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Intermolecular sp^3 C–H Amination of Complex Molecules

Nicholas D. Chiappini, James B. C. Mack and J. Du Bois*

Dedication ((optional))

Abstract: *A general and operationally convenient method for intermolecular amination of sp^3 C–H bonds is described. This technology allows for efficient functionalization of complex molecules, including numerous pharmaceutical targets. The combination of pivalonitrile as solvent, Al_2O_3 as an additive, and phenyl sulfamate as a nitrogen source affords differential reaction performance and substrate scope. Mechanistic data strongly implicate a pathway for catalyst decomposition that initiates with solvent oxidation, thus providing rationale for the marked influence of pivalonitrile on this reaction process.*

Due to the ubiquity of nitrogen containing molecules in Nature, pharmaceuticals, and agrochemicals, the development of reaction technologies for the construction of C–N bonds remains a problem of central importance.[1a-f] As a general process, the selective oxidation[2a,b] of C–H bonds to form amine derivatives offers numerous salient features, not the least of which is the ability for late stage diversification of existing molecular architectures.[3a-r] Arguably, the full potential of this technology has not been realized owing to the limited substrate scope and performance of available intermolecular C–H amination reactions. Here, we disclose a general and efficient method for the single step amination of complex molecules, a process that uses one equivalent of substrate, minimal reaction additives, and a convenient nitrogen source (Figure 1). Mechanistic studies identify a link between solvent oxidation and catalyst stability, and provide a basis for understanding improved turnover numbers under the new protocol.

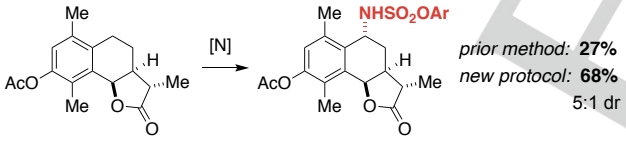

Figure 1. General method for sp^3 C–H amination.[2b]

Previously disclosed reports of intermolecular C–H amination demonstrate good to excellent performance on substrates bearing a limited number of heteroatom groups.[2b],[3d,m,n,p-r] These processes, however, often fail to show comparable efficacy on densely functionalized complex molecules and polar substrates such as salts of basic amines and azacycles. Intent to solve these problems, we became interested in testing amination reactions in polar solvent media to facilitate dissolution of nitrogen-rich substrates and amine salts. Exploratory reactions were conducted utilizing a substrate derived from isomenthol **1a** and $PhOSO_2NH_2$ ($PhsNH_2$) as the nitrogen source. This sulfamate was selected for its ease of synthesis and the chromatographic stability of the sulfonamidated products.[4] Different base additives, including MgO, molecular sieves, and Al_2O_3, were also examined as part of this study.[5]

With *i*-PrOAc as solvent, the effectiveness of 1 mol% [Rh_2(esp)$_2$], $PhOSO_2NH_2$, and Al_2O_3 closely matched a previously disclosed method from our lab[2b] (entries 1, 2, Table 1), each giving < 50% of the desired product **2a**.[6] Switching to alternative reaction solvents such as DMA and DMF was, unsurprisingly, found to arrest the Rh-catalyzed process (entries 3, 4, Table 1). We were encouraged, however, that other high dielectric solvents, including sulfolane, propylene carbonate, and CH_3CN, afforded reasonable levels of conversion to the sulfamate product **2a** (entries 6–8). The reaction performed in sulfolane also produced a side product, which was identified as the C3-sulfonamidated sulfolane. This result prompted us to consider other solvents that would be impervious to oxidation. From this analysis, *t*-BuCN and PhCN were revealed as superior solvents for C–H amination reactions, providing a substantial increase in the formation of **2a** (entry 10, 11). Interestingly, the combination of *i*-PrOAc with 10% *t*-BuCN, propylene carbonate, or sulfolane (entries 12–14) showed evident improvement over the reaction conducted in neat *i*-PrOAc, suggesting that the ability of these agents to coordinate [Rh_2(esp)$_2$] might have some role in improving catalyst turnover numbers.

