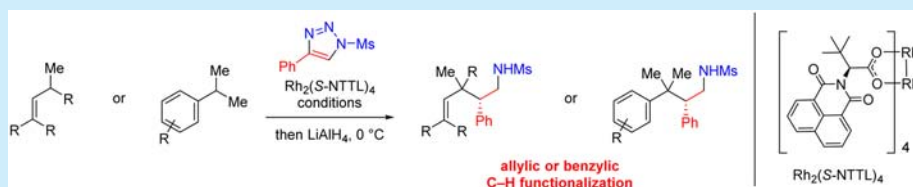# Enantioselective Intermolecular C−H Functionalization of Allylic and Benzylic sp³ C−H Bonds Using *N*-Sulfonyl-1,2,3-triazoles

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S *Supporting Information*

ABSTRACT: The enantioselective intermolecular sp³ C−H functionalization at the 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.

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 methods[4] 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 aryldiazoacetates in the presence of dirhodium(II) tetracarboxylate 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 can exist 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 co-workers 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 Rh₂(*S*-NTTL)₄ or Rh₂(*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 oxonium 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*-sulfonyltriazoles 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 details), Rh₂(*S*-NTTL)₄ was identified as the optimal catalyst for 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 % of Rh₂(*S*-NTTL)₄ led to the formation of C−H insertion product **3a** (after 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

Scheme 1. Previous Work on Intermolecular C−H Functionalization Using *N*-Sulfonyl-1,2,3-triazoles
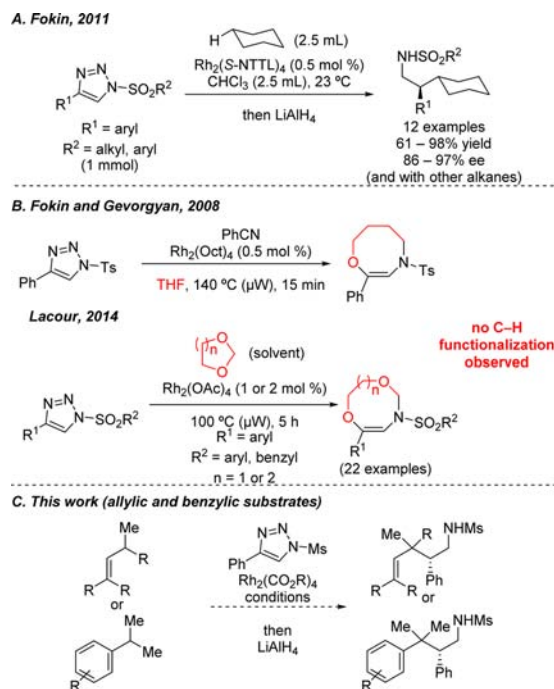
Table 1. Optimization of the Allylic C−H Functionalization Reaction[a,b]

entry	solvent	equiv of 2	T (°C)	concn of 1 (M)	3°:1° insertion	yield (%) of 3a	% ee of 3a
1	CHCl₃	2	rt	0.50	>30:1	74	77
2	CHCl₃	4	rt	0.50	>30:1	83	84
3	CHCl₃	8	rt	0.50	>30:1	77	84
4	CHCl₃	4	rt	1.0	>30:1	77	83
5	CHCl₃	4	rt	0.25	>30:1	76	83
6	CHCl₃	4	40	0.50	>30:1	78	83
7	CHCl₃	4	0	0.50	n/a	0	n/a
8[c]	CHCl₃	4	rt	0.50	>30:1	74	84
9[d]	CHCl₃	4	rt	0.50	>30:1	82	83
10[e]	CHCl₃	4	rt	0.50	>30:1	80	83
11	CH₂Cl₂	4	rt	0.50	>30:1	73	85
12	CH₂Cl₂	4	reflux	0.50	>30:1	70	82
13	1,2-DCE	4	rt	0.50	>30:1	63	86
14	1,2-DCE	4	40	0.50	>30:1	72	67
15	TFT	4	rt	0.50	n/a	0	n/a
16	TFT	4	40	0.50	>30:1	69	79
17	EtOAc	4	rt	0.50	n/a	0	n/a
18	EtOAc	4	40	0.50	n/a	0	n/a

[a]Reaction conditions: Rh₂(*S*-NTTL)₄ (1.0 mol %), 1.0 mmol of triazole **1**. [b]18 h reaction time unless otherwise stated. [c]4 Å molecular sieves. [d]6 h reaction time. [e]12 h reaction time. DCE = dichloroethane, TFT = α,α,α-trifluorotoluene.

