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Enantioselective Synthesis of Isochromans and Tetrahydroisoquinolines by C–H Insertion of Donor/Donor Carbenes

Leslie A. Nickerson, Benjamin D. Bergstrom, Mingchun Gao, Yuan-Shin Shiuie, Croix J. Laconsay, Matthew R. Culberson, Walker A. Knauss, James C. Fettinger, Dean J. Tantillo, Jared T. Shaw*

ABSTRACT: Reports of C–H insertions forming six-membered rings containing heteroatoms are rare due to Stevens rearrangements occurring after nucleophilic attack on the carbene by a heteroatom. Using donor/donor carbenes and Rh$_2$(R-PTAD)$_4$ as a catalyst, we have synthesized a collection of isochroman substrates in good yield, with excellent diastereo- and enantioselectivity, and no rearrangement products were observed. Furthermore, we report the first synthesis of six-membered rings containing nitrogen by C–H insertion to form tetrahydroisoquinolines. In one case, a Stevens rearrangement product was isolated at elevated temperature from a carbamate-protected amine substrate and computational evidence suggests formation through a free ylide not bound to rhodium.

Insertion reactions of metal carbenes into C–H bonds are useful methods for making C–C bonds.\(^1\)–\(^6\) In most cases, C–H insertion reactions are catalyzed with dirhodium tetracarboxylate complexes, often using chiral ligands to provide enantioselectivity.\(^1,\)\(^6\)–\(^8\) Asymmetric C–H insertion has been well-documented for carbenes with two electron withdrawing substituents (CO$_2$R, COR, CN, SO$_2$R, acceptor/acceptor)\(^7\) or with one electron donating (aryl, alkenyl) and one electron withdrawing group (donor/acceptor).\(^9\) Acceptor and acceptor/acceptor carbenes are very reactive and can react indiscriminately with other functionalities on the molecule.\(^7,\)\(^10,\)\(^11\) Donor/acceptor carbenes are less electrophilic due to the donating substituent, which increases selectivity for C–H insertion (Figure 1).\(^3,\)\(^5,\)\(^8\) Recently, we have been interested in donor/donor carbenes,\(^12–14\) which have two electron-donating groups and, as a result, are highly selective for C–H insertion while also tolerating many functional groups present in complex substrates.\(^15,\)\(^16\) Although C–H insertion reactions have been used in the synthesis of a wide variety of five-membered ring (1,5-C–H insertion) heterocycles,\(^1,\)\(^7,\)\(^10\) there are few examples of six-membered ring (1,6-C–H insertion) formation and the substrates are limited to oxygen-containing rings.\(^17–24\)

Accessing 1,6-C–H insertion is difficult due to the kinetic favorability of 1,5-C–H insertion and the potential for rearrangement products when heteroatoms are present (Figure 1). Previous work to synthesize 1,6-C–H insertion products...
without heteroatoms consistently observed mixtures of five- and six-membered ring products when a 1,5-C–H insertion site was available. Installing heteroatoms can eliminate 1,5-C–H insertion however this introduces the possibility of nucleophilic attack on the carbene by the heteroatom. This reaction forms an ylide that undergoes the Stevens rearrangement (or a Stevens-type rearrangement when the heteroatom is oxygen), forming a five-membered ring. 

Despite these challenges, there are scattered reports of forming tetrahydrofuran, chroman, and chromane cores through 1,6-C–H insertion using donor/acceptor or acceptor carbenes. In 2012, Cossy and coworkers demonstrated the use of donor carbenes generated from cyclopentenes in the synthesis of tetrahydrofurans by C–H insertion, further expanding the diazo-free insertion work demonstrated by Zhu. In the cases where chiral catalysts were used, enantioselectivity was often moderate; it wasn’t until 2015 when Hashimoto achieved higher levels of enantioselectivity using Rh\(_2\)(S-PTTL)\(_4\) in reactions leading to isochromans. Stevens-type rearrangement products were also not observed for unsaturated substrates. Notably, 12a did not undergo any Stevens-type rearrangement under reaction conditions, in contrast to a similar substrate derived from a donor/acceptor carbene in work by Hashimoto and co-workers. These results appear to support our hypothesis that the reduced electrophilicity of the donor/donor carbene prevents the competing rearrangement reaction. Additionally, while an unsubstituted allyl group underwent insertion with modest yield, the addition of a single substituent resulted in yields of 90% or greater. The crystal structure of 13b demonstrated that the absolute configuration produced with Rh\(_2\)(R-PTAD)\(_4\) is the same for isochromans as was observed with benzodihydrofurans and related heterocycles. Cis and trans alkene hydrazones and trans alkene hydrazones led to their respective insertion products with no detectable isomerization. A propargyl substituted insertion site proved to be the lowest yielding isochroman. Although the yield was comparatively lower than the other unsaturated substrates, no evidence of dipolar cycloaddition was observed. We hypothesize that a larger ring size helps to limit the dipolar cycloaddition pathway.

