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N-Tosyloxycarbamates as Reagents in Rhodium-Catalyzed C–H Amination Reactions

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Abstract: Metal nitrenes for use in C–H insertion reactions were obtained from *N*-tosyloxycarbamates in the presence of an inorganic base and a rhodium(II) dimer complex catalyst. The C–H amination reaction proceeds smoothly, and the potassium tosylate that forms as a byproduct is easily removed by filtration or an aqueous workup. This new methodology allows the amination of ethereal, benzylic, tertiary, secondary, and even primary C–H bonds. The intramolecular reaction provides an interesting route to various substituted oxazolidinones, whereas the intermolecular reaction gives trichloroethoxycarbonyl-protected amines that can be isolated with moderate to excellent yields and that cleave easily to produce the corresponding free amine. The development, scope, and limitations of the reactions are discussed herein. Isotopic effects and the electronic nature of the transition state are used to discuss the mechanism of the reaction.

Keywords: amination · carbamates · catalysis · insertion · rhodium

Introduction

Because the amine functionality is abundant in natural products and plays a key role in many biologically active compounds, the formation of C–N bonds is of great importance in organic synthesis. The progress that has been made in the area of metal-catalyzed transformations[1] has led to the development of new catalytic methods, such as reductive amination of carbonyl compounds,[2] hydrogenation of enamides,[3] hydroamination of olefins,[4] or C–N coupling.[5] These new methods allow the efficient formation of amines through functional-group manipulation. The direct and selective introduction of a nitrogen atom into a C–H bond is an alternative approach and an attractive method because the introduction of another functional group is not required prior to amine formation. Recent investigations into the catalytic amination reaction have led to the discovery of new and efficient nitrene-transfer processes.[6] In recent amination methods, the nitrene precursors were azides,[7] haloamines[8] or, most frequently, iminoiodinanes (PhI=NR).[9] The use of hypervalent iodine reagents, such as (diacetoxyiodo)benzene for the oxidation of carbamates and sulfamates, has considerably simplified the use of iminoiodinanes[10] and led to practical and efficient processes. However, the generation of a stoichiometric amount of iodobenzene is still a major drawback associated with the use of hypervalent iodine reagents. Amination reactions have been developed by using various metal complexes, such as Co,[7b,c] Ru,[7a] Cu,[8,9f,l,s] Au,[9p] Ag,[9i,q] and Pd[9m] to catalyze nitrene insertion, but rhodium dimers remain the most employed complexes.[9a–c,g,h,j,k,n,o,r,t] With all these methods in hand, intramolecular C–H insertion is now an established reaction that is used in total synthesis to form β- or γ-amino alcohols.[11,12] However, the intermolecular reaction has so far been limited to the use of sulfamate or sulfonimidamide derivatives, and in some cases restricted to benzylic and ethereal positions.

Our interest in the activation of nitrogen-containing compounds has prompted us to study new sources of nitrene precursors for the metal-catalyzed C–H bond-insertion reaction, which would be more suitable for industrial applications. *N*-Arylsulfonyloxycarbamates ($ArSO_3NHCO_2R$) are stable,[13] easy-to-handle, crystalline compounds, which are obtained from commercially available alcohols in two steps. Recently, they have been used in osmium-catalyzed aminohydroxylation reactions[14] and in copper-catalyzed[15] and uncatalyzed[16] aziridination reactions. Similar compounds have also been used for the generation of free nitrenes by

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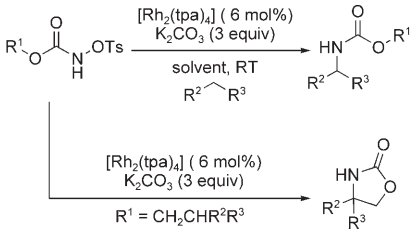
deprotonation and α-elimination, but unselective reactions were often observed.[17] We have recently shown that metal nitrenes formed by the decomposition of *N*-tosyloxycarbamates ($TsONHCO_2R$) under basic conditions in the presence of a rhodium dimer complex can be used for C–H insertion reactions (Scheme 1).[18] Both the intra- and intermolecular insertion reactions proceed smoothly under mild reaction conditions at room temperature to give substituted oxazolidinones and Troc-protected amines (Troc = trichloroethoxycarbonyl), respectively, in moderate to excellent yields. Herein, we report the scope and limitations of this new method, and also the functional-group tolerance. Insights about the mechanism of rhodium-catalyzed C–H amination reactions with *N*-tosyloxycarbamates are also discussed.

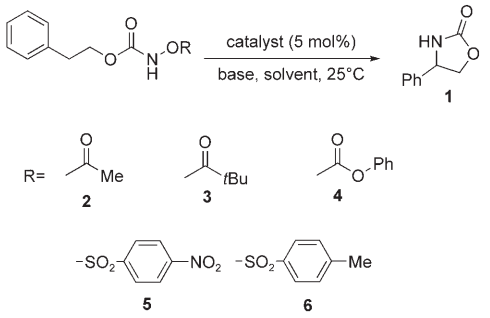


Scheme 1. Rhodium-catalyzed inter- and intramolecular C–H amination with *N*-tosyloxycarbamates.