Table 1. Optimizing conditions for Rh-catalyzed C–H amination of **1a**

Entry	Yield[a,b]	RSM[b]	Solvent
1	47	13	*i*-PrOAc[c]
2	45	22	*i*-PrOAc
3	5	60	N,N-dimethylacetamide
4	0	75	N,N-dimethylformamide
5	25	57	2,2,2-trifluoroethanol
6	35	61	sulfolane
7	33	59	propylene carbonate
8	37	45	CH_3CN
9	35	47	*i*-PrCN
10	**80**	**10**	***t*-BuCN**
11	**75**	**12**	**PhCN**
12	64	22	9:1 *i*-PrOAc/*t*-BuCN
13	60	23	9:1 *i*-PrOAc/propylene carbonate
14	58	31	9:1 *i*-PrOAc/sulfolane

[a] Reactions were performed at ambient temperature for 6 h in the indicated solvent with 1 mol % [Rh_2(esp)$_2$], 1.0 equiv of **1**, 1.3 equiv of $PhOSO_2NH_2$, 1.5 equiv of $PhI(OPiv)_2$, and 4.0 equiv Al_2O_3. [b] Percent recovered starting material (RSM) estimated by ^{1}H NMR integration against methyl benzoate as a standard. [c] Reaction performed with 1.3 equiv 2,6-difluorophenyl sulfamate ($DfsNH_2$) in place of $PhOSO_2NH_2$, 2.0 equiv $PhI(OAc)_2$, 0.5 equiv $PhMe_2CCO_2H$, 4 equiv MgO, and 5Å molecular sieves, providing product as corresponding $DfsNH_2$ derivative.[2b]

Using our new protocol, we have examined reaction performance with an array of functionally diverse starting materials (Table 2, Table S1). Archetypal substrates for atom-transfer C–H oxidation reactions such as cycloheximide (**2b**), estrone (**2c**), and sclareolide (**2d**), in addition to numerous active pharmaceutical ingredients (**2g, 2k, 2o, 2p**) can be successfully functionalized in synthetically useful yields (40–75%). The reaction generally delivers product and recovered starting material, and shows exceptional selectivity for oxidation of benzylic and tertiary C–H bonds. Substrates bearing stereogenic centers proximal to the site of amination demonstrate modest levels of diasteroselectivity (*cf,* **2c**, **2d, 2m**).

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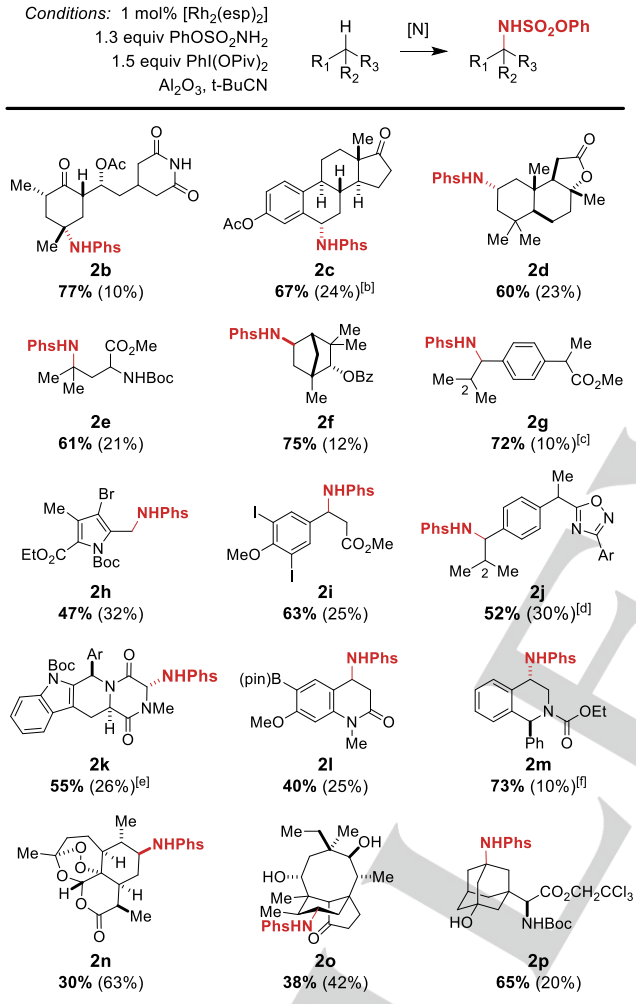
As expected for a reaction of this type, electron-deficient, and sterically encumbered substrates generally afford lower product yields;[11f],[2c] however, if limiting substrate is not a strict requirement, use of 2–3 equivalents typically leads to product conversions that are nearly quantitative with respect to the nitrogen source. Importantly, the sulfamate products can be unmasked to the corresponding 1° amines by heating with pyridine in aqueous CH_3CN (Figure 2).[2b,7] These conditions are tolerant of other hydrolytically sensitive functional groups, including aryl acetates, β-acyloxy ketones, lactones, and methyl esters.

