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Expanding the Substrate Scope for C–H Amination Reactions: Oxidative Cyclization of Urea and Guanidine Derivatives

Mihyong Kim, John V. Mulcahy, Christine G. Espino, and J. Du Bois*

Department of Chemistry, Stanford University, Stanford, California 94305-5080

jdubois@stanford.edu

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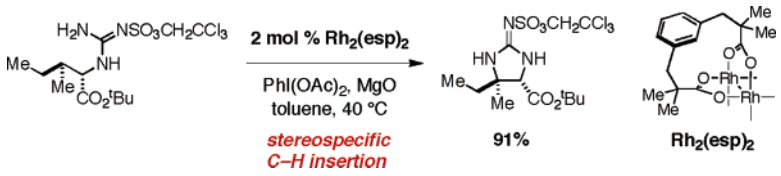
ABSTRACT



Oxidative C–H amination of *N*-trichloroethoxysulfonyl-protected ureas and guanidines is demonstrated to proceed in high yield for tertiary and benzylic-derived substrates. The success of these reactions is predicated on the choice of the electron-withdrawn 2,2,2-trichloroethoxysulfonyl (Tces) protecting group, the commercial catalyst $Rh_2(esp)_2$ (1–2 mol %), and toluene as solvent. The frequency with which the heterocyclic imidazolidin-2-ones and 2-aminoimidazolines appear as structural elements in both natural products and therapeutically designed molecules confers these methods with a large number of potential applications.

Direct methods for the amination of C−H bonds have been established as tools for the assembly of nitrogen-based heterocycles and related amine derivatives.[1] Our laboratory has delineated such processes, which enable the catalytic, oxidative cyclization of both primary carbamate and sulfamate esters to give the corresponding 5- and 6-membered ring products, respectively (Figure 1).[2,3] These value-added compounds may be readily transformed into 1,2- or 1,3-disubstituted amine derivatives. Although simple dirhodium tetracarboxylate complexes (i.e., $Rh_2(OAc)_4$, $Rh_2(O_2CCPh_3)_4$) have proven effective as catalysts in many instances, we have recently demonstrated that a tethered carboxylate, $Rh_2(esp)_2$, is superior in performance to all others.[4,5] This new catalyst has allowed us to expand the collection of substrates that will engage in high-yielding C−H amination reactions

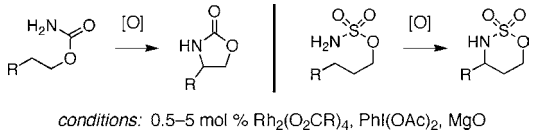


Figure 1. Catalytic methods for C−H amination.

(1) (a) Espino, C. G.; Du Bois, J. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, 2005; pp 379−416. (b) Halfen J. A. *Curr. Org. Chem.* **2005**, *9*, 657−669. (c) Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905−2920. (d) Dauban, P.; Dodd, R. H. *Synlett* **2003**, 1571−1586.

(2) (a) Du Bois, J. *CHEMTRACTS−Org. Chem.* **2005**, *18*, 1−13. (b) Fiori, K. W.; Fleming, J. J.; Du Bois, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 4349−4352. (c) Wehn, P. M.; Lee, J.; Du Bois, J. *Org. Lett.* **2003**, *5*, 4823−4826. (d) Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935−6936. (e) Espino, C. G.; Du Bois, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 598−600.

(3) For recent related studies, see: (a) Lebel, H.; Huard, K.; Lectard, S. *J. Am. Chem. Soc.* **2005**, *127*, 14198−14199. (b) Cui, Y.; He, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 4210−4212. (c) Fruit, C.; Müller, P. *Tetrahedron: Asymmetry* **2004**, *15*, 1019−1026. (d) Liang, J.-L.; Yuan, S.-X.; Huang, J.-S.; Yu, W.-Y.; Che, C.-M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3465−3468. Also see: Yu, X.-Q.; Huang, J.-S.; Zhou, X.-G.; Che, C.-M. *Org. Lett.* **2000**, *2*, 2233−2236.

(4) Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378−15379.