Results and Discussion

Development and optimization: Carbamates are attractive starting materials for the development of a rhodium-catalyzed C–H amination reaction for many reasons. Not only they are readily available and easy to prepare, but they also lead to carbamate-protected amination products, which are very convenient synthetic intermediates. Moreover, in contrast with metal nitrenes obtained from aliphatic or amide derivatives, carbamate-derived metal nitrenes do not undergo rearrangements.[19] We envisioned the deprotonation of *N*-substituted carbamates in the presence of a metal complex as a new approach to access metal–nitrene species. A number of *N*-alkoxycarbamates were tested in the presence of various bases and rhodium(II) dimer complexes (Table 1). By using optimal reaction conditions (potassium carbonate and rhodium(II) triphenylacetate dimer complex ($[Rh_2(tpa)_4]$) in dichloroethane, see below), we observed that carbamates that had acetate (**2**), pivaloate (**3**), or phenylcarbonate (**4**) as the leaving group were remarkably stable (Table 1, entries 1–3), and the starting material was recovered unchanged. Conversely, starting materials that had an *N*-arylsulfonyloxy group were found to be more reactive. For *N*-nosyloxycarbamate **5**, 15% conversion to the desired oxazolidinone **1** was observed, together with the formation of other products that included the carbamate $PhCH_2CH_2OC(O)NH_2$,[9b] which is typical of a free nitrene pathway (Table 1, entry 4).[17] By using the less electron-withdrawing *N*-tosyloxycarbamate **6**, we observed the exclusive formation of oxazolidinone **1** in the presence of potassium carbonate and $[Rh_2(tpa)_4]$ (Table 1, entry 5). Both dichloroethane (DCE) and dichloromethane (CH_2Cl_2) were convenient solvents for these reactions, as was benzene (Table 1, entries 5–7). Other rhodium dimer complexes were tested with *N*-tosyloxycarbamate **6**, but the yield for the formation of oxazolidinone **1** was lower (Table 1, entries 8 and 9) or no conversion was observed (Table 1, entries 10 and 11). The more hindered and soluble $[Rh_2(tpa)_4]$ was the most effective complex. This rhodium dimer is readily prepared by treating $Rh_2(OAc)_4$ with triphenylacetic acid in PhCl under reflux.[9b,20] We do not believe that an exchange of ligands on the rhodium atom occurred during the C–H amination reaction because the tosylate byproduct produced is only slightly soluble and is not very nucleophilic. This is in sharp contrast with C–H amination methods that use simple carbamates and stoichiometric amounts of diacetoxyiodobenzene[9] and produce acetate that makes ligand exchange and the formation of $Rh_2(OAc)_4$ possible. In the presence of soluble organic bases, such as pyridine or triethylamine, decomposition of the starting material was observed, which suggested that formation of the free nitrene had occurred

Table 1. Rhodium-catalyzed intramolecular C–H insertion reactions with *N*-alkoxycarbamates **2–6.**[a]



Entry	R	Catalyst	Base	Solvent	Conv.[b] [%]
1	**2**	$[Rh_2(tpa)_4]$	K_2CO_3	DCE	≤5
2	**3**	$[Rh_2(tpa)_4]$	K_2CO_3	DCE	≤5
3	**4**	$[Rh_2(tpa)_4]$	K_2CO_3	DCE	≤5
4	**5**	$[Rh_2(tpa)_4]$	K_2CO_3	DCE	15
5	**6**	$[Rh_2(tpa)_4]$	K_2CO_3	DCE	≥98
6	**6**	$[Rh_2(tpa)_4]$	K_2CO_3	benzene	95
7	**6**	$[Rh_2(tpa)_4]$	K_2CO_3	CH_2Cl_2	≥98
8	**6**	$[Rh_2(OAc)_4]$	K_2CO_3	CH_2Cl_2	70
9	**6**	$[Rh_2(oct)_4]$	K_2CO_3	CH_2Cl_2	60
10	**6**	$[Rh_2(O_2CC_3F_7)_4]$	K_2CO_3	CH_2Cl_2	≤5
11	**6**	$[Rh_2(tfa)_4]$	K_2CO_3	CH_2Cl_2	≤5
12	**6**	$[Rh_2(tpa)_4]$	pyridine	CH_2Cl_2	≤5
13	**6**	$[Rh_2(tpa)_4]$	Et_3N	CH_2Cl_2	≤5
14	**6**	$[Rh_2(tpa)_4]$	MgO	CH_2Cl_2	18
15	**6**	$[Rh_2(tpa)_4]$	$NaHCO_3$	CH_2Cl_2	17
16	**6**	$[Rh_2(tpa)_4]$	Na_2CO_3	CH_2Cl_2	15
17	**6**	$[Rh_2(tpa)_4]$	$CaCO_3$	CH_2Cl_2	11
18	**6**	$[Rh_2(tpa)_4]$	$BaCO_3$	CH_2Cl_2	14
19	**6**	$[Rh_2(tpa)_4]$	Cs_2CO_3	CH_2Cl_2	≥98

[a] All reactions were run in the indicated solvent (0.1 M) at 25 °C for 6–12 h with base (1 equiv). [b] Conversion detected by GC–MS.

(Table 1, entries 12 and 13). Furthermore, the magnesium oxide and sodium, calcium, and barium carbonate bases did not appear to be strong or soluble enough to generate the metal–nitrene species, and most of the starting material was recovered (Table 1, entries 14–18). Only the more expensive cesium carbonate could be used to produce the desired oxazolidinone in high yields (Table 1, entry 19). From these results, we concluded that combining *N*-tosyloxycarbamates with $[Rh_2(tpa)_4]$ and potassium carbonate gave the optimal conditions for performing intramolecular C–H amination reactions because it avoided formation of the free nitrene responsible for the nonselective reaction pathway (see below for mechanistic considerations).

