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Rhodium-Catalyzed Intermolecular C–H Functionalization as a Key Step in the Synthesis of Complex Stereodefined β -Arylpyrrolidines

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Abstract

The synthesis of β -arylpyrrolidines via a catalytic enantioselective intermolecular allylic C(sp)³–H functionalization of *trans* alkenes followed by immediate reduction, ozonolysis, and then in situ diversification of the resulting cyclic hemiaminal to furnish highly-substituted, stereo-enriched β -arylpyrrolidines is reported. This methodology utilizes 4-aryl-1-sulfonyl-1,2,3-triazoles as carbene precursors and the dirhodium tetracarboxylate catalyst Rh₂(S-NTTL)₄. A variety of β -arylpyrrolidines were prepared in good yields with high levels of diastereo- and enantioselectivity over four linear steps, requiring only a single purification procedure.

Graphical Abstract

In the past two decades the field of C–H functionalization has grown extensively, ushering in a variety of enabling new methodologies for organic synthesis.^{1–3} In particular, the ability of organic chemists to utilize simple C–H bonds to effect meaningful, enantioselective chemical transformations has caused a shift in the logical approach towards synthesis.⁴ Donor/acceptor carbenes have been especially attractive synthons for C–H insertion reactions because they are sufficiently reactive to functionalize C–H bonds. The donor group attenuates the reactivity of the adjacent carbene affording an impressive range of site-selectivity,⁵ which can be further controlled by the steric nature of the catalyst.⁶ Traditionally, donor/acceptor metallocarbenes are accessed *via* the metal-catalyzed decomposition of diazo compounds utilizing dirhodium tetracarboxylates as optimal chiral

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Full experimental data for the compounds described in the paper (PDF) and X-ray crystallographic data for compounds **8a**, **21a**, and **30** (CIF)

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catalysts,^{5–6} which can be sterically tuned, such that primary, secondary, or tertiary C–H bonds are selectively functionalized.⁷

In recent years, 4-aryl-*N*-sulfonyl-1,2,3-triazoles, which undergo a *retro*-6 π electrocyclozation in solution to unveil latent diazo compounds possessing an α -imino acceptor group (Scheme 1a),⁸ have been shown to act as competent alternates to aryldiazoacetates, demonstrating the ability to access a wide-variety of traditional Rh(II)-catalyzed transformations.^{9–13} However, to date, their application towards intermolecular C–H functionalization has been relatively limited in comparison to their aryldiazoacetate congeners. C–H functionalization of alkanes and cycloalkanes was achieved using naphthalimido based Rh2(S-NTTL)₄ as an optimal catalyst to provide high yields and enantioselectivities.^{14a} Attempts to extend C–H functionalization to substrates containing functional groups have been limited. Cyclic ethers were shown to be ineffective because ylide formation followed by ring-expansion preferentially occurred to C–H insertion.¹⁵ In 2016, our group demonstrated that benzylic and allylic C–H functionalization is a viable process (Scheme 1b),^{14b} and we have recently shown that cyclic and acyclic silanes are prone to C–H functionalization at the beta position to silicon.^{14c} A key reason for choosing 4-aryl-*N*-sulfonyl-1,2,3-triazoles in favor of aryldiazoacetates in synthetic strategy is the ability to map the nitrogen functionality of the α -imino acceptor group into target-oriented synthesis. In this paper, we demonstrate that allylic C–H functionalization with α -imino carbenes can be employed to gain access to a wide-variety of highly substituted and stereodefined β -arylprrrolidines.

In our preliminary asymmetric investigation into allylic C(sp³)–H functionalization, we described our initial findings using three *trans* alkenes and *para*-cymene as substrates with 4-phenyl-*N*-me-thanesulfonyl-1,2,3-triazole as a donor/acceptor carbene precursor in the presence of Rh2(S-NTTL)₄ as an optimal chiral catalyst (Scheme 1b).^{14b} One of the resulting products from this study was methanesulfonamide **6a**, generated in 83% yield and 84% ee by lithium aluminum hydride reduction of the initial C–H functionalization product. We recognized that these types of C–H functionalization products could be useful precursors towards the formation of highly-diversified β -arylprrrolidines. In order to evaluate this possibility, initial studies were conducted to determine if **6a** could be readily converted to the desired pyrrolidine **8a** (Scheme 2).¹⁶ Ozonolysis of **6a** followed by quenching with dimethyl sulfide generated cyclic hemiaminal **7a** in 90% yield. Reduction of **7a** with triethylsilane and boron trifluoride diethyl etherate furnished the desired pyrrolidine **8a** in 95% yield with retention of the asymmetric induction achieved during C–H functionalization. Next, we sought to streamline the synthetic sequence to increase the practicality of this strategy. The sequence of C–H functionalization, imine reduction, ozonolysis, and reductive amination was conducted without chromatographic purification until the last step. Using these conditions, the pyrrolidine **8a** was formed in analogous yield and enantioselectivity to the stepwise procedure (66% yield, 81% ee). Similar results were obtained in a multi gram-scale reaction.