(5) $Rh_2(esp)_2$ is known by its chemical name as $Rh_2(\alpha,\alpha,\alpha',\alpha'$-tetramethyl-1,3-benzenedipropionate$)_2$; see ref 4. This catalyst may be purchased from Aldrich Chemical Co. or conveniently prepared on large scale (40 g) in three steps: Fiori, K. W.; Du Bois, J. Manuscript in preparation.

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(Figure 2). As a result of these efforts, we now report that primary urea and guanidine derivatives function with general

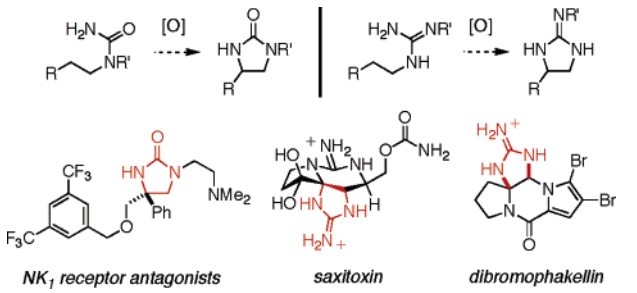


Figure 2. Oxidative cyclization of ureas and guanidines.

utility as substrates for this process. With the former class of starting materials, the products of oxidation can be elaborated to vicinal diamines.[6] Additionally, heterocylic ureas and guanidines are found as structural elements in a growing number of complex, biologically efficacious targets, including a spectacularly diverse family of bromopyrrole metabolites (Figure 2).[7,8] The demonstration that two new substrate types can engage in C−H amination reactions affirms the power of this methodology as a unified strategy for the preparation of structurally disparate molecules.

With our initial success developing carbamate ester insertion reactions, we anticipated that *N*-alkylureas would perform as substrates in an analogous fashion. Phenethylurea **1** was tested under conditions that employed 5 mol % of $Rh_2(OAc)_4$, $PhI(OAc)_2$, and MgO (Figure 3). From this

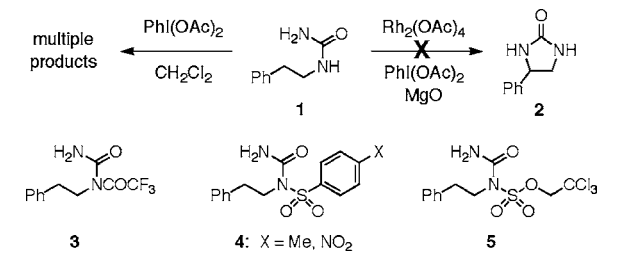
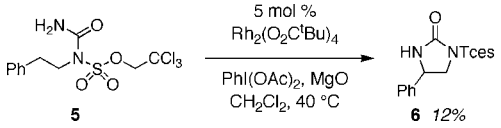


Figure 3. Control experiments and initial test substrates.

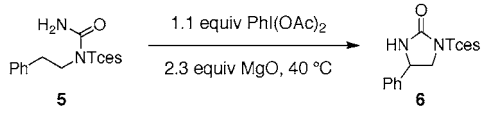
reagent mixture, multiple products were generated; none, however, corresponded to the desired imidazolidin-2-one **2**. Subsequent control experiments indicated that a rapid reaction between **1** and $PhI(OAc)_2$ ensues in the absence of Rh catalyst and/or MgO.[9] This process effectively out-competes the Rh-mediated insertion pathway. As such, we considered modifying the urea substrates with an electron-withdrawing group so as to attenuate the unfavorable reaction with $PhI(OAc)_2$. Both *N*-alkyl-*N*-acylurea **3** and *N*-alkyl-*N*-sulfonylurea **4** substrates were synthesized and tested in this capacity.[10] Although the background reaction with oxidant was indeed avoided, only the trichloroethoxysulfonyl (Tces) substrate **5** proved effective for oxidative cyclization. The resulting Tces-blocked imidazolidinone **6** was thus formed, albeit in modest yield (12%), using 5 mol % of $Rh_2(O_2C\text{-}^tBu)_4$, $PhI(OAc)_2$, and MgO (eq 1).[11]



(1)

Prior work from our lab has demonstrated the unique effectiveness of $Rh_2(esp)_2$ for catalyzing both intra- and intermolecular C−H amination reactions of sulfamate esters.[4] We were therefore pleased to find that this complex was equally adept at promoting high-yielding oxidation of Tces-urea **5** (Table 1). Other Rh-tetracarboxylates examined, which