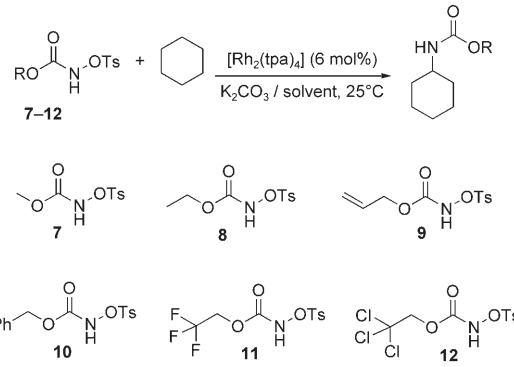
The optimization of the reaction conditions was achieved on a 0.5 mmol scale by addition of a mixture of base and catalyst to a solution of *N*-tosyloxycarbamate in the requisite solvent. Anhydrous conditions were not required, so wet solvent and nondried vessels were used. When we scaled up the reaction to more than 1 mmol, we discovered that not only were anhydrous reaction conditions not necessary, but that the addition of water was indeed required. Furthermore, we observed that the reaction became very exothermic when the base and the catalyst were added. To overcome these problems, we changed the order of addition; thus either a solution of *N*-tosyloxycarbamate in CH_2Cl_2 was slowly added to a mixture of base and catalyst in CH_2Cl_2/water (8:1), or a solution of base in water was slowly added to a mixture of *N*-tosyloxycarbamate and catalyst in CH_2Cl_2. When performing the intramolecular C–H amination on a 50 mmol scale, it was also possible to decrease the catalyst loading to 1 mol%.[20]

We also tested various *N*-tosyloxycarbamates to develop the first rhodium-catalyzed intermolecular C–H amination reaction with this reagent (Table 2). The challenge was to find a reagent that would not react intramolecularly and that contained less reactive or no active C–H bonds.

Starting materials that contained simple alkyl chains, such as methyl or ethyl groups, were found to be quite unstable, and readily decomposed under typical reaction conditions with cyclohexane (10 equiv; Table 2, entries 1 and 2). Allyl- and benzyl-*N*-tosyloxycarbamates led to a mixture of products, whereas reagents that contained halogen-substituted alkyl chains showed good reactivity (Table 2, entries 3–6). The optimal result was obtained with 2,2,2-trichloroethyl *N*-tosyloxycarbamate (**12**), which led to Troc-protected cyclohexylamine **25** in 80% yield when the reaction was run in CH_2Cl_2 with cyclohexane (5 equiv; Table 2, entry 6).[21] Further optimization led to 85% yield of the desired product by starting from cyclohexane (5 equiv) in tetrachloroethane (TCE) (entry 8).[9k,t]

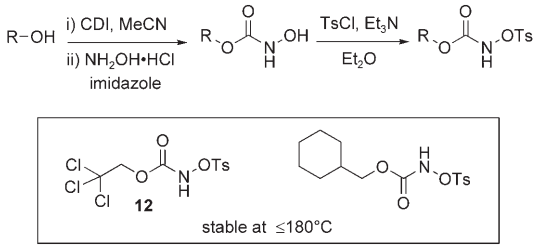
The purification of both oxazolidinone and Troc–amine products was very simple because potassium tosylate, the only stoichiometric byproduct formed, was simply removed by filtration or an aqueous workup. Furthermore, *N*-tosyloxycarbamates were easily prepared in two steps from commercially available alcohols and were all crystalline compounds (Scheme 2). Thermogravimetric analysis (TGA) experiments were run with **12** and cyclohexylmethyl tosyloxycarbamate, and both proved to be stable up to 180°C.

Table 2. Rhodium-catalyzed intermolecular C–H insertion reactions with *N*-tosyloxycarbamates **7**–**12**.[a]



Entry	Starting material	Solvent	Cyclohexane [equiv]	Yield[b] [%]
1	**7**	CH_2Cl_2	10	≤5
2	**8**	CH_2Cl_2	10	≤5
3	**9**	CH_2Cl_2	10	≤5
4	**10**	CH_2Cl_2	10	≤5
5	**11**	CH_2Cl_2	10	30
6	**12**	CH_2Cl_2	5	80
7	**12**	TCE	10	92
8	**12**	TCE	5	85
9	**12**	PhCl	5	74

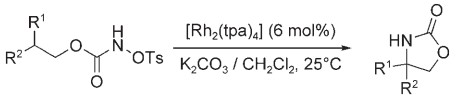
[a] All reactions were run in the indicated solvent (0.5 M) at 25°C for 16 h with K_2CO_3 (3 equiv). [b] Isolated yields.

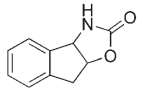
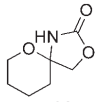
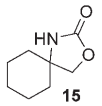
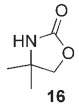
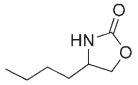


Scheme 2. Synthesis and thermal stability of *N*-tosyloxycarbamates.