| Entry | Product | R\(^1\) | R\(^2\) | Solvent | Yield (%) | E.r. |
|-------|---------|--------|--------|---------|-----------|------|
| 1     | 14a     | Ph     | H      | CH\(_2\)Cl\(_2\) | 97:3      |      |
| 2     | 14b     | Ph     | OCH\(_3\) | CH\(_2\)Cl\(_2\) | 99:5:0.5  |      |
| 3     | 14c     | 4-CNCH\(_3\) | OCH\(_3\) | CH\(_2\)Cl\(_2\) | 99:1      |      |
| 4     | 14d     | H\(_2\)NCOCH\(_3\) | OCH\(_3\) | CH\(_2\)Cl\(_2\) | 99:1      |      |
| 5     | 14e     | 3-pyridyl | OCH\(_3\) | CH\(_2\)Cl\(_2\) | 94:6      |      |
| 6     | 14f     | CH\(_3\) | OCH\(_3\) | CH\(_2\)Cl\(_2\) | 60:40     |      |

* With Rh\(_2\)(S-PTTL)\(_4\) as catalyst; \(^{\text{a}}\) catalyst added at rt

Figure 2. Unsaturated isochroman substrates.
Aliphatic substrates also react with high diastereoselectivity. With one alkyl substituent the yields decreased significantly (15d-e, 54-62%) indicating some substrate preference for inserting into more highly substituted carbons. Importantly, throughout the isochroman examples, all products were formed as a single diastereomer and no Stevens-type rearrangement products were observed.

**Figure 3.** Aliphatic isochroman substrates. \(^{10}\)Run with Rh\(_2\)(S-PTAD)\(_n\).

With the formation of six-membered rings comes the opportunity to explore the influence of 1,3-diaxial interactions in the diastereoselective formation of the stereogenic centers that form during insertion (Figure 4). A single diastereomer (17a) was observed from hydrazone 16a using Rh\(_2\)(Mes)_4 as the catalyst, the configuration of which was determined by a NOE NMR experiment. This indicates that the C–H insertion step occurs in a diastereoselective manner despite having a bulky group close to the rhodium carbene. Furthermore, compounds 17b and 17c were also isolated in good yields with excellent diastereoselectivity when Rh\(_2\)(R-TCPTTL)\(_4\) was used as the catalyst to accelerate the rate of C–H insertion. The chiral phthalimido catalysts generally exhibit higher activity than any of the achiral catalysts used with donor/carbene carbenes. The structure of compound 17c was also determined by X-ray diffraction.\(^{38}\)

Our success in synthesizing isochromans motivated our attempts to synthesize the more challenging nitrogen analogues. To the best of the authors’ knowledge, 1,6-C–H insertion on aliphatic systems has never been done to synthesize nitrogen-containing heterocycles. Joffard and coworkers demonstrated related work involving a C(sp\(^2\))–H insertion on pyrrole using an acceptor carbene.\(^{39-41}\) Using our prior work to synthesize indolines as inspiration,\(^{16}\) we first developed amine- and aniline-based substrates. These substrates proved unsuccessful as the crude reactions were often complex mixtures with no discernible traces of product. In order to reduce the possibility of side reactions, N-sulfonyl groups were installed to reduce the nucleophilicity of the nitrogen lone pair. No identifiable products were isolated with these substrates.