Table 2. C–H amination of complex molecule substrates[a]



[a] All reactions were conducted at ambient temperature under air with non-anhydrous solvent for 6 h on 0.15 mmol scale using 1.0 equiv substrate in *t*-BuCN with 1 mol % $[Rh_2(esp)_2]$, 1.3 equiv $PhOSO_2NH_2$, 1.5 equiv $PhI(OPiv)_2$, and 4 equiv Al_2O_3. Percent yield of recovered starting material is shown in parentheses. [b] Isolated as 5:1 mixture of diastereomers; [c] Isolated as 1:1 inseparable mixture of regioisomers; [d] Ar = *p*-C_6H_4F, isolated as 1.25:1 inseparable mixture of regioisomers; [e] Ar = 1,3-benzodioxol-5-yl, 20:1 diastereomer ratio; [f] 20:1 diastereomer ratio. Further exposition of substrate scope and limitations can be found in Supporting Information.

We have conducted a series of experiments to understand the origin of the marked performance enhancement imparted by *t*-BuCN in intermolecular C–H amination reactions. A long-standing question in our lab has been the identity and role of the ligand coordinated to the distal Rh-center in the putative metal-nitrene oxidant.[8,9] The affinity of nitrile groups for axial coordination to dirhodium complexes and the use of *t*-BuCN as solvent seemingly removes this ambiguity.[10] UV-visible spectroscopy of the $[Rh_2(esp)_2]$ complex indicates that CH_3CN, *t*-BuCN, and PhCN have similar σ-donating strengths and are, not surprisingly, more electron-donating than *i*-PrOAc, sulfolane, and

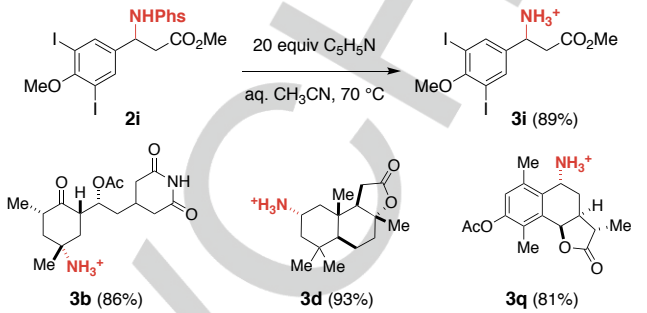


Figure 2. Deprotection of *N*-alkyl phenylsulfamates. Products were obtained as trifluoroacetate salts following preparative reversed-phase HPLC purification (see Supporting Information for details).

propylene carbonate (Figure 3).[9-11] As we and others have demonstrated previously, intermolecular C–H amination reactions result in one-electron catalyst oxidation to furnish the red-colored Rh(II)/Rh(III) dimer.[12] The stability and lifetime of this complex is critical for achieving high reaction turnover numbers. It is possible that the nitrene-bound Rh(II)/Rh(III) dimer itself functions as a competent oxidant for C–H functionalization.[8] A strongly coordinating solvent such as *t*-BuCN could help to stabilize the oxidized complex, thus enabling increased turnover numbers. Such an explanation, however, is incomplete, as the reaction is decidedly more effective in *t*-BuCN and PhCN than in CH_3CN.