Scope of the reaction: A variety of substituted oxazolidinones were prepared from *N*-tosyloxycarbamates by C–H amination reactions and isolated in yields of 41–92% (Table 3). C–H bond insertion is effective at benzylic positions (Table 3, entries 1 and 2) and ethereal positions (Table 3, entry 3). The amination also proceeded very well with tertiary C–H bonds (Table 3, entries 4 and 5). Furthermore, the oxazolidinones that resulted from the insertion of the nitrene into a deactivated secondary or primary C–H bond were isolated in yields of 64% and 41%, respectively (Table 3, entries 6 and 7). This is quite spectacular because it is one of the first examples of such a reaction taking place at a primary non-benzylic position, which clearly illustrates the power of this method. The formation of the C–N bond is also stereospecific because the reaction of a chiral, enantioenriched *N*-tosyloxycarbamate occurred with complete

Table 3. Synthesis of oxazolidinones from *N*-tosyloxycarbamates.[a]

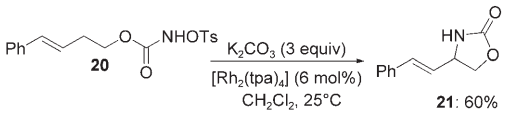


Entry	Product	Yield[b] [%]
1	 **1**	92
2	 **13**	84
3	 **14**	87
4	 **15**	84
5	 **16**	71
6	 **17**	64
7	 **18**	41
8	 **19**	73[c]

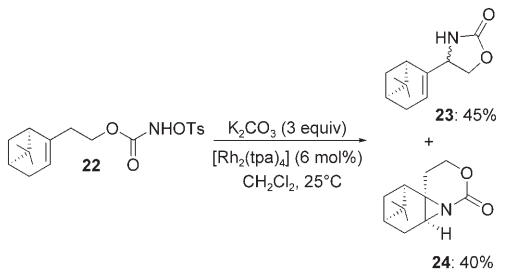
[a] All reactions were run in CH_2Cl_2 (0.1 M) at 25 °C for 6 h with K_2CO_3 (3 equiv). [b] Isolated yields. [c] ≥98% enantiomeric excess of the enantiomer shown.

retention of configuration and led to the corresponding oxazolidinone **19** without racemization (Table 3, entry 8).

We also tested this reaction with *N*-tosyloxycarbamates derived from homoallylic alcohols that could lead, in theory, to both insertion and aziridination products.[22] In the case of *N*-tosyloxycarbamate **20**, only oxazolidinone **21** was isolated, in 60% yield and with no trace of the aziridination product [Eq. (1)]. However, both the insertion and aziridination products were isolated in similar yields from the homoallylic *N*-tosyloxycarbamate **22**, which contains a more electron-rich double bond [Eq. (2)]. These two examples illustrate that the nucleophilic character of the double bond dictates the chemoselectivity of the reaction. Furthermore, oxazolidinone **23** was produced as a 1:1 mixture, whereas aziridine **24** was isolated as a single diastereomer.



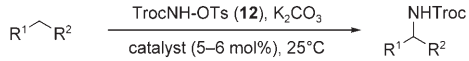
(1)

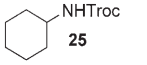
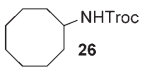
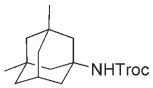
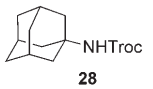
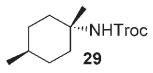
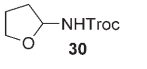


(2)

The rhodium-catalyzed intermolecular reaction with **12** and aliphatic alkanes was tested by using $[Rh_2(tpa)_4]$ in TCE, and also by using the chiral catalyst $[Rh_2\{(S)\text{-nttl}\}_4]$[23,9g] (nttl = *N*-1,8-napthoyl-*tert*-leucinate) in CH_2Cl_2 (Table 4). Troc-protected cyclohexylamine and cyclooctylamine were isolated in excellent yields when the corresponding alkane (5 equiv) and $[Rh_2(tpa)_4]$ were used (Table 4, entries 1 and 2). The isolated yield was influenced by the stoichiometry of the starting material, and higher yields were obtained if ten equivalents of substrate were used. It was also possible to use two equivalents of substrate, although this was to the detriment of the product yield. A good yield

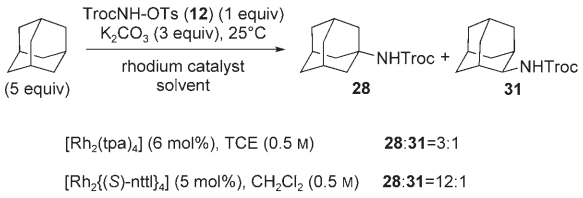
Table 4. Rhodium-catalyzed intermolecular C–H insertion reactions with aliphatic alkanes.



Entry	Product	Isolated yield [%] $[Rh_2(tpa)_4]$[a]	Isolated yield [%] $[Rh_2\{(S)\text{-nttl}\}_4]$[b]
1	 **25**	73[c]/85/92[d]	80
2	 **26**	62[c]/81/86[d]	74
3	 **27**	63	51
4	 **28**	39	58/70[d]
5	 **29**	45	64
6	 **30**	68	83

[a] Unless otherwise specified, all reactions were run with 6 mol% of $[Rh_2(tpa)_4]$ (0.5 M) in TCE at 25 °C for 16 h with alkane (5 equiv), reagent **12** (1 equiv), and of K_2CO_3 (3 equiv). [b] Unless otherwise specified, all reactions were run with 5 mol% of $[Rh_2\{(S)\text{-nttl}\}_4]$ (0.5 M) in CH_2Cl_2 at 25 °C for 16 h with alkane (5 equiv), reagent **12** (1 equiv), and K_2CO_3 (3 equiv). [c] Two equivalents of alkane. [d] Ten equivalents of alkane.

was also obtained for the synthesis of Troc-protected dimethyladamantanamine **27**, a product derived from a substrate that contained both secondary and tertiary C–H bonds (Table 4, entry 3). In all these cases, no advantage was observed when the chiral catalyst $[Rh_2\{(S)\text{-nttl}\}_4]$ was used (Table 4, entries 1–3). However, this catalyst showed better chemoselectivity with other, less reactive, substrates that contained nonequivalent C–H bonds. The reaction with adamantane and a $[Rh_2(tpa)_4]$ catalyst led to a mixture of Troc-protected 1-adamantanamine **28** and 2-adamantanamine **31**, which were isolated in yields of 39% and 14%, respectively (Scheme 3). Conversely, $[Rh_2\{(S)\text{-nttl}\}_4]$ led to a 12:1 ratio of



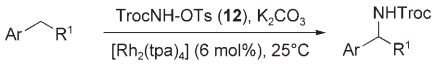
Scheme 3. Chemoselective C–H amination.

