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Enantioselective Intermolecular C–H Functionalization of Allylic and Benzylic sp³ C–H Bonds using N-Sulfonyl-1,2,3-triazoles

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Abstract

The enantioselective intermolecular sp³ C–H functionalization at allylic and benzylic positions was achieved using rhodium-catalyzed reactions with 4-phenyl-N-methanesulfonyl-1,2,3-triazole. The optimum dirhodium tetracarboxylate catalyst for these reactions was Rh₂(S-NTTL)₄. The rhodium-bound α-imino carbene intermediates preferentially reacted with tertiary over primary C–H bonds in good yields and moderate levels of enantioselectivity (66-82% ee). This work demonstrates that N-sulfonyltriazoles can be applied to the effective C–H functionalization at sp³ C–H bonds of substrates containing additional functionality.

Graphical Abstract

The selective functionalization of C–H bonds is becoming a powerful approach for the construction of various organic compounds of academic and medicinal interest.¹–³ Of the many new methods⁴ to achieve selective C–H functionalization, donor-acceptor metallocarbenes have emerged as privileged reactive intermediates for the functionalization of sp³ C–H bonds because their reactions are often highly site-selective, diastereoselective, and enantioselective.⁵ Donor-acceptor metallocarbenes are typically generated by extrusion of dinitrogen from aryl diazoacetates in the presence of dirhodium(II)-tertracarboxylate...
catalysts, and these intermediates insert into C–H bonds through a concerted mechanism where site-selectivity is determined by the competing influences of the steric bulk of the dirhodium carbene complex and the ability of the insertion site carbon to stabilize developing positive charge.\(^6\)

As an alternative to aryldiazoacetates, 4-aryl-N-sulfonyl-1,2,3-triazoles have become valuable synthons in Rh(II)-catalyzed reactions in recent years because these heterocycles are in equilibrium with their open-chain α-diazo imine forms in solution.\(^7\) Consequently, N-sulfonyl-1,2,3-triazoles undergo many similar Rh(II)-catalyzed transformations known to their diazo ester congeners such as cyclopropanation, \([3+2]\) dipolar cycloaddition, arylation, and \([4+3]\) cycloaddition reactions.\(^8\)

In contrast, the utility of N-sulfonyl-1,2,3-triazoles for selective intermolecular C–H functionalization reactions, to date, has been limited to a single study.\(^9^,\(^10\)\) In 2011, Fokin and coworkers showed that α-diazo imines generated from the requisite 4-aryl-N-sulfonyl-1,2,3-triazole precursors undergo intermolecular C–H functionalization reactions with hydrocarbons (as cosolvent) in the presence of \(\text{Rh}_2(\text{S-NTTL})_4\) or \(\text{Rh}_2(\text{S-PTAD})_4\) at room temperature (Scheme 1, A).\(^9\) Comparatively, when 4-aryl-N-sulfonyl-1,2,3-triazoles were reacted with tetrahydrofuran or 1,3-dioxolane, both favorable substrates for C–H functionalization reactions with α-diazoesters,\(^11\) no observable C–H functionalization products were reported. Instead, ring-expanded products were obtained, derived from rearrangement of oxo-nium ylide intermediates (Scheme 1, B).\(^12\) Presumably because of these results, there are no further reports on intermolecular sp³ C–H functionalization with N-sulfonyltriazoles. Thus, we decided to explore whether N-sulfonyl triazoles could be used for C–H functionalization of other activated C–H bonds. Herein we describe our initial evaluation of C–H functionalization of allylic and benzylic C–H bonds (Scheme 1, C).

We began our studies by optimizing the reaction of 4-phenyl-1-methanesulfonyl-1,2,3-triazole (1) with trans-4-methyl-2-pentene (2) (Table 1). After a brief survey of dirhodium tetracarboxylate catalysts (see the Supporting Information for de- was identified as the optimal catalyst for tails), \(\text{Rh}_2(\text{S-NTTL})_4\) this transformation.\(^13\) Thus, taking compound 1 and 2.0 equiv of 2 in CHCl₃ (0.5 M with respect to 1) and stirring the reaction mixture for 18 h at ambient temperature with 1 mol % \(\text{Rh}_2(\text{S-NTTL})_4\) led to the formation of C–H insertion product 3a (after \textit{in situ} reduction of the intermediate sulfonyl imine) in 74% isolated yield with a >30:1 regioselective preference for the tertiary C–H insertion over the primary C–H insertion product 3b in 77% ee (Table 1, entry 1). Increasing the amount of alkene 2 from 2.0 to 4.0 equiv resulted in a slight improvement in the isolated yield (83%) and enantioselectivity (84% ee) (Table 1, entries 2–3). Changes to the concentration of triazole 1 (Table 1, entries 4–5) had little effect on the isolated yield and enantioselectivity. Increasing the reaction temperature to 40 °C (Table 1, entry 6) resulted in a decrease in yield of 3a, while lowering the reaction temperature to 0 °C resulted in no product formation (Table 1, entry 7). Shorter reaction times resulted in slightly diminished yield and no advantage was observed when using molecular sieves (Table 1, entries 8–10). Using other chlorinated solvents such as CH₂Cl₂ and 1,2-dichloroethane (Table 1, entries 11 and 13) typically resulted in slightly diminished isolated yields with modest increases in enantioselectivity to 85% and 86% ee, respectively. Other solvents such as α,α,α-
trifluorotoluene\textsuperscript{14} (Table 1, entry 16) gave lower isolated yields and enantioselectivity, and coordinating solvents, such as ethyl acetate, (Table 1, entry 18) were ineffective for this transformation. The absolute configuration of 3a was determined to be (S)- by X-ray crystallographic analysis.\textsuperscript{15} The absolute configurations of the other C–H functionalization products are tentatively assigned assuming the same face selectivity during the approach of the substrate to the rhodium-bound carbene.