Table 1. Evaluating Reaction Conditions for Urea Oxidation



entry	Rh catalyst[a]	solvent	% conversion[b]
1	$Rh_2(O_2C^tBu)_4$	CH_2Cl_2	15
2	$Rh_2(O_2C\text{-}1\text{-}Ph^cHx)_4$	CH_2Cl_2	20
3	$Rh_2(O_2CCPh_3)_4$	CH_2Cl_2	20
4	$Rh_2(esp)_2$	CH_2Cl_2	60
5	$Rh_2(esp)_2$	C_6H_6	70
6	$Rh_2(O_2C^tBu)_4$	toluene	40
7	$Rh_2(O_2C\text{-}1\text{-}Ph^cHx)_4$	toluene	85
8	**$Rh_2(esp)_2$**	**toluene**	90

[a] A 5 mol % catalyst charge was employed. [b] Estimated product conversion is based on integration of the ^1H NMR spectrum of the unpurified reaction mixture.

included $Rh_2(O_2CCPh_3)_4$ and $Rh_2(O_2C\text{-}1\text{-}Ph^cHx)_4$, gave reduced product conversions, particularly as the loading was decreased from 5 to 1 mol %.[12] Aside from the identification of $Rh_2(esp)_2$ as an optimal catalyst for this process, the choice of toluene as solvent was found to be another important factor contributing to increased reaction yields. It is interesting to

(6) For a general review on vicinal diamine synthesis, see: Lucet, D.; Le Gall, T.; Mioskowski, C.; *Angew. Chem., Int. Ed.* **1998**, *37*, 2580−2627. Also, see: (a) Dunn, P. J.; Häner, R.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 5017−5025. (b) Jones, R. C. F.; Schofield, J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 375−383.

(7) (a) Shue, H.-J.; Chen, X.; Shih, N.-Y.; Blythin, D. J.; Paliwal, S.; Lin, L.; Gu, D.; Schwerdt, J. H.; Shah, S.; Reichard, G. A.; Piwinski, J. J.; Duffy, R. A.; Lachowicz, J. E.; Coffin, V. L.; Liu, F.; Nomeir, A. A.; Morgan, C. A.; Varty, G. B. *Biorg. Med. Chem. Lett.* **2005**, *15*, 3896−3899. (b) Berlinck, R. G. S.; Kossuga, M. H. *Nat. Prod. Rep.* **2005**, *22*, 516−550. (c) Brackeen, M. F.; Cowan, D. J.; Stafford, J. A.; Schoenen, F. J.; Veal, J. M.; Domanico, P. L.; Rose, D.; Strickland, A. B.; Verghese, M.; Feldman, P. L. *J. Med. Chem.* **1995**, *38*, 4848−4854.

(8) (a) Dembitsky, V. M. *Russ. J. Bioorg. Chem.* **2002**, *28*, 170−182. (b) Al Mourabit, A.; Potier, P. *Eur. J. Org. Chem.* **2001**, 237−243.

(9) The mixture of unidentified products does not appear to contain any derived from C−H functionalization.

(10) Espino, C. G. Ph.D. Thesis, Stanford University, Stanford, CA, 2004.

(11) When conducted with 5 mol % $Rh_2(OAc)_4$, the reaction of **5** gives <10% of the desired product **6**. With either catalyst, recovered starting material accounts for the mass balance in these reactions.

note that products derived from solvent oxidation have never been obtained under these reaction conditions. A standard protocol employing urea **5**, 1 mol % of $Rh_2(esp)_2$, 1.5 equiv of $PhI(OAc)_2$, and 2.5 equiv of MgO in toluene at 40 °C thus afforded 87% of the heterocyclic product **6**.

The ease by which Tces-protected ureas may be fashioned further enhances the value of these substrates for C−H amination (Figure 4). In a single operation, the commodity

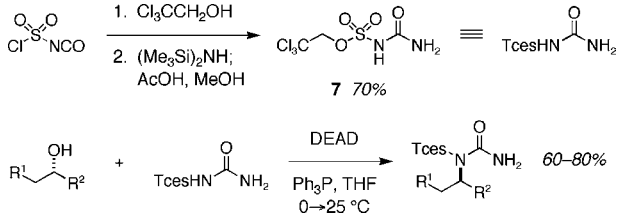


Figure 4. Preparative method for Tces-urea assembly.

chemical $ClSO_2NCO$ can be transformed to *N*-(2,2,2-trichloroethoxy)sulfonylurea **7**.[13] This compound reacts with primary and secondary alcohols using Ph_3P and DEAD to furnish the *N*-alkylated materials. Accordingly, access to a number of differentially substituted ureas is possible by employing this straightforward protocol (Table 2).