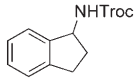
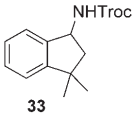
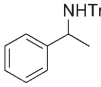
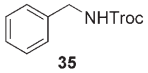
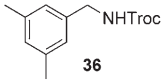
tertiary and secondary C–H bond insertions and gave the desired 1-adamantanamine **28** in 58% yield (Table 4, entry 4). Similar results were observed for the synthesis of Troc-protected amine **29** and **30** (Table 4, entries 5 and 6).

Benzylic amines were also prepared by using a similar approach with **12** (Table 5). We found that no solvent was required because the reagents and $[Rh_2(tpa)_4]$ were soluble enough in the substrate, so the reactions were run neat. The best results were obtained by using 15 equivalents of the aromatic substrate, but benzylic amines could also be isolated in good yields by using only five equivalents of substrate, although in this case the reaction led to a very heterogeneous mixture (slurry). Benzylic secondary C–H bond amination proceeded very efficiently and led to secondary benzylic amines in yields of 61–78% from five equivalents of substrate (Table 5, entries 1–3). Primary benzylic positions were also reactive enough to be functionalized and benzylic amines **35** and **36** were obtained in yields of 50% and 67%, respectively, by using 15 equivalents of toluene or mesitylene (Table 5, entries 4 and 5). If more precious starting materials are required, it is possible to use only five equivalents of substrate, but $[Rh_2\{(S)\text{-nttl}\}_4]$ in CH_2Cl_2 must be used to produce the desired product in good yields.

Benzhydrylamines are an important class of compounds that have various pharmacologic properties, such as anticonvulsant activity.[24] They could be accessed easily by rhodium-catalyzed C–H amination of the corresponding diphenylmethane (Table 6). No solvent was required; a solution of potassium carbonate in water was added dropwise to a mixture of *N*-tosyloxycarbamate **12**, the substrate (5 equiv), and $[Rh_2(tpa)_4]$. A very good functional group tolerance was

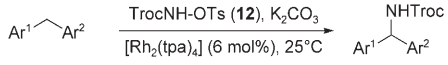
Table 5. Rhodium-catalyzed intermolecular C–H insertion with aromatic alkanes.

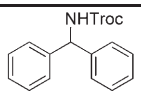
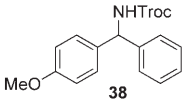
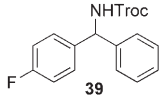
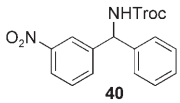
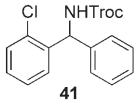
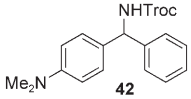


Entry	Product	Isolated yield [%] 5 equiv[a]	15 equiv[b]
1	 **32**	68	75
2	 **33**	78	87
3	 **34**	61	71
4	 **35**	35/42[c]	50
5	 **36**	52/65[c]	67

[a] Unless otherwise specified, all reactions were run with 6 mol% of $[Rh_2(tpa)_4]$ at 25°C for 16 h with alkane (5 equiv), reagent **12** (1 equiv), and K_2CO_3 (3 equiv). [b] Unless otherwise specified, all reactions were run with 6 mol% of $[Rh_2(tpa)_4]$ at 25°C for 16 h with alkane (15 equiv), reagent **12** (1 equiv), and K_2CO_3 (3 equiv). [c] Reaction with 5 mol% of $[Rh_2\{(S)\text{-nttl}\}_4]$ (0.5 M) in CH_2Cl_2.

Table 6. Rhodium-catalyzed C–H insertion reactions with substituted diphenylmethanes.[a]

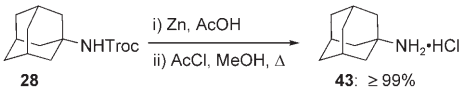


Entry	Product	Yield[b] [%]
1	 **37**	64
2	 **38**	66
3	 **39**	71
4	 **40**	75
5	 **41**	37
6	 **42**	0

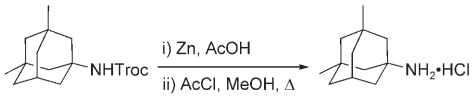
[a] Unless otherwise specified, all reactions were run with 6 mol% of $[Rh_2(tpa)_4]$ at 25°C for 16 h with alkane (5 equiv), reagent **12** (1 equiv), and K_2CO_3 (2 equiv, 12.5 M) in H_2O. [b] Isolated yields.

observed because the *para*- and *meta*-substituted electron-donating and -withdrawing groups were compatible, and the corresponding Troc-protected amines were isolated in yields of 64–75% (Table 6, entries 1–4). However, the steric hindrance of an *ortho*-substituted aryl substrate appeared to have a negative influence on the C–H amination and a lower yield was observed (Table 6, entry 5). Furthermore, amino groups seemed to inhibit the reaction because no conversion was observed with 4-(*N*,*N*-dimethylamino)diphenylmethane (Table 6, entry 6). When preparing a solution of this substrate with $[Rh_2(tpa)_4]$, the color of the metal complex turned from dark green to purple, which suggested that coordination of the amino group with the catalyst had occurred and inhibited its activity.