Computational evidence suggests that donor/donor C–H insertions forming benzodihydrofurans proceed through a stepwise mechanism that has a zwitterionic intermediate in which a carboxylation is formed on the insertion carbon.\(^{36}\) Based on this observation we reasoned that a sulfonyl protecting group on nitrogen might be too electron withdrawing, to the detriment of stabilizing a possible carboxylation intermediate. We hypothesized that an amide would reduce the nucleophilicity of the nitrogen but to a lesser extent than a sulfonyl protecting group.

We next attempted substrates using lactams and were pleased to synthesize tetrahydroisoquinoline 23a as a single diastereomer in 54% yield and with 99:1 er (Figure 5).

**Figure 4.** Diastereoselective insertions to form tri-substituted isochromans. \(^{14}\)With Rh\(_2\)(Mes)_4; \(^{15}\)With Rh\(_2\)(R-TCPTTL).

**Figure 5.** Scope of tetrahydroisoquinoline substrates.
We went on to synthesize tetrahydroisoquinoline 23b in good yield and with slightly reduced er. Carbamate derived tetrahydroisoquinoline 23c was also synthesized in moderate yield and with excellent stereoselectivity. X-ray crystallography of 23c showed the same absolute stereochemistry as is observed with isochromans.\textsuperscript{38} As these insertions occur rapidly, we found that reducing the temperature before the addition of catalyst allowed the reaction to complete within 30 minutes to 3 hours while producing a cleaner reaction mixture.

In analogy to our work with indolines, in which insertion into methyl C–H bonds was possible,\textsuperscript{16} we attempted to synthesize a mono-substituted tetrahydroisoquinoline. We synthesized hydrazone 24 with a carbamate protecting group, which we reasoned would provide roughly an equivalent level of electron withdrawing potential as an amide and is easily removed for further functionalization. This substrate reacted much more slowly and eventually required heating to reflux for the diazo to be fully consumed. Upon consumption of diazo no insertion product was observed. The sole identifiable product was isoindoline 26, resulting from an apparent Stevens [1,2]-rearrangement (Figure 4A).\textsuperscript{42,43} A similar product involving attack by an amide nitrogen leading to Stevens rearrangement was observed by Padwa.\textsuperscript{42}

![Diagram](image.png)

**Figure 6.** A) Stevens rearrangement product synthesis. B) The DFT (UB3LYP/LANL2DZ[6-31G(d)]) computed mechanism suggests that N-attack to the rhodium carbene and the subsequent Stevens rearrangement is energetically feasible at experimental conditions; relative free energies (electronic energies in parentheses) for metal-bound (normal text) and ylide (italics) reactions are reported in kcal mol\textsuperscript{-1}.

After identifying the isoindoline as the primary product of the reaction using Rh$_2$(R-PTAD)$_4$, a second run using Rh$_2$(TFA)$_4$ proceeded in 50% yield. The isolation of Stevens product 26 indicates that the properties of the insertion site are as important as the electron withdrawing effect on the nitrogen, given that tetrahydroisoquinoline 23c was isolated from insertion of hydrazone 22c. Although previous studies propose a stepwise diradical mechanism for the Stevens rearrangement,\textsuperscript{43} density functional theory (DFT) studies support N-attack to the metal carbene, but then a concerted free ylide Stevens rearrangement (Figure 4B).\textsuperscript{44} This model suggests that the metal catalyst is not essential in the Stevens rearrangement step.\textsuperscript{45}

**Conclusions**

In conclusion, we have used donor/donor rhodium carbenes to synthesize isochromans in good to excellent yields and with overall excellent stereoselectivity. For isochroman substrates, no Stevens-type rearrangement products were observed. Furthermore, we also explored the synthesis of isochromans in a diastereoselective fashion by installing a substituent on the benzylic carbon alpha to oxygen and were gratified to see a single diastereomer formed. Additionally, we synthesized the first six-membered rings containing nitrogen through 1,6-C(sp\textsuperscript{3})–H insertion in moderate yields and with excellent stereoselectivity. A Stevens rearrangement product was isolated from one substrate using increased temperature and computational evidence suggests that isoindoline formation occurs via a free ylide not bound to rhodium.

**Conflicts of interest**

There are no conflicts to declare.

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