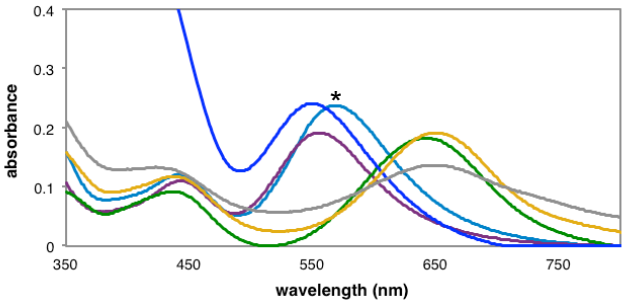
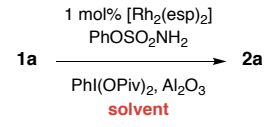


Figure 3. UV-visible spectra of $[Rh_2(esp)_2]$ in *t*-BuCN ■, MeCN ■, PhCN ■, *i*-PrOAc ■, sulfolane ■, and propylene carbonate ■ are shown above. The axial ligand donor strength of these solvents if reflected in the λ_{max} (*) of the lower energy π*→σ* band.[10d,11]

We have noted previously that C–H amination reactions performed in CH_2Cl_2 can result in solvent oxidation to liberate chloride ion.[2a] Based on these insights, we have evaluated performance differences in protio- and deuterio- solvents for the oxidation of **1a** (Table 3). Deuterated solvents, particularly CD_3CN, clearly outperform the corresponding protiated forms. These data give weight to the proposal that solvent oxidation, even in CH_3CN, is deleterious to reaction turnover.[13]

Table 3. Effect of solvent deuteration on C–H amination performance.



Entry	Solvent	TON[a,b]
1	CH_3CN	37
2	CD_3CN	55
3	CH_2Cl_2	22
4	CD_2Cl_2	33

[a] Reactions were conducted with 1.0 equiv substrate in solvent with 1 mol % $[Rh_2(esp)_2]$, 1.3 equiv $PhOSO_2NH_2$, 1.5 equiv $PhI(OPiv)_2$, 4 equiv neutral Al_2O_3. [b] Turnover numbers (TON) were determined by ^1H NMR integration against methyl benzoate as a standard.

To examine whether solvent has an influence on $[Rh_2(esp)_2]$ stability, we have developed an assay to quantify the amount of intact catalyst at a given time point over the course of the reaction. Due to the low catalyst loading employed in this process and the paramagnetic nature of the Rh(II)/Rh(III) dimer, we have modified the H_2(esp) ligand to include a ^{19}F-label (Figure 4). The sensitivity of ^{19}F NMR allows us to perform the amination reaction under our standard protocol and to record a strong F-signal of the $[Rh_2(F\text{-}esp)_2]$ adduct. Attempts to follow the reaction progress in real-time by ^{19}F NMR, however are complicated by paramagnetic line-broadening. We have thus resorted to quenching the reaction by addition of Zn powder at a fixed time point. The red color of the Rh(II)/Rh(III) dimer is extinguished upon addition of the reducing agent, and the blue-green color of $[Rh_2(F\text{-}esp)_2]$ is restored. ^{19}F NMR allows us to quantify against an internal standard (1,3-dbromo-2,5-difluorobenzene) the percentage of Rh(II)/Rh(II) dimer remaining in solution.