An advantage of using **12** for these insertions is the generation of Troc-protected amines, which can be easily cleaved to produce the corresponding hydrochloride salt by using a known procedure.[25] Indeed, when Troc-protected adamantanamine **28** was treated with zinc in acetic acid, followed by acetyl chloride in methanol, amantadine hydrochloride (**43**) was isolated in quantitative yield [Eq. (3)]. Memantine hydrochloride (**44**), which is used to treat moderately severe to severe Alzheimer's disease, was similarly obtained from Troc-protected dimethyladamantanamine **27** [Eq. (4)].[26]

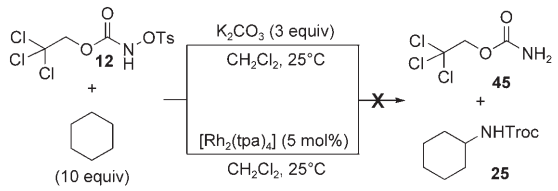


28 **43**: ≥99% (3)



27 **44**: ≥99% (4)

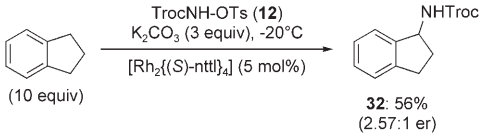
Mechanistic considerations: We have performed a series of experiments with the goal of clarifying the mechanism and catalytic cycle of the rhodium-catalyzed C–H amination of *N*-tosyloxycarbamates. An important aspect is the identification of the various intermediates (and how they are generated), which may include free nitrenes and/or nitrene–metal species. Indeed, Lwowski et al. have described the use of $NsO{-}NHCO_2Et$ (Ns = 4-nitrophenylsulfonyl) and a base to generate free nitrenes, which led to unselective reactions (including C–H insertion) and the formation of ethylcarbamate (H_2NCO_2Et).[17] In this case, deprotonation of $NsO{-}NHCO_2Et$ followed by expulsion of NsO^- initially led to the singlet nitrene intermediate that could undergo C–H insertion but could also rapidly form the triplet nitrene. The latter reacts via radical pathways that include the abstraction of hydrogen to produce ethylcarbamate (H_2NCO_2Et). We have observed similar pathways in the intramolecular C–H amination of **5** in the presence of $[Rh_2(tpa)_4]$; a mixture of products was observed that included the C–H insertion product (oxazolidinone **1**) and the corresponding carbamate. We postulated that the deprotonation of **5** with potassium carbonate occurred prior to the coordination of this reagent with the rhodium complex, which led to the formation of a free nitrene and unselective reactions. However, it seems unlikely that free nitrenes would be involved in the case of *N*-tosyloxycarbamates because these reagents led to very selective and stereospecific reactions. To confirm this hypothesis, we treated a mixture of **12** and cyclohexane in CH_2Cl_2 with potassium carbonate for 16 h in the absence of $[Rh_2(tpa)_4]$ (Scheme 4). Not only was the starting material



Scheme 4. Control experiments.

recovered, but no carbamate **45** or any other product was produced either. Furthermore, no reaction took place when a control experiment was run in the presence of $[Rh_2(tpa)_4]$ but in the absence of base.

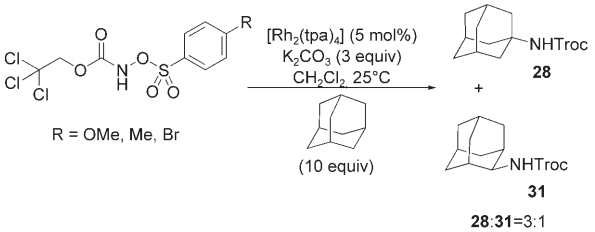
These control experiments showed that both the rhodium catalyst and the base are required for **12** to react. Coordination of the rhodium dimer with tosyloxycarbamate **12** is thus required prior to deprotonation with the base that leads to the active species. Because we observed a moderate level of stereoinduction for the C–H amination of indane with $[Rh_2\{(S)\text{-nttl}\}_4]$[23] [Eq. (5)],[18c] we hypothesized the formation of a rhodium–nitrene species (er = enantiomeric ratio).



(5)

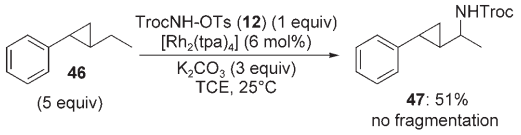
If this premise is true, the C–H insertion pathway should be completely independent of the type of leaving groups involved. Indeed, when we tested various *N*-arylsulfonyloxycarbamates in the intermolecular C–H amination reaction of adamantane, the exact same chemoselectivity (tertiary vs. secondary C–H bonds) was observed in all cases [Eq. (6)].

Metal nitrenes are also known to exist as singlet or triplet states. It is commonly accepted that the former reacts through a concerted mechanism and the latter by a radical



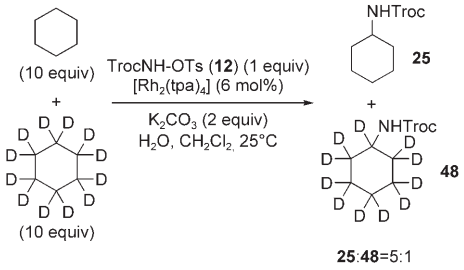
(6)

C–H abstraction followed by rapid recombination.[27] To distinguish between these two possibilities, the reaction was carried out with the radical clock substrate **46** [Eq. (7)].[28] A moderate yield of the insertion product was obtained and no trace of product that resulted from cyclopropane fragmentation was observed. Because the lifetime of the hypothetical radical would be extremely short (ca. 200 fs),[9r,29] this result suggests that a singlet rhodium nitrene is the reactive intermediate, which is supported by the stereospecificity observed for the reaction with chiral substrates (Table 3, entry 8).