With these optimized conditions in hand, we then explored the scope of this transformation with various alkenes (Table 2). A tri-substituted alkene with two potential sites of reactivity, such as \textit{trans}-(2,4-dimethyl)-2-pentene (4) gave a mixture of the C–H insertion products 7a and 7b in 52% combined yield (1.5:1 \textit{rr}) under the optimized reaction conditions. Interestingly, we found that 7b, resulting from primary C–H insertion, was obtained in 94% ee whereas 7a, resulting from insertion into the tertiary C–H bond, was obtained in 74% ee. Similar higher enantioselectivity for primary C–H insertion versus tertiary C–H insertion was seen in the rhodium-catalyzed reactions with aryl-diazoacetates.\textsuperscript{5b} In the case of 3-hexene which has a secondary C–H site, product 8 was furnished in 80% yield with moderate diastereoselectivity (7:3 \textit{dr}) and high enantioselectivity (97% and 89% ee for the major and minor diastereomer, respectively). When \textalpha{}-terpinene (6) was used as a reaction substrate, a reversal of site-selectivity in the C–H insertion reaction was observed. Specifically, the product resulting from primary insertion (9) was formed as the major product in 51% isolated yield and 96% ee in addition to less than 3% of a mixture of various other insertion products. In all of the presented scenarios, no products derived from cyclopropanation of the olefin were observed.

With the allylic C–H functionalization reaction established, we then investigated the selective functionalization of benzylic C–H bonds (Table 3). Using \textit{p}-cymene 10 as a model substrate, Rh\textsubscript{2}(S-NTTL)\textsubscript{4} again proved to be the best catalyst to produce products 11a and 11b in terms of yields, regioselectivity, and enantioselectivity (Table 3, entry 1). Other catalysts such as Rh\textsubscript{2}(S-PTAD)\textsubscript{4} and Rh\textsubscript{2}(S-TCPTAD)\textsubscript{4} gave diminished yields and/or stereoselectivity (Table 3, entries 4–7). Reducing the reaction time to 3 h resulted in slightly lower isolated yields (Table 3, entry 3). A similar solvent effect was observed between chloroform and 1,2-dichloroethane where the former gave slightly better yields and the latter better levels of enantioselectivity (Table 3, entries 1 and 2). In all cases, the tertiary C–H insertion product 11a was favored over the primary insertion product 11b.

For comparison, when methyl phenyldiazoacetate (12) was used instead of triazole 1 as the C–H insertion partner (Eq 1) in the Rh\textsubscript{2}(S-NTTL)\textsubscript{4}-catalyzed reaction with \textit{p}-cymene, the tertiary C–H insertion product 13 was formed in 51% yield, but with low enantioinduction (20% ee). When the analogous reaction was performed with \textit{trans}-4-methyl-2-pentene, the C–H insertion product 14 was isolated in 41% yield and 20% ee (Eq 2). These results suggest that even though Rh\textsubscript{2}(S-NTTL)\textsubscript{4} is generally the most effective chiral catalyst to date for the reactions of N-sulfonyltriazoles, its performance is inferior for the reactions of aryl-diazoacetates.\textsuperscript{5e}
Further exploration with a variety of isopropylbenzene substrates is presented in Figure 1. Substrates such as p-isopropyl anisole, 1,4-disopropylbenzene, cumene, and 4-bromo cumene all afforded their corresponding tertiary C–H insertion products 15 – 18 in moderate yields (24 – 64% yield) and enantioselectivity (66 – 82% ee). Interestingly, when using isopropylbenzene as a substrate which does not feature a 1,4-substitution pattern, we isolated dihydroindole 18b in 10% yield and 92% ee resulting from an intermolecular [3+2] dipolar cycloaddition reaction, in addition to the desired C–H insertion product 18a.