With the optimized procedure for the synthesis of 3-arylprrrolidines in hand, we continued our investigation by examining the scope of the reaction with a wide range of 4-aryl-*N*-sulfonyl-1,2,3-triazoles, as summarized in Figure 1. Varying the *N*-sulfonyl group had little

influence on the reaction outcome. The *N*-mesyl protecting group gave the highest yield as illustrated for **8a** (66% yield, 82% ee), but the 2-(trimethylsilyl)ethanesulfonyl protecting group provided the highest levels of enantioinduction as illustrated for **8c** (56% yield, 86% ee). Moving forward with the *N*-mesyl protecting group, we explored the influence of varying the arene component on the triazole ring, as seen with **8d-n**. A variety of electronically and sterically diverse triazoles were amenable to the insertion event allowing for downstream access to the 3-arylpyrrolidine motif. Electron withdrawing groups gave slightly decreased product yields with moderate levels of enantioinduction **8d-f**. Electron neutral and donating groups both gave excellent yields of **8i-l** with moderate to good levels of enantioinduction. Varying the *meta*-position of the arene ring gave similar results, but the *ortho*-substituted arenes demonstrated significant increases in enantioinduction with lower overall yields, as illustrated for the *ortho*-bromo derivative **8h** (22% yield, 98% ee).

Aiming to generate two new stereogenic centers in one synthetic operation, we turned our attention towards the secondary C–H functionalization of *trans* alkenes to provide stereodefined 3-aryl-4-alkylpyrrolidines (Figure 2). In our previous study we demonstrated that *trans*-3-hexene undergoes secondary C–H functionalization providing a 70:30 mixture of diastereomers **9a:9b**. Therefore, we conducted a brief study to enhance the level of diastereoselectivity prior to downstream pyrrolidine synthesis. Initially, we explored substrates with increased steric bulk on the alkene (Figure 2a). Using *trans*-2,2-dimethyl-3-hexene as a substrate switched the diastereoselectivity of **10** but still led to lower diastereoselective ratios overall (38:62 dr, **10a:10b**). Attempting the reaction using tri-substituted 2-methyl-2-pentene failed to generate any of the desired C–H functionalization product. This result is not too surprising given that previous studies with aryldiazoacetates have also shown that allylic C–H functionalization is sterically blocked by using *cis*-substituted alkenes.¹⁷ Next, we examined the effect of decreasing steric bulk on the alkene component by using *trans*-2-pentene as a substrate, which also provides the possibility for two distinct regiochemical outcomes, insertion at the primary methyl or secondary ethyl group. Previous C–H functionalization studies using 4-aryl-*N*-sulfonyl-1,2,3-triazoles have shown that Rh₂(*S*-NTTL)₄ has a preference for insertion into more substituted secondary and tertiary sites,^{14a–b} and we were pleased to observe the reaction go cleanly for the secondary site furnishing the desired insertion product **12** in 84:16 dr, 73% combined yield, and 97% ee for the major diastereomer. The phthalimido based rhodium tetracarboxylate catalysts, Rh₂(*S*-PTAD)₄ and Rh₂(*S*-PTTL)₄ were examined for comparison to the naphthalimido based Rh₂(*S*-NTTL)₄ but both resulted in the formation of **12** with inferior yields, diastereo-, and enantioselectivities (Figure 2b). Finally, we examined the effect of varying the electronic environment of the arene component on the triazole ring (Figure 2c). Using electron withdrawing and slightly donating *para*-substituents furnished the desired insertion products **13–15** but in decreased yields, diastereo-, and enantioselectivities. The strongly donating *para*-methoxy substituent gave desired product **16** with improved yields and diastereoselectivities with a moderate decrease in enantioselectivity (84% yield, 92:8 dr, 85% ee).