(7)

We have also performed a series of experiments to study the kinetic isotope effect of the C–H insertion step. A competition experiment between cyclohexane and deuterated cyclohexane showed an important primary isotope effect that suggested that the C–H bond is at least partially broken in the transition state [Eq. (8)].



(8)

A Hammett analysis similar to that used by Muller[9a] and Du Bois[9r] was used to assess the electronic nature of the transition state. A series of 4-substituted ethylbenzene derivatives that contained both electron-rich and electron-poor groups were studied in an intermolecular competition experiment with ethylbenzene in the presence of **12** and $[Rh_2(tpa)_4]$. A small but significant preference for electron-rich substrates was established (Figure 1, Table 7). Furthermore, when a mixture of *p*-nitroethylbenzene and ethylbenzene was used, no reaction with the former was observed.[30]

The obtained Hammett ρ-value of -0.47 is smaller than the value for the amination of C–H with sulfamates measured by Fiori and Du bois[9r] and the value for rhodium-catalyzed carbene insertion.[31] It suggests, therefore, that electronic factors are less important for rhodium carbamate nitrenes than for rhodium carbenes or sulfamate nitrenes.[32] Indeed, rhodium-catalyzed C–H amination with **12** is capable of reacting with less reactive primary C–H bonds (which has never been reported previously), but led to less selective reactions compared with the sulfamate analogue. We believe that a small partial positive charge is generated on the

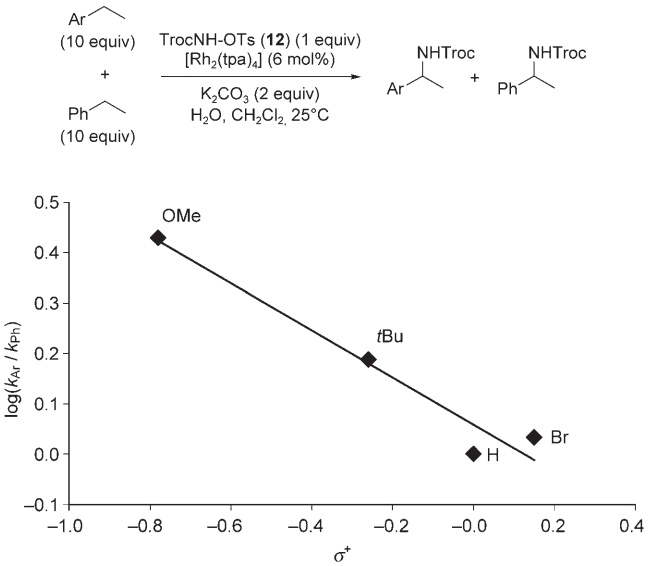


Figure 1. Competitive rhodium-catalyzed C–H amination between ethylbenzene and 4-substituted ethylbenzene with *N*-tosyloxycarbamate **12**. $y=-0.4685x+0.0585$, $R^2=0.9521$. See Table 7 for the data.

Table 7. Hammett analysis data.

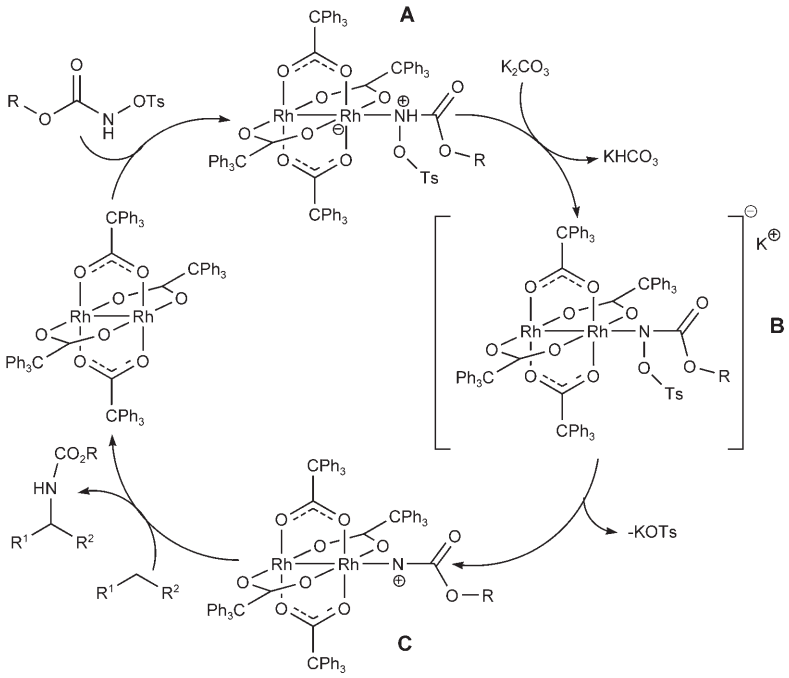
Ar	σ^+[a]	Ar:Ph
OMe	−0.78	2.69:1
*t*Bu	−0.26	1.54:1
H	0	1:1
Br	0.15	1.08:1
NO_2	0.79	0:1

[a] The Hammett σ-constant.

