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De Novo Synthesis of Troc-Protected Amines: Intermolecular Rhodium-Catalyzed C–H Amination with *N*-Tosyloxycarbamates

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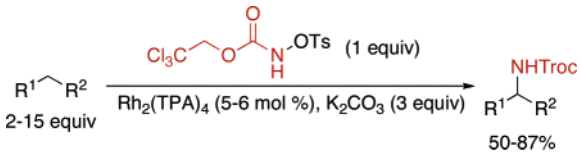
ABSTRACT



The rhodium-catalyzed intermolecular C–H insertion of the nitrene derived from 2,2,2-trichloroethyl-*N*-tosyloxycarbamate proceeded in good to excellent yields to produce a variety of Troc-protected amines. With cyclic aliphatic alkanes, it is possible to use only 2 equiv of substrate, whereas the reaction with aromatic alkanes is run neat. Not only does the nitrene insertion proceed in benzylic, secondary, and tertiary C–H bonds but also primary C–H insertion products were obtained in good yields. Finally, the use of chiral rhodium catalysts to provide an enantioselective version of this process is discussed.

Synthetic methods to access amines are of primary importance due to the major role of nitrogen-containing molecules in the pharmaceutical industries. Recent advances have led to the development of various processes to produce amines,[1] including the hydrogenation of enamides,[2] the reductive amination of carbonyl compounds,[3] and the addition of organometallic reagents to imines.[4] Among them, very efficient catalytic enantioselective versions have been reported leading to α-chiral amines.[2−4] In contrast to the previous processes based on functional group transformations, the C−H amination reactions[5] allow the direct transformation of a C−H bond into a C−N bond. Hypervalent oxidative iodine reagents[6] are typically used in transition-metal-catalyzed C−H insertion reactions of nitrene species. Whereas a number of intramolecular C−H aminations have been reported,[7] only a few intermolecular processes have been developed[8] and examples of highly enantioselective reactions are even more limited.[9] We have

(1) Review: Salvatore, R. N.; Yoon, C. H.; Jung, K. W. *Tetrahedron* **2001**, *57*, 7785−7811.

(2) (a) Hsiao, Y.; Rivera, N. R.; Rosner, T.; Krska, S. W.; Njolito, E.; Wang, F.; Sun, Y. K.; Armstrong, J. D.; Grabowski, E. J. J.; Tillyer, R. D.; Spindler, F.; Malan, C. *J. Am. Chem. Soc.* **2004**, *126*, 9918−9919. (b) Bunlaksananusorn, T.; Rampf, F. *Synlett* **2005**, 2682−2684. (c) Dai, Q.; Yang, W. R.; Zhang, X. M. *Org. Lett.* **2005**, *7*, 5343−5345. (d) Clausen, A. M.; Dziadul, B.; Cappuccio, K. L.; Kaba, M.; Starbuck, C.; Hsiao, Y.; Dowling, T. M. *Org. Process Res. Dev.* **2006**, *10*, 723−726. (e) Kubryk, M.; Hansen, K. B. *Tetrahedron: Asymmetry* **2006**, *17*, 205−209.

(3) Nugent, T. C.; Ghosh, A. K.; Wakchaure, V. N.; Mohanty, R. R. *Adv. Synth. Catal.* **2006**, *348*, 1289−1299 and references therein.

(4) Reviews: (a) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984−995. (b) Groger, H. *Chem. Rev.* **2003**, *103*, 2795−2827. (c) Cordova, A. *Acc. Chem. Res.* **2004**, *37*, 102−112. (d) Ding, H.; Friestad, G. K. *Synthesis* **2005**, 2815−2829. (e) Vilaivan, T.; Bhanthumnavin, W.; Sritana-Anant, Y. *Curr. Org. Chem.* **2005**, *9*, 1315−1392.

(5) Reviews: (a) Muller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905−2919. (b) Dauban, P.; Dodd, R. H. *Synlett* **2003**, 1571−1586. (c) Halfen, J. A. *Curr. Org. Chem.* **2005**, *9*, 657−669. (d) Davies, H. M. L.; Long, M. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 3518−3520. (e) Du Bois, J. *Chemtracts* **2005**, *18*, 1−13.