Following optimization for the secondary C–H functionalization, initial attempts at accessing stereoenriched 3-aryl-4-alkylpyrrolidines were hindered by enamine induced

epimerization of the 4-alkyl stereocenter. Allylic insertion product **13** was chosen as an optimal substrate to study the effects of epimerization due to its relatively low levels of diastereoselectivity along with the ease of isolating the diastereomers (Table 1). Examining the reaction conditions, we discovered that epimerization could be controlled using chloroform as a solvent and reducing the temperature of the triethylsilane, boron trifluoride diethyl etherate mediated reduction of the cyclic hemiaminal. In addition, the reagents were added in two portions at zero and thirty minutes to minimize the potential for rapid epimerization of iminium ion **17** due to the presence of excessive Lewis acid. The results were confirmed using both diastereomeric mixtures and diastereopure allylic insertion products **13a** and **13b** leading to the desired pyrrolidines with less than five percent epimerization under the optimized conditions.

Having gained control of the enamine induced epimerization, we examined the scope of the reaction with a range of 4-aryl-N-sulfonyl-1,2,3-triazoles and *trans*-2-alkenes. The overall yields were generally good with all substrates (Figure 3). Utilizing the *para*-methoxy-substituted arene ring with *trans*-2-pentene gave pyrrolidine **25** with the highest diastereoselectivity (**25a**:**25b**, 92:8) but increasing the alkene chain length resulted in modest decreases in diastereoselectivity. The unsubstituted phenyl ring gave relatively consistent diastereoselectivity regardless of the alkene chain length. In all cases, excellent levels of enantioselectivity were observed (>92% ee) except for pyrrolidine **24** derived from *trans*-2-octene and 4-phenyl-*N*-methanesulfonyl-1,2,3-triazole, which provided the major and minor diastereomer in 82 and 80% ee, respectively.

Trapping the iminium ion with nucleophiles other than hydride would generate β -aryl pyrrolidines with a stereogenic center at the C2 position of the pyrrolidine ring. Representative systems were examined to determine the feasibility of such a process. Reaction of cyclic hemiaminal **7a** and **7i** with allyltrimethylsilane using boron trifluoride diethyl etherate as a Lewis acid led to the formation of pyrrolidines **29** and **30** with exceptional diastereocontrol. Nucleophilic addition into the C2 position was also possible in the boron trifluoride diethyl etherate induced reactions with 1-methylindole but in this case the diastereoselectivity was relatively low.

The synthetic sequence described herein affords access to *N*-protected stereodefined β -arylpyrrolidines. The free amine can be also readily obtained by cleaving the mesyl group in the presence of phenol and hydrobromic acid at reflux for 72 h to produce **33** in 87% yield and 84% ee (eq 1).

(1)