carbon at the site of insertion and that resonance is a factor that contributes to the stabilization of the transition state. Overall, these data suggest a concerted asynchronous transition state for the rhodium-catalyzed C–H amination reaction with *N*-tosyloxycarbamates, and the proposed catalytic cycle is illustrated in Scheme 5. The activation of the starting material by the rhodium dimer (intermediate **A**) is shown as a N–Rh connection, although this interaction could also occur through an oxygen atom. Intermediate **B** could be obtained after deprotonation with potassium carbonate. The breaking of the Rh–Rh bond or the partial release of a carboxylate ligand might also be involved.[33] Because the general effects of the reaction (regiospecificity, stereospecificity, electronic character) are similar to those observed for previously described methods that involve a Rh-bound nitrene,[9r,34] the intermediate **C** was proposed to be responsible for the C–H insertion step. Formation of the amination product with release of the catalyst completes the catalytic cycle.

Conclusion

In conclusion, *N*-tosyloxycarbamates have been described as a useful source of metal nitrenes for rhodium-catalyzed



Scheme 5. Proposed catalytic cycle.

C–H amination reactions. Not only was this starting material stable and easy to prepare and handle, but the reaction also proceeded under mild reaction conditions. The intramolecular reaction gave oxazolidinones in good yields and the intermolecular version gave Troc-protected amines. This is the first intermolecular C–H insertion process that uses carbamates. The purification of the amination product was very easy to carry out because potassium tosylate was the only stoichiometric byproduct produced. This paper also features novel syntheses of products with important biological activities, such as amantadine hydrochloride, memantine hydrochloride, and various benzhydrylamines. Finally, mechanistic studies suggested that a singlet rhodium nitrene was the reactive species and that the C–H insertion step proceeded via a concerted asynchronous transition state.

Experimental Section

General procedure A

Intramolecular C–H bond insertion: $[Rh_2(tpa)_4]$ (0.040 g, 0.030 mmol) and potassium carbonate (0.210 g, 1.50 mmol) were added to a solution of *N*-tosyloxycarbamate (0.500 mmol) in CH_2Cl_2 (5.0 mL). The resulting green suspension was stirred at room temperature for 6 h. The mixture was then diluted with CH_2Cl_2, filtered through a Celite pad, rinsed with CH_2Cl_2, and the solvent was removed under vacuum. The corresponding oxazolidinone was purified by flash chromatography on silica gel by using EtOAc/CH_2Cl_2 as the eluent.

General procedure B

Intramolecular C–H bond insertion for reactions of ≥1 mmol: $[Rh_2(tpa)_4]$ (0.080 g, 0.060 mmol) was added to a solution of the *N*-tosyloxycarbamate (1.00 mmol) in CH_2Cl_2 (10.0 mL). Potassium carbonate (0.280 g, 2.00 mmol) in water (0.50 mL) was added dropwise, and the resulting green suspension was stirred at room temperature for 6 h. The mixture was then filtered through a Celite pad, rinsed with CH_2Cl_2, and the solvent was removed under vacuum. The corresponding oxazolidinone was purified by flash chromatography on silica gel by using EtOAc/CH_2Cl_2 as the eluent.

General procedure C

Intermolecular C–H bond insertion with aliphatic alkanes: Potassium carbonate (0.210 g, 1.50 mmol) and either $[Rh_2(tpa)_4]$ (0.040 g, 0.030 mmol) or $[Rh_2\{(S)\text{-nttl}\}_4]$ (0.036 g, 0.025 mmol) were added to a solution of 2,2,2-trichloroethyl-*N*-tosyloxycarbamate (0.181 g, 0.500 mmol) and alkane (2.50 mmol) in the appropriate solvent (TCE or CH_2Cl_2; 1 mL). The resulting green suspension was stirred overnight at room temperature. The mixture was then diluted with CH_2Cl_2, filtered through a Celite pad, rinsed with CH_2Cl_2, and the solvent was removed under vacuum. The corresponding Troc-protected amine was purified by flash chromatography on silica gel.

General procedure D

Intermolecular C–H bond insertion with aromatic alkanes: $[Rh_2(tpa)_4]$ (0.040 g, 0.030 mmol) and potassium carbonate (0.210 g, 1.50 mmol) were added to a solution of 2,2,2-trichloroethyl-*N*-tosyloxycarbamate (0.181 g, 0.500 mmol) and the aromatic substrate (2.50 or 7.50 mmol). The resulting green suspension was stirred overnight at room temperature. The mixture was then filtered through a Celite pad, rinsed with CH_2Cl_2, and the solvent was removed under vacuum. The corresponding Troc-protected amine was purified by flash chromatography on silica gel.

General Procedure E

Intermolecular C–H bond insertion reaction with substituted diphenylmethanes or for intermolecular reactions of ≥1 mmol: 2,2,2-trichloroethyl *N*-tosyloxycarbamate (0.181 g, 0.500 mmol) and $[Rh_2(tpa)_4]$ (0.041 g, 0.030 mmol) were added to the substituted diphenylmethane (2.5 mmol). Potassium carbonate (0.183 g, 1.00 mmol) in water (0.2 mL) was added dropwise over a 15 min period. The heterogeneous mixture was stirred overnight at room temperature, then diluted with CH_2Cl_2, filtered through a Celite pad, and rinsed with CH_2Cl_2. Pyridine[35] (0.10 mL) was added and the solvent was removed under vacuum. The corresponding Troc-protected amine was purified by flash chromatography on silica gel by using EtOAc/hexanes as the eluent.

Acknowledgements

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