Encouraged by the high levels of enantioselectivity obtained for primary C–H insertion products 9 and 11b (95% ee), we finally investigated the insertion of α-diazo imine intermediates into primary benzylic positions. Specifically, we found that reacting 4-methylanisole (19) with triazole 1 under the optimized reaction conditions, produced the primary insertion product 20 in 37% yield and 93% ee after LiAlH₄ reduction. Even though at this stage the yield of the C–H functionalization products at primary benzylic C–H bonds is relatively low, these systems are capable of high levels of enantiominduction with Rh₂(S-NTTL)₄ as the catalyst, which is promising for future reaction development.

In conclusion, we have demonstrated C–H functionalization reactions of allylic and benzylic sp³ C–H bonds using donor-acceptor carbenes generated from 4-aryl-N-sulfonyl-1,2,3-triazoles. These reactions show modest selectivity for tertiary C–H bonds in most cases and proceed with good asymmetric induction. In cases where mixtures of tertiary and primary insertion products are obtained, we observed the highest levels of enantioselectivity for the primary C–H insertion products. Future directions include extending the scope and selectivity of this reaction and developing a mechanistic understanding of the transformation.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

**Acknowledgments**

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Japan. We wish to thank Dr. John Bacsa from the Emory University X-ray Crystallography Center for the X-ray crystallographic structure determination.

References


15. The crystal structure for 3a has been deposited in the Cambridge Database (1475827).

16. Murakami and coworkers have reported an intramolecular version of this transformation; however, the authors state that they were unable to observe the intermolecular formation of dihydroindoles even up to 140 °C with microwave heating. See: Miura T, Funakoshi Y, Murakami M. J Am Chem Soc. 2014; 136:2272–2275. [PubMed: 24437578]
Figure 1.
Substrate scope for benzylic C–H functionalization reaction.
Scheme 1.
Previous work on intermolecular C–H functionalization using N-sulfonyl-1,2,3-triazoles.

A. Fokin, 2011

\[
\text{R}^1 = \text{aryl} \\
\text{R}^2 = \text{alkyl, aryl (1 mmol)} \\
\text{then LiAlH}_4 \\
\text{12 examples} \\
61 - 98% yield \\
85 - 97% ee \\
\text{(and with other alkanes)}
\]

B. Fokin and Gevorgyan, 2008

\[
\text{PhCN} \\
\text{R}^1 = \text{aryl} \\
\text{R}^2 = \text{aryl, benzyl} \\
\text{100 °C (μW), 5 h} \\
\text{(22 examples)}
\]

C. This work (allylic and benzylic substrates)

\[
\text{Ph or} \\
\text{Me} \\
\text{then LiAlH}_4
\]
Scheme 2.
Reaction of triazole 1 with 4-methylanisole
Table 1