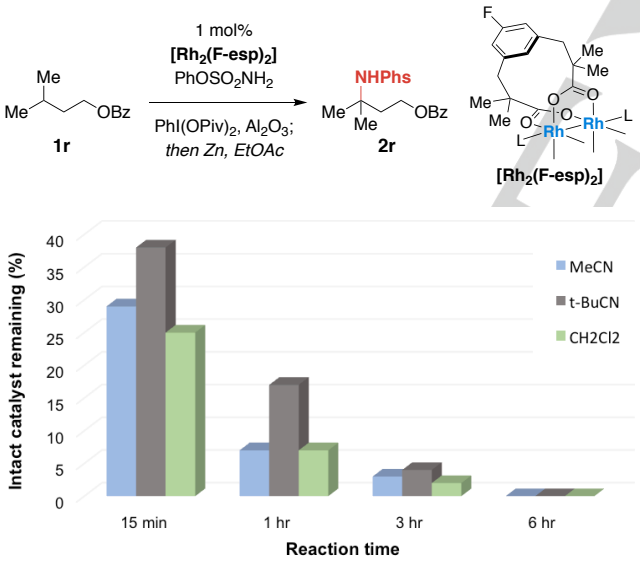


Figure 4. Assay of intact $[Rh_2(F\text{-}esp)_2]$ as a function of reaction time performed using quantitative ^{19}F NMR (details are in supporting information).

For reactions performed in *t*-BuCN, our analysis indicates that ~20% of $[Rh_2(F\text{-}esp)_2]$ is present one hour after initiating the reaction (Figure 4). By contrast, reactions conducted in CH_3CN or CH_2Cl_2 show ~5% of the intact complex along with two uncharacterized species, neither of which correspond to free H_2(F-esp) ligand (see Supporting Information for details). Differential levels of catalyst decomposition are also noted at both the 15 min and 3 h marks. These data give evidence that the choice of solvent, namely *t*-BuCN vis-à-vis CH_3CN or CH_2Cl_2, influences $[Rh_2(esp)_2]$ lifetime and, possibly, the pathway(s) for degradation.

Interestingly, quantitative ^{19}F NMR analyses of spent reaction mixtures reveal a substantial deficit in the mass balance of F-esp-derived material. We have discovered that a considerable amount of free ligand (~25%) is associated with the Al_2O_3 solids; nevertheless, the mass balance remains incomplete. Current efforts are aimed at identifying the fate of this missing material and associated catalyst decomposition products.

We have developed a general method for intermolecular C–H amination capable of generating sulfamate derivatives of complex molecules, including APIs and natural products. The streamlined process utilizes limiting quantities of substrate, 1 mol % of commercially available $[Rh_2(esp)_2]$, $PhI(OPiv)_2$, and Al_2O_3. The identification of *t*-BuCN as solvent affords substantial improvements in catalyst turnover and unprecedented reaction scope. Hallmarks of this method also include product selectivity and outstanding mass balance. Mechanistic investigations have shown that a larger fraction of the dirhodium catalyst remains intact for reactions performed in *t*-BuCN. Additional studies comparing amination performance in protio- and deuterio- solvents intimate a correlation between solvent oxidation and catalyst decomposition. Future studies are aimed at understanding stepwise details of the mechanism(s) for catalyst decomposition with the goal of informing subsequent efforts in catalyst design and reaction development.

Acknowledgements

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Keywords: oxidation • sulfamate • $[Rh_2(esp)_2]$ • *t*-BuCN

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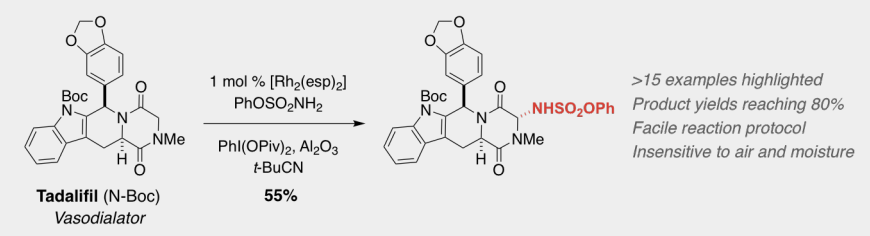

Tadalifil (N-Boc)
Vasodialator

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Page No. – Page No.

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