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

and 3). Changes to the concentration of triazole **1** (Table 1, entries 4 and 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 molecular sieves were used (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[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.[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 trisubstituted alkene with two potential sites of reactivity, such as *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 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 aryldiazoacetates.[5b] In the

Table 2. Substrate Scope for Allylic C−H Functionalization

[a]Traces (<3%) of a mixture of other insertion products were observed.

case of 3-hexene, which has a secondary C—H site, product **8** was furnished in 80% yield with moderate diastereoselectivity (7:3 dr) and high enantioselectivity (97% and 89% ee for the major and minor diastereomer, respectively). When α-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 *p*-cymene **10** as a model substrate, Rh$_2$(*S*-NTTL)$_4$ 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$_2$(*S*-PTAD)$_4$ and Rh$_2$(*S*-TCPTAD)$_4$ 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$_2$(*S*-NTTL)$_4$-catalyzed reaction with *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 *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$_2$(*S*-NTTL)$_4$ is generally the most effective chiral catalyst to date for the reactions of *N*-sulfonyltriazoles, its performance is inferior for the reactions with methyl phenyldiazoacetate.[5e]

Further exploration with a variety of isopropylbenzene substrates is presented in Figure 1. Substrates such as *p*-isopropyl anisole, 1,4-diisopyropylbenzene, cumene, and 4-bromocumene all afforded their corresponding tertiary C—H insertion products **15**−**18** in moderate yields (24−64% yield) and enantioselectivity (66−82% ee). Interestingly, when isopropylbenzene was used as a substrate which does not feature a 1,4-substitution pattern, we
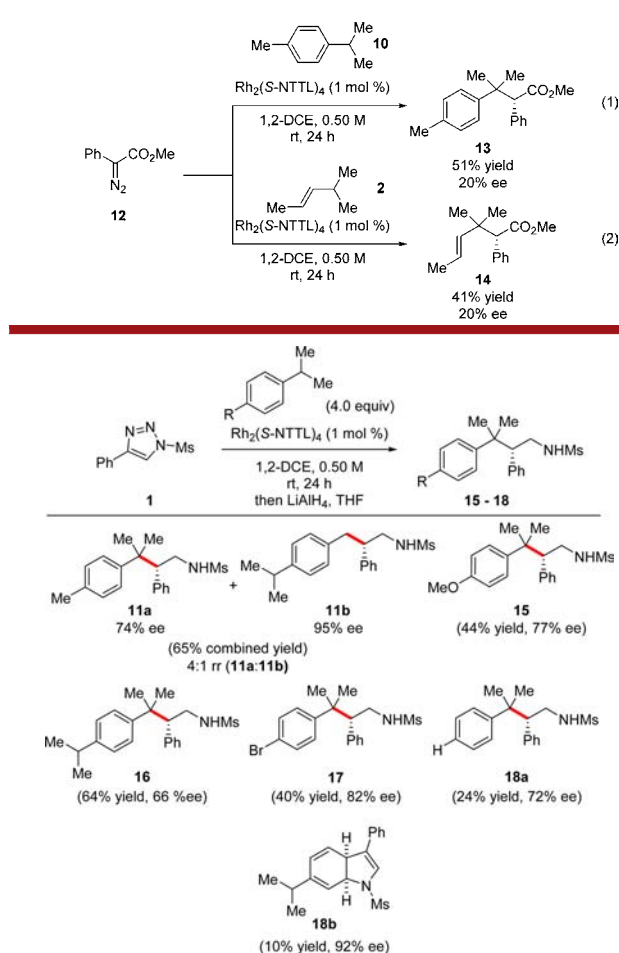
Table 3. Optimization for Benzylic C—H Functionalization Reaction[a]

entry	solvent	catalyst	time (h)	3º:1º insertion	combined yield (%)	% ee (of 11a)
1	CHCl$_3$	Rh$_2$(*S*-NTTL)$_4$	24	79:21	75	68
2	1,2-DCE	Rh$_2$(*S*-NTTL)$_4$	24	80:20	65	74
3	1,2-DCE	Rh$_2$(*S*-NTTL)$_4$	3	80:20	54	77
4	1,2-DCE	Rh$_2$(*S*-PTAD)$_4$	24	64:36	16	70
5	1,2-DCE	Rh$_2$(*S*-TCPTAD)$_4$	24	67:33	13	50
6	1,2-DCE	Rh$_2$(*S*-PTTL)$_4$	24	71:29	28	65
7	1,2-DCE	Rh$_2$(*S*-NTV)$_4$	18	83:17	64	62

[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.

Figure 1. Substrate scope for benzylic C—H functionalization reaction.

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**[16]

Encouraged by the high levels of enantioselectivity obtained for primary C—H insertion products **9** and **11b** (95−96% 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 LiAlH$_4$ reduction (Scheme 2). 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 enantioinduction with Rh$_2$(*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 sp^3 C—H bonds using donor−acceptor carbenes generated from 4-phenyl-*N*-sulfonyl-1,2,3-triazoles. These reactions show modest selectivity for tertiary C—

Scheme 2. Reaction of Triazole 1 with 4-Methylanisole

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.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01298.

> Full experimental data for the compounds described in the paper (PDF)
> X-ray crystallographic data for compound 3a (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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