(6) Wirth, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3656−3665.

(7) Recent examples: (a) Espino, C. G.; Du Bois, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 598−600. (b) Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935−6936. (c) Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378−15379. (d) Cui, Y.; He, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 4210−4212. (e) Fiori, K. W.; Fleming, J. J.; Du Bois, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 4349−4352. (f) Kim, M.; Mulcahy, J. V.; Espino, C. G.; Du Bois, J. *Org. Lett.* **2006**, *8*, 1073−1076.

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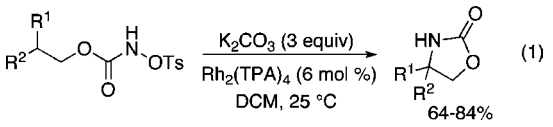
recently reported a rhodium-catalyzed intramolecular C−H insertion using *N*-tosyloxycarbamates, the first alternative method that does not require the use of hypervalent oxidative iodine reagents.[10] In this communication, we now present the first *intermolecular* rhodium-catalyzed C−H amination of 2,2,2-trichloroethyl-*N*-tosyloxycarbamate to produce amines in high yields. Furthermore, chiral rhodium catalysts were evaluated for the preparation of α-chiral amines.

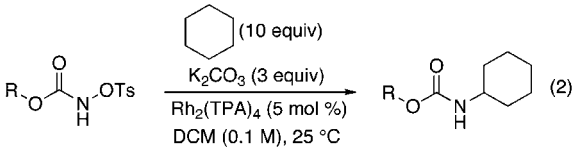
Our recent publication showed that a variety of oxazolidinones could be synthesized from *N*-tosyloxycarbamates in the presence of potassium carbonate and a rhodium(II) triphenylacetate dimer as the catalyst, via an intramolecular C−H insertion reaction (eq 1).[10]



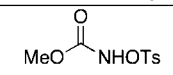
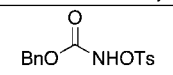
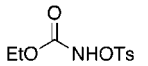
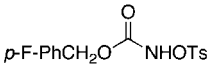
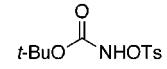
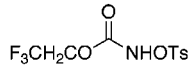
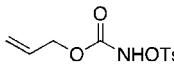
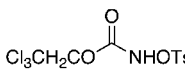
(1)

Intermolecular nitrene insertion processes are more challenging due to the propensity of the metal nitrene species to readily decompose.[11] Furthermore, competition between intermolecular and intramolecular reactions must be avoided, and thus an intermolecular reaction also requires a *N*-tosyloxycarbamate reagent with no (or less) reactive C−H bonds that could compete via an intramolecular pathway. We prepared a number of *N*-tosyloxycarbamate derivatives[12] to be tested as reagents in the intermolecular C−H insertion of cyclohexane (Table 1). Initially, we used 10 equiv of cyclohexane and the same reaction conditions developed for the intramolecular process. Both methyl- and ethyl-*N*-tosyloxycarbamates were found to be quite unstable under the reaction conditions and readily decomposed (entries 1 and 2). Primary C−H bonds of the *tert*-butyl-*N*-tosyloxycarbamate were reactive enough to lead to the formation of the corresponding oxazolidinone in 41% yield (entry 3). Allyl- and benzyl-*N*-tosyloxycarbamates, in which the reactive C−H bond is replaced by an alkene or a phenyl group, led to a mixture of products (entries 4−6). Conversely,

Table 1. Intermolecular Rhodium-Catalyzed C−H Amination using Various *N*-Tosyloxycarbamates (Equation 2)



(2)

entry	substrate	yield (%)[a]	entry	substrate	yield (%)[a]
1		≤5	5		≤5
2		≤5	6		10
3		≤5[b]	7		30
4		≤5	8		71

[a] Isolated yields. [b]Intramolecular insertion product isolated in 41% yield.