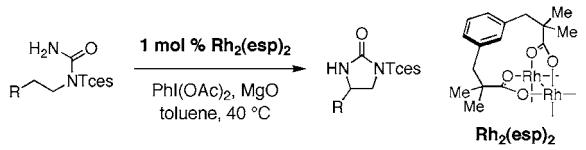
As with reactions of carbamates, high-yielding amination proceeds for Tces-ureas having tertiary and benzylic β-C−H centers (entries 1−5, Table 2). Importantly, amination of optically pure tertiary C−H bonds is stereospecific (entry 5), thereby giving access to tetrasubstituted amine products with absolute stereochemical fidelity. Oxidative cyclization of the homoallyl urea (entry 6) also occurs efficiently but generates a nearly equal mixture of both insertion and aziridine products. Similar chemoselectivites have been noted for reactions of unsaturated carbamates and sulfamates.[2] One of the more difficult classes of substrates for amination is represented by the straight chain, unsubstituted *n*-butylurea (entry 7). Not surprisingly, product yields are reduced from other entries even when higher catalysts loadings are employed. Overall, the observed reactivity trends are quite comparable to those of carbamates and sulfamates; as with the former starting materials, five-membered ring formation is highly favored.[2e]

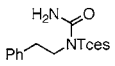
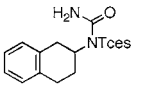
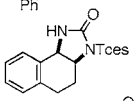
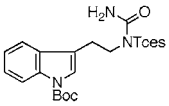
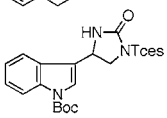
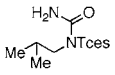
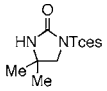
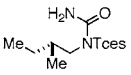
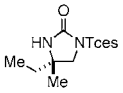
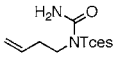
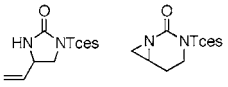
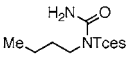
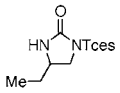
Motivated by the complex architectures of a number of intriguing guanidine natural products, we wished to extend the C−H amination methodology to include such substrates. Again it was discovered that the reactivity of the *N*-alkylguanidine needed to be tempered by the incorporation of an electron-withdrawn protecting group. A focused screen of *N*-carbamoyl and *N*-sulfonyl alkylguanidines afforded results analogous to those of the urea reactions, as the Tces

(12) $Rh_2(O_2CCPh_3)_4$ is easily prepared from $Rh_2(OAc)_4$ and Ph_3CCO_2H; see: Hashimoto, S.-i.; Watanabe, N.; Ikegami, S. *Tetrahedron Lett.* **1992**, *33*, 2709−2712. $Rh_2(O_2C\text{-}1\text{-}Ph^cHx)_4$ is prepared in an analogous fashion from 1-phenylcyclohexane carboxylic acid.

(13) The reaction of Cl_3CCH_2OH with $ClSO_2NCO$ is precedented, see: Lohaus, G. *Chem. Ber.* **1972**, *105*, 2791−2799.

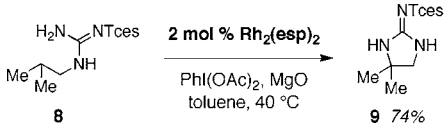
Table 2. Oxidative Cyclization of *N*-Tces Urea Substrates



entry	substrate	product	% yield[a]
1			87
2			93
3			73
4			92
5			84
6			41[b]
7			31[c]

[a] Reactions were performed with 1 mol % of $Rh_2(esp)_2$, 1.5 equiv of $PhI(OAc)_2$, and 2.5 equiv of MgO in toluene at 40 °C. [b] Isolated yield of imidazolidin-2-one. The ratio of insertion/aziridine products is ~1:1.3 based on integration of the ^1H NMR spectrum of the unpurified product. [c] The starting urea is recovered in 50% yield.

group proved most effective. By employing Tces-guanidine **8** with 2 mol % $Rh_2(esp)_2$, $PhI(OAc)_2$, and MgO in toluene, 74% yield of the cyclized product **9** was obtained (eq 2). The ability to effect such a reaction at low catalyst loadings given the polar, Lewis basic nature of the protected guanidine is particularly striking and underscores the functional group compatibility of these Rh-tetracarboxylate systems.