In conclusion, we have developed a method for the synthesis of complex, stereodefined β -arylpyrrolidines enabled *via* a Rh(II)-catalyzed intermolecular allylic C(sp³)-H functionalization of *trans* alkenes with downstream ozonolysis and reduction. Moreover, we have demonstrated the synthetic utility of mapping the α -imino acceptor group into target-oriented synthesis to access a challenging class of *N*-heterocycles. Our current investigations are focused around developing new asymmetric transformations using 4-*N*-sulfonyl-1,2,3-triazoles as donor/acceptor rhodium carbene precursors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. For reviews on C-H functionalization, see: Crabtree RH; Lei A Chem. Rev 2017, 117, 8481. [PubMed: 28697603] Davies HML; Morton D J. Org. Chem 2016, 81, 343. [PubMed: 26769355] Farmer ME; Laforteza BN; Yu J-Q Bioorg. Med. Chem 2014, 22, 4445. [PubMed: 24909676]
2. For C-H functionalization in materials chemistry and natural product synthesis, see: Kuninobu Y; Sueki S Synthesis, 2015, 47, 3823. McMurray L; O'Hara F; Gaunt M J. Chem. Soc. Rev 2011, 40, 1885. Yamaguchi J; Yamaguchi AD; Itami K Angew. Chem. Int. Ed 2012, 51, 8960.
3. For a review on the use of C-H functionalization in medicinal chemistry, see: Cernak T; Dykstra KD; Tyagarajan S; Vachal P; Krska SW Chem. Soc. Rev 2016, 45, 546. [PubMed: 26507237] Also see reference 2c.
4. For reviews on the logic of C-H in total synthesis, see: Brückl T; Baxter RD; Ishihara Y; Baran PS Acc. Chem. Res 2012, 45, 826. [PubMed: 22017496] Gutekunst WR; Baran PS Chem. Soc. Rev 2011, 40, 1976. [PubMed: 21298176] Newhouse T; Baran PS Angew. Chem. Int. Ed 2011, 50, 3362. Morton D; Davies HML ACS Cent. Sci 2017, 3, 936. [PubMed: 28979934]
5. For reviews on the use of donor/acceptor metallocarbenes, see: Davies HML; Lian Y Acc. Chem. Res 2012, 45, 923. [PubMed: 22577963] Davies HML; Morton D Chem. Soc. Rev 2011, 40, 1857. [PubMed: 21359404]
6. For recent mechanistic studies of Rh(II)-tetracarboxylate-catalyzed C-H insertion reactions with donor/acceptor carbenes, see: Hansen J; Autschbach J; Davies HML J. Org. Chem 2009, 74, 6555. [PubMed: 19637894] Bess EN; Guptill DM; Davies HML; Sigman MS Chem. Sci 2015, 6, 3057. [PubMed: 29403640]
7. For recent examples, see: Liao K; Yang Y-F; Li Y; Sanders J; Houk KN; Musaev DG; Davies HML Nature Chem. 2017, 551, 609. Liao K; Pickel TC; Boyarskikh V; Bacsá J; Musaev DG; Davies HML Nature 2017, 551, 609. [PubMed: 29156454] Liao K; Negretti S; Musaev DG; Bacsá J; Davies HML Nature 2016, 533, 230. [PubMed: 27172046]
8. For initial work demonstrating the formation of latent diazos from *N*-sulfonyl triazoles, see: Chuprakov S; Kwok SW; Zhang L; Lercher L; Fokin VV J. Am. Chem. Soc 2009, 131, 18034. [PubMed: 19928917] Grimster N; Zhang L; Fokin VV J. Am. Chem. Soc 2010, 132, 2510. [PubMed: 20131915]
9. For reviews on the use of *N*-sulfonyl triazoles, see: Gulevich AV; Gevorgyan V Angew. Chem. Int. Ed 2013, 52, 1371. Davies HML; Alford JS Chem. Soc. Rev 2014, 43, 5151. [PubMed: 24802192]

10. For cyclopropanation reactions using N-sulfonyl-1,2,3-triazoles, see:Reference 8.Shultz EE; Lindsay VNG; Sarpong R Angew. Chem. Int. Ed 2014, 53, 9904.Tian Y; Wang Y; Shang H; Xu X; Tang Y Org. Biomol. Chem 2015, 13, 612. [PubMed: 25382173]
11. For arylation reactions using N-sulfonyl-1,2,3-triazoles, see:Selander N; Worrell BT; Chuprakov S; Velaparthi S; Fokin VV J. Am. Chem. Soc 2012, 134, 14670. [PubMed: 22913576]
12. For dipolar cycloadditions using N-sulfonyl-1,2,3-triazoles with indoles, see:Spangler JE; Davies HML J. Am. Chem. Soc 2013, 135, 6802. [PubMed: 23607705]
13. For intramolecular C–H insertion reactions using N-sulfonyl-1,2,3-triazole substrates, see:Shen M-H; Pan Y-P; Jia Z-H; Ren X-T; Zhang P; Xu H-D Org. Biomol. Chem 2015, 13, 4851. [PubMed: 25826185] Lindsay VNG; Viart HM-F; Sarpong RJ Am. Chem. Soc 2015, 137, 8368.Senoo M; Furukawa A; Hata T; Urabe H Chem. Eur. J 2016, 22, 890. [PubMed: 26549045]
14. For C–H functionalization reactions using N-sulfonyl triazoles, see:Chuprakov S; Malik JA; Zibinsky M; Fokin VV J. Am. Chem. Soc 2011, 133, 10352. [PubMed: 21619004] Scheme 1b:Kubiak II RW; Mighion JD; Wilkerson-Hill SM; Alford JS; Yoshidomi T; Davies HML Org. Lett 2016, 18, 3118. [PubMed: 27333162] Garlets Zachary J., Z. J.; Davies HML Org. Lett 2018, 20, 2168. [PubMed: 29638130]
15. For ring expanded products using cyclic ethers as substrates, see: Footnote 11 inHorneff T; Chuprakov S; Chernyak N; Gevorgyan V; Fokin VV J. Am. Chem. Soc 2008, 130, 14972. [PubMed: 18855475] Medina F; Besnard C; Lacour J Org. Lett 2014, 16, 3232. [PubMed: 24885761] Pospech J; Ferraccioli R; Neumann H; Beller M Chem. Asian. J 2015, 10, 2460. [PubMed: 26206484]
16. The absolute stereochemical configurations of compounds 8a (CDCC 1837567), 21a (CCDC 1837568), and 30 (CCDC 1837569) was determined by X-ray crystallography and the other products were tentatively assigned by analogy.
17. For work with aryl diazoacetates and sterically hindered cis-alkenes, see:Ventura DL; Li Z; Coleman MG; Davies HML Tetrahedron 2009, 65, 3052.