replacing the reactive C−H bond by a carbon−halogen bond, such as in 2,2,2-trifluoroethyl- or 2,2,2-trichloroethyl-*N*-tosyloxycarbamate, proved to be successful (entries 7 and 8). The 2,2,2-trifluoroethyl-*N*-tosyloxycarbamate is prone to readily decompose and led mostly to the corresponding carbamate ($CF_3CH_2OC(O)NH_2$). This is probably due to the strong electronegativity of the fluorine atom. Using the 2,2,2-trichloroethyl-*N*-tosyloxycarbamate, which contained less electronegative chlorine atoms, led to higher yields, and the desired Troc-carbamate product was obtained in 71% yield (entry 8). Generating amines containing a Troc protecting group is very convenient, as it can be readily and selectively removed using mild reaction conditions.[13]

We have optimized the reaction conditions for the intermolecular C−H insertion of 2,2,2-trichloroethyl-*N*-tosyloxycarbamate with cyclohexane and Indane using various catalysts and solvents (see Supporting Information for details). We found that a higher concentration helps the desired intermolecular reaction. Furthermore, for aliphatic alkanes, a more polar and aprotic solvent such as tetrachloroethane led to a better yield for the C−H insertion product. Indeed, when using 10 equiv of cyclohexane, 92% yield of the desired amine was obtained (Table 2, entry 1). Decreasing the number of equivalents of cyclohexane to 5 and 2 provided the protected cyclohexylamine in 85% and 73% yield, respectively. Similar yields were obtained with cyclooctane (entry 2). For substrates containing different C−H bonds, moderate yields were obtained, due to a lack of selectivity (entries 3−5). For instance, adamantane furnished a 3:1 ratio of tertiary C−H vs secondary C−H insertion products using the standard reaction conditions with $Rh_2(TPA)_4$. Other achiral catalysts such as $Rh_2(OAc)_4$ or $Rh_2(oct)_4$ led to a better selectivity but with low reactivity.[14] Conversely, chiral catalyst $Rh_2[(S)\text{-NTTL}]_4$[9e] showed good selectivity and

(8) Recent example: (a) Albone, D. P.; Challenger, S.; Derrick, A. M.; Fillery, S. M.; Irwin, J. L.; Parsons, C. M.; Takada, H.; Taylor, P. C.; Wilson, D. J. *Org. Biomol. Chem.* **2005**, *3*, 107−111. (b) Fructos, M. R.; Trofimenko, S.; Diaz-Requejo, M. M.; Perez, P. J. *J. Am. Chem. Soc.* **2006**, *128*, 11784−11791. (c) Fiori, K. W.; DuBois, J. J. *J. Am. Chem. Soc.* **2007**, *129*, 562−568.

(9) (a) Kohmura, Y.; Katsuki, T. *Tetrahedron Lett.* **2001**, *42*, 3339−3342. (b) Yamawaki, M.; Tsutsui, H.; Kitagaki, S.; Anada, M.; Hashimoto, S. *Tetrahedron Lett.* **2002**, *43*, 9561−9564. (c) Liang, J. L.; Yuan, S. X.; Huang, J. S.; Yu, W. Y.; Che, C. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3465−3468. (d) Liang, J. L.; Huang, J. S.; Yu, X. Q.; Zhu, N. Y.; Che, C. M. *Chem.−Eur. J.* **2002**, *8*, 1563−1572. (e) Liang, C. G.; Robert-Pedlard, F.; Fruit, C.; Muller, P.; Dodd, R. H.; Dauban, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 4641−4644. (f) Reddy, P. R.; Davies, H. M. L. *Org. Lett.* **2006**, *8*, 5013−5016.

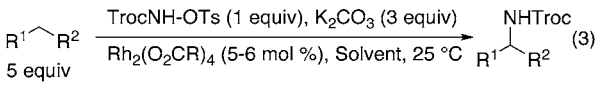
(10) (a) Lebel, H.; Huard, K.; Lectard, S. *J. Am. Chem. Soc.* **2005**, *127*, 14198−14199. (b) Lebel, H.; Leogane, O.; Huard, K.; Lectard, S. *Pure Appl. Chem.* **2006**, *78*, 363−375.