Optimization of the allylic C–H functionalization reaction.$^a,b$

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>equiv of 2</th>
<th>t (°C)</th>
<th>concn of 1 (M)</th>
<th>3:1$^a$ insertion</th>
<th>yield (%) of 3a</th>
<th>% ee of 3a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CHCl$_3$</td>
<td>2</td>
<td>rt</td>
<td>0.50</td>
<td>&gt;30:1</td>
<td>74</td>
<td>77</td>
</tr>
<tr>
<td>2</td>
<td>CHCl$_3$</td>
<td>4</td>
<td>rt</td>
<td>0.50</td>
<td>&gt;30:1</td>
<td>83</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>CHCl$_3$</td>
<td>8</td>
<td>rt</td>
<td>0.50</td>
<td>&gt;30:1</td>
<td>77</td>
<td>84</td>
</tr>
<tr>
<td>4</td>
<td>CHCl$_3$</td>
<td>4</td>
<td>rt</td>
<td>1.0</td>
<td>&gt;30:1</td>
<td>77</td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td>CHCl$_3$</td>
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<td>rt</td>
<td>0.25</td>
<td>&gt;30:1</td>
<td>76</td>
<td>83</td>
</tr>
<tr>
<td>6</td>
<td>CHCl$_3$</td>
<td>4</td>
<td>40</td>
<td>0.50</td>
<td>&gt;30:1</td>
<td>78</td>
<td>83</td>
</tr>
<tr>
<td>7</td>
<td>CHCl$_3$</td>
<td>4</td>
<td>0</td>
<td>0.50</td>
<td>n/a</td>
<td>0</td>
<td>n/a</td>
</tr>
<tr>
<td>8$^c$</td>
<td>CHCl$_3$</td>
<td>4</td>
<td>rt</td>
<td>0.50</td>
<td>&gt;30:1</td>
<td>74</td>
<td>84</td>
</tr>
<tr>
<td>9$^d$</td>
<td>CHCl$_3$</td>
<td>4</td>
<td>rt</td>
<td>0.50</td>
<td>&gt;30:1</td>
<td>82</td>
<td>83</td>
</tr>
<tr>
<td>10$^e$</td>
<td>CHCl$_3$</td>
<td>4</td>
<td>rt</td>
<td>0.50</td>
<td>&gt;30:1</td>
<td>80</td>
<td>83</td>
</tr>
<tr>
<td>11</td>
<td>CH$_2$Cl$_2$</td>
<td>4</td>
<td>rt</td>
<td>0.50</td>
<td>&gt;30:1</td>
<td>73</td>
<td>85</td>
</tr>
<tr>
<td>12</td>
<td>CH$_2$Cl$_2$</td>
<td>4</td>
<td>reflux</td>
<td>0.50</td>
<td>&gt;30:1</td>
<td>70</td>
<td>82</td>
</tr>
<tr>
<td>13</td>
<td>1,2-DCE</td>
<td>4</td>
<td>rt</td>
<td>0.50</td>
<td>&gt;30:1</td>
<td>63</td>
<td>86</td>
</tr>
<tr>
<td>14</td>
<td>1,2-DCE</td>
<td>4</td>
<td>40</td>
<td>0.50</td>
<td>&gt;30:1</td>
<td>72</td>
<td>67</td>
</tr>
<tr>
<td>15</td>
<td>TFT</td>
<td>4</td>
<td>rt</td>
<td>0.50</td>
<td>n/a</td>
<td>0</td>
<td>n/a</td>
</tr>
<tr>
<td>16</td>
<td>TFT</td>
<td>4</td>
<td>40</td>
<td>0.50</td>
<td>&gt;30:1</td>
<td>69</td>
<td>79</td>
</tr>
<tr>
<td>17</td>
<td>EtOAc</td>
<td>4</td>
<td>rt</td>
<td>0.50</td>
<td>n/a</td>
<td>0</td>
<td>n/a</td>
</tr>
<tr>
<td>18</td>
<td>EtOAc</td>
<td>4</td>
<td>40</td>
<td>0.50</td>
<td>n/a</td>
<td>0</td>
<td>n/a</td>
</tr>
</tbody>
</table>

$^a$Reaction conditions: Rh$_2$(S-NTTL)$_4$ (1.0 mol %), 1.0 mmol triazole 1.

$^b$18 h reaction time unless otherwise stated.

$^c$4 Å molecular sieves.
6 h reaction time.

12 h reaction time. DCE = dichloroethane, TFT = α,α,α-trifluorotoluene.
Table 2

Substrate scope for allylic C–H functionalization.

<table>
<thead>
<tr>
<th>entry</th>
<th>alkene</th>
<th>insertion product(s) (isolated yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3a (93% yield, 94% ee)</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>7a 74% ee, 94% ee (52% combined yield)</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>8 (80% yield, 73:3 dr)</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>9 (51% yield, 96% ee)</td>
</tr>
</tbody>
</table>

Traces (< 3%) of a mixture of other insertion products were observed.
### Table 3

Optimization for benzylic C–H functionalization reaction.\(^a\)

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>catalyst</th>
<th>time (h)</th>
<th>3°:1° insertion</th>
<th>combined yield (%)</th>
<th>% ee of 3a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CHCl₃</td>
<td>Rh₂(S-NTTL)₄</td>
<td>24</td>
<td>79:21</td>
<td>75</td>
<td>68</td>
</tr>
<tr>
<td>2</td>
<td>1,2-DCE</td>
<td>Rh₂(S-NTTL)₄</td>
<td>24</td>
<td>80:20</td>
<td>65</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>1,2-DCE</td>
<td>Rh₂(S-NTTL)₄</td>
<td>3</td>
<td>80:20</td>
<td>54</td>
<td>77</td>
</tr>
<tr>
<td>4</td>
<td>1,2-DCE</td>
<td>Rh₂(S-PTAD)₄</td>
<td>24</td>
<td>64:36</td>
<td>16</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>1,2-DCE</td>
<td>Rh₂(S-TCPTAD)₄</td>
<td>24</td>
<td>67:33</td>
<td>13</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>1,2-DCE</td>
<td>Rh₂(S-PTTL)₄</td>
<td>24</td>
<td>71:29</td>
<td>28</td>
<td>65</td>
</tr>
<tr>
<td>7</td>
<td>1,2-DCE</td>
<td>Rh₂(S-NTV)₄</td>
<td>18</td>
<td>83:17</td>
<td>64</td>
<td>62</td>
</tr>
</tbody>
</table>

\(^a\)Reactions were run at ambient temperature at 0.5 M concentration, with 1 mol % of catalyst. See the supporting information for the structures of the catalysts.