^aInsertion reactions run at 4.0 equiv of **4a**; ozonolysis reactions run at 4.0 equiv DMS; reduction reactions run at 3.2 equiv of HSiEt₃ and BF₃·OEt₂. ^bIsolated yields. ^cee determined by HPLC analysis after purification. ^dInsertion reaction run at 60 °C.

Figure 1. Scope of triazole component^{a-c}

^aInsertion reactions run at 4.0 equiv of **4a**; ozonolysis reactions run at 4.0 equiv DMS; reduction reactions run at 3.2 equiv of HSiEt₃ and BF₃·OEt₂. ^bIsolated yields. ^cee determined by HPLC analysis after purification. ^dInsertion reaction run at 60 °C.

a. Substrate Effects

b. Catalyst Effects

c. Electronic Effect from Carbene Precursor

^aReactions run with 4.0 equiv of alkene. ^bIsolated yields. ^cdr determined by ¹H NMR of crude reaction mixture. ^dee determined by HPLC analysis after purification. ^eRh₂(S-NTTL)₄ used unless otherwise indicated. ^fReaction run at 60 °C.

Figure 2. Optimization of secondary C–H insertion reaction^{a–c}

^aReactions run with 4.0 equiv of alkene. ^bIsolated yields. ^cdr determined by ¹H NMR of crude reaction mixture. ^dee determined by HPLC analysis after purification. ^eRh₂(S-NTTL)₄ used unless otherwise indicated. ^fReaction run at 60 °C.

^aInsertion reactions run at 4.0 equiv of alkene; ozonolysis reactions run at 4.0 equiv dimethyl sulfide; reduction reactions run at 2.2 equiv of HSiEt₃ and 2.0 equiv of BF₃.OEt₂.
^bIsolated yields. ^cdr determined by ¹H NMR of crude reaction mixture. ^dee determined by HPLC analysis after purification.

Figure 3. Synthesis of 3,4-disubstituted pyrrolidines^{a-d}

^aInsertion reactions run at 4.0 equiv of alkene; ozonolysis reactions run at 4.0 equiv dimethyl sulfide; reduction reactions run at 2.2 equiv of HSiEt₃ and 2.0 equiv of BF₃.OEt₂. ^bIsolated yields. ^cdr determined by ¹H NMR of crude reaction mixture. ^dee determined by HPLC analysis after purification.

Scheme 1. Previous allylic C–H functionalization

a. Proof of Principle **b. Development of Four-Step Single-Isolation Process**

Scheme 2. Preliminary studies

Scheme 3. Synthesis of tetrasubstituted pyrrolidines

Table 1.

Minimizing enamine induced epimerization^a

entry	Dr (13a:13b)	solvent	T (°C) ^b		equiv BF ₃ ·OEt ₂	equiv Et ₃ SiH	combined yield ^c	dr ^d (20a:20b)	%ee ^e 20a	%ee ^e 20b
			[O]	[R]						
1	68:32	CH ₂ Cl ₂	-78	-10	3.2	3.2	52	60:40	94	86
2 ^b	68:32	CHCl ₃	-65	-65	2.2	2.0	48	66:34	94	88
3	>97:3	CH ₂ Cl ₂	-78	-10	3.2	3.2	61	92:8	93	90
4 ^b	>97:3	CHCl ₃	-65	-65	2.2	2.0	68	>97:3	93	-
5	3:>97	CH ₂ Cl ₂	-78	-10	3.2	3.2	66	8:92	88	85
6 ^b	3:>97	CHCl ₃	-65	-65	2.2	2.0	64	3:>97	-	85

^a Ozonolysis reactions run at 4.0 equiv dimethyl sulfide.^b All reactions proceed to 23 °C.^c Isolated yields.^d dr determined by ¹H NMR of crude reaction mixture.^e ee determined by HPLC analysis after purification.^f Reactions run by adding half the equiv of HSiEt₃ and BF₃·OEt₂ at *t*₀ and *t*₃₀.