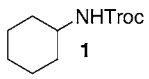
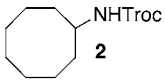
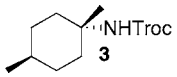
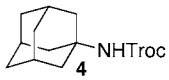
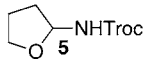
(11) In spite of that, others have established the feasibility of performing such a reaction even with a single equivalent of starting material: see ref 8 and 9 for details.

(12) These *N*-tosyloxycarbamate reagents have been chosen, as neither contained reactive C−H bonds (entries 1 and 5−8) that could compete via an intramolecular pathway. Furthermore, substrates containing primary C−H bonds or terminal alkenes (which are typically less reactive) were also tested (entries 2−4).

(13) Mineno, T.; Choi, S. R.; Avery, M. A. *Synlett* **2002**, 883−886.

Table 2. Rhodium-Catalyzed Intermolecular C−H Insertion with Aliphatic Alkanes (Equation 3)



entry	product	$Rh_2(TPA)_4$[a,b]	$Rh_2[(S)\text{-NTTL}]_4$[a,c]
1	 **1**	92%[d] 85% 73%[e]	80%
2	 **2**	86%[f] 81% 62%[e]	74%
3	 **3**	45% (2:1)[g]	64% (9:1)[g]
4	 **4**	39% (3:1)[g]	58% (12:1)[g] 70%[f] (14:1)[g]
5	 **5**	68%	84%

[a] Isolated yield. [b]6 mol % of TCE (0.5 M). [c]5 mol % of DCM (0.5 M). [d]10 equiv of substrate. [e]2 equiv of substrate. [f]10 equiv of substrate in DCM (0.1 M). [g]Ratio of tertiary C−H insertion vs secondary C−H insertion.

reactivity, thus the desired tertiary and secondary amines were obtained in good yields (58−84%) using 5 equiv of starting material (Figure 1).

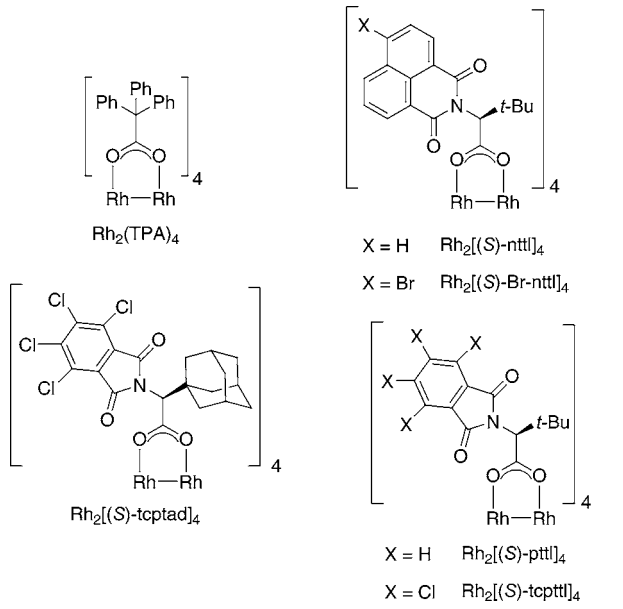
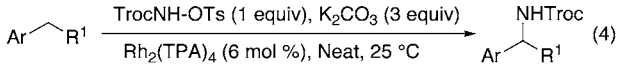
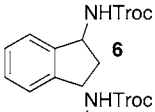
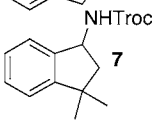
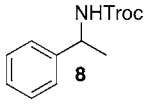
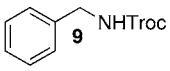
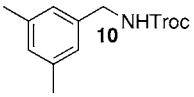


Figure 1. Chiral rhodium complexes.

