as no words would do justice to the amount that I love and appreciate you or to what you have meant to my growth. You are the single purest and most loving person I have ever met, and you have loved me as much as anyone can hoped to be loved as a son. You are part of my conscience,

and our hearts are inextricably intertwined. I am so happy that I will be coming home soon and that I will be able to see you on a regular basis again. It has been a long time, but we finally made it.

## ABSTRACT

In the Stoltz group, chemical research leverages the interplay between methods development and total synthesis, wherein new synthetic technologies enable the pursuit of novel target compounds and challenges encountered during synthetic campaigns inspire the invention of methodologies. Given the stereochemical complexity of natural products and emerging pharmaceuticals, methods development in our group has focused in particular on the asymmetric construction of all-carbon quaternary centers. Herein is described the development of transition metal catalyzed approaches to the formation of such centers with high levels of stereocontrol. Chapter 1 describes the discovery of an Ir-catalyzed asymmetric allylic alkylation reaction efficiently merging linear, trisubstituted allylic electrophiles with prototypical malonate nucleophiles to generate enantioenriched β-quaternary carbonyl products. The reaction proceeds with low catalyst loadings of iridium and at ambient temperature, marking the first reaction of its kind to be performed under such mild conditions. Appendix 2 highlights recent efforts to develop an Ir-catalyzed process for the doubly stereoselective formation of vicinal quaternary stereocenters. Chapter 2 discloses a more sustainable, Mo-catalyzed alternative to the Ir-catalyzed process in Chapter 1, unveiling thus far unknown reactivity with molybdenum and generating the desired products with outstanding enantioselectivity. This advance was enabled by exhaustive investigation of suitable ligand scaffolds, ultimately leading to the creation of the novel, C1-symmetric ShabyDACH ligand. Chapter 3 discusses the elaboration of a Pd-catalyzed a-vinylation of lactam nucleophiles to forge a-quaternary carbonyls. These products could further be diversified to a range of elusive scaffolds, highlighting their synthetic utility.

## PUBLISHED CONTENT AND CONTRIBUTIONS

1. **Moghadam, F. A**.‡; Hicks, E. F.‡; Sercel, Z. P.; Cusumano, A. Q.; Bartberger, M. D.; Stoltz, B. M. Ir-Catalyzed Asymmetric Allylic Alkylation of Dialkyl Malonates Enabling the Construction of Enantioenriched All-Carbon Quaternary Centers. *J. Am. Chem. Soc.* **2022**, *144*, 7983–7987. DOI:10.1021/jacs.2c02960.
    - F. A. M participated in reaction optimization, experimental work, data analysis, and manuscript preparation.
2. Reimann, C. E.; Kim, K. E.; Rand, A. W.; **Moghadam, F. A**.; Stoltz, B. M. *Tetrahedron* **2023**, *130*, 133176. DOI: 10.1016/j.tet.2022.133176.
    - F. A. M participated in collecting references and manuscript preparation.
3. **Moghadam, F. A**.‡; Barbor, J. P.‡; Chan, M.‡; Jette, C.; Sakurai, S.; Stoltz, B. M. Formation of All-Carbon Quaternary Centers via Enantioselective Pd-catalyzed α-Vinylation of γ-Lactams. *Org. Lett.* **2024**, *26*, 7551–7554. DOI: 10.1021.acs.orglett.4c02551.
    - F. A. M participated in reaction optimization, experimental work, data analysis, and manuscript preparation.
4. **Moghadam, F. A**.‡; Cerione, C. S.‡; Stoltz, B. M. Mo-Catalyzed Asymmetric Allylic Alkylation Enabling the Construction of Highly Enantioenriched 1,4-Dicarbonyl Scaffolds. *ChemRxiv* **2025**. DOI: 10.26434/chemrxiv-2025-41644.
    - F. A. M participated in reaction optimization, experimental work, data analysis, and manuscript preparation.

5. Xuyu, Y.; Lee, J.; **Moghadam, F. A**.; Steiner, J.; Soo-Kyung, S.; de Almenara, A. J.; Stoltz, B. M. Predicted new molecules followed by experimental validation for protecting human neurons from oxidative stress induced cytotoxicity. *PNAS* **2025**, submitted.
    - F. A. M participated in reaction optimization, experimental work, data analysis, and manuscript preparation.

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| $[\alpha]_D$ | specific rotation at wavelength of sodium D line |
| ºC | degrees Celsius |
| Å | Angstrom |
| λ | wavelength |
| μ | micro |
| Aq | aqueous |
| Ar | aryl |
| atm | atmosphere |
| Bn | benzyl |
| Boc | *tert*-butyloxycarbonyl |
| bp | boiling point |
| br | broad |
| Bz | benzoyl |
| *c* | concentration for specific rotation measurements |
| calc'd | calculated |
| $cm^{-1}$ | wavenumer(s) |
| d | doublet |
| D | deuterium |
| dba | dibenzylideneacetone |
| DIBAL | diisobutylaluminum hydride |
| DMAP | 4-dimethylaminopyridine |

| | |
|---|---|
| DMF | *N,N*-dimethylformamide |
| dr | diastereomeric ratio |
| e.g. | for example (Latin exempli gratia) |
| *ee* | enantiomeric excess |
| EI+ | electron impact |
| equiv | equivalent(s) |
| ESI | electrospray ionization |
| Et | ethyl |
| EtOAc | ethyl acetate |
| G | grams |
| GC | gas chromatography |
| h | hours |
| HPLC | high-performance liquid chromatography |
| HRMS | high-resolution mass spectrometry |
| Hz | hertz |
| i.e. | that is (Latin id est) |
| IPA | isopropanol |
| *i*-Pr | *iso*-propyl |
| IR | infrared (spectroscopy) |
| *J* | coupling constant (NMR), exchange coupling constant (diradicals) |
| K | Kelvin (absolute temperature) |

| | |
|---|---|
| kcal | kilocalorie |
| KHMDS | potassium hexamethyldisilazide |
| L | liter; ligand |
| LDA | lithium diisopropylamide |
| LHMDS | lithium hexamethyldisilazide |
| M | multiplet, milli |
| *m/z* | mass to charge ratio |
| *m*-CPBA | *meta*-chloroperoxybenzoic acid |
| Me | methyl |
| MeCN | acetonitrile |
| MeOH | methanol |
| mg | milligram(s) |
| MHz | megahertz |
| min | minutes |
| mol | mole(s) |
| *n*-Bu | *n*-butyl |
| NMR | nuclear magnetic resonance |
| Pd/C | palladium on carbon |
| Ph | phenyl |
| PHOX | phosphinooxazoline (ligand) |
| PHOX=O | phosphinooxazoline oxide (ligand) |
| ppm | parts per million |
| PTSA | *para*-toluenesulfonic acid |

| | |
|---|---|
| q | quartet |
| R | generic for any atom or functional groups |
| S | singlet |
| SCF | self-consistent field |
| SFC | supercritical fluid chromatography |
| t | triplet |
| TBS | *tert*-butyldimethylsilyl |
| *t*-Bu | *tert*-butyl |
| TES | triethylsilyl |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| TLC | thin-layer chromatography |
| $t_R$ | retention time |
| UV | ultraviolet |
| X | anionic ligand or electronegative element |