With aromatic alkanes, it was possible to run the reaction without solvent, as both 2,2,2-trichloroethyl-*N*-tosyloxycarbamate and the rhodium catalyst were soluble enough to perform the reaction (Table 3). Using 5 equiv of substrate,

Table 3. Rhodium-Catalyzed Intermolecular C−H Insertion with Aromatic Alkanes (Equation 4)



entry	product	5 equiv[a]	15 equiv[a]
1	 **6**	68%	75%
2	 **7**	78%	87%
3	 **8**	61%	71%
4	 **9**	35% 42%[b]	50%
5	 **10**	52% 65%[b]	67%

[a] Isolated yield. [b]$Rh_2[(S)\text{-NTTL}]_4$ (5 mol %) as catalyst in DCM (0.5 M).

61−78% yields were obtained for benzylic secondary C−H insertion products (entries 1−3). Primary C−H insertion was also possible using toluene or mesitylene as substrate. Better yields could be obtained by using 15 equiv of substrate or $Rh_2[(S)\text{-NTTL}]_4$ as catalysts (entries 4 and 5).

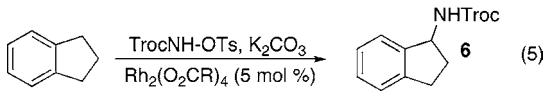
We have also examined the enantioselectivity of the reaction using various chiral dirhodium tetracarboxylate catalysts, particularly, the one derived from *tert*-leucine.[12] The best results were achieved using $Rh_2[(S)\text{-NTTL}]_4$,[9e] and product **6** was isolated in 56% and 2.57:1 er (eq 4, Table 4).[15] In contrast to previous results reported with preformed or in situ generated sulfonyliminophenyliodinane,[9b,f] catalysts derived from tetrachlorophtaloyl led to lower enantioselectivity. This clearly illustrates that the decomposition of tosyloxycarbamates to a nitrene metal species may involve a different pathway, and further experiments will have to be performed to explain these intriguing results. Furthermore, these results also suggest that a new catalyst design will be necessary to achieve high enantioselectivities.[16]

In conclusion, we have devised the first tosyloxycarbamate reagent to perform *intermolecular* C−H insertion reactions.

(14) For instance, C−H insertion into adamantane with 5 mol % of $Rh_2(OAc)_4$ led to 27% of the desired amine **4** with a ratio of tertiary C−H insertion vs secondary C−H insertion, of 21:1, whereas 5 mol % of $Rh_2(Oct)_4$ gave 42% yield of amine **4** with a 15:1 ratio.

(15) The enantiomeric ratio was measured on the crude material. A purification procedure cannot be used as an argument to explain the enantiomeric enrichment, thus the chiral catalyst must be involved to account for the observed enantioselectivity.

Table 4. Rhodium-Catalyzed Intermolecular Enantioselective C−H Insertion with Indane (Equation 5)



entry	$Rh_2(O_2CR)_4$	temp	er[a]
1	Rh_2[(*S*)-PPTL]$_4$	25 °C	1.83:1
2	Rh_2[(*S*)-TCPTTL]$_4$	25 °C	1.78:1
3	Rh_2[(*S*)-NTTL]$_4$	25 °C	2.08:1
4	**Rh_2[(*S*)-NTTL]$_4$**	**−20 °C**	**2.57:1 (56% yield)**
5	Rh_2[(*S*)-Br-NTTL]$_4$	25 °C	1.95:1
6	Rh_2[(*S*)-TCPTAD]$_4$	25 °C	1.67:1

[a] Determined by HPLC using a Chiralcel OD column.

This very practical rhodium-catalyzed process does not require the use of hypervalent iodine reagents and led to the desired amine products with good yields. With cyclic aliphatic alkanes, it is possible to use only 2 equiv of substrate. Furthermore, this process is one of the rare examples which provides primary C−H insertion products in decent yields. Studies are currently underway to develop novel reagents and chiral catalysts to reach high enantioselectivities.

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Supporting Information Available: Experimental procedures, compound characterization data, and ^{1}H spectra of all the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) We do not think that the low er's are due to a background reaction, as under our reaction conditions in the absence of the rhodium catalyst *N*-tosyloxycarbamates only decomposed to lead to the corresponding carbamate $ROC(O)NH_2$.