(2)

Two methods have been developed for the efficient synthesis of Tces-protected guanidines from primary amines. Both of these protocols rely on imidodithionate **11**, which is easily prepared as a crystalline compound in a single step from trichloroethylsulfamate **10**.[14,15] Subsequent conversion of this reagent to either isothiourea **12** or imidochloride **13** is accomplished with NH_3 and SO_2Cl_2, respectively (Figure 5).[16] We have found that isothiourea **12** will react with most primary amines in H_2O at 100 °C (eq 3). Isolation by silica gel chromatography affords the desired guanidines in high

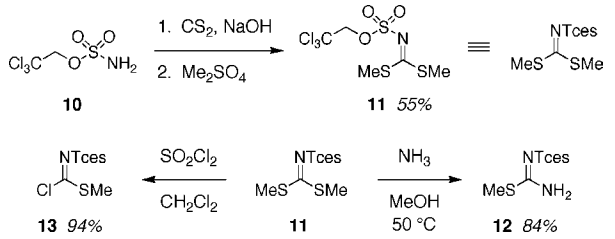
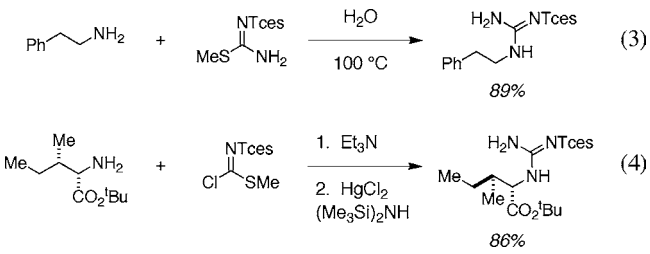


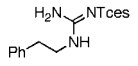
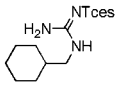
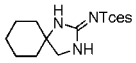
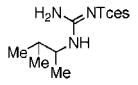
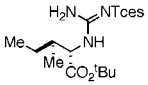
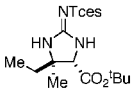
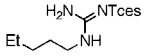
Figure 5. Reagents for the synthesis of *N*-Tces alkylguanidines.

yields. For certain, more functionalized amines, a second strategy is utilized in which the desired amine is first condensed with **13** (eq 4). The resulting pseudothiourea can be transformed to the requisite guanidine using $(Me_3Si)_2NH$ as an ammonia source. In general, the guanidine starting materials are highly crystalline materials and readily available on preparative scales.

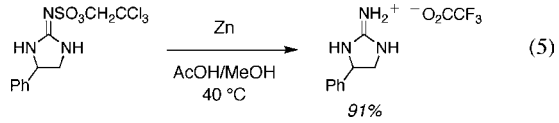


The scope of the C−H amination reaction with Tces-guanidines was examined, and the results are summarized in Table 3. Substrates bearing tertiary β-C−H bonds are clearly superior to those having benzylic or unactivated secondary methylene centers. In contrast to our prior experience with secondary-alcohol derived carbamates, cyclization of α-branched guanidines (entries 3 and 4) can be promoted with reasonable success.[17] Oxidation of *N*-pentylguanidine (entry 5), although low yielding, gives only the five-membered imidazoline product in keeping with results from both carbamate and urea studies. Finally, it should be noted that the Tces group serves as a useful, robust protecting agent for the polar guanidine moiety. The insertion products are easily purified by normal phase chromatography on silica gel. Ultimately, the Tces group can be cleaved smoothly and quantitatively using powdered Zn (5 equiv) in 1:1 AcOH/MeOH to give the deprotected guanidinium salt (purified by rp HPLC).[18]

Table 3. C−H Insertion of *N*-Tces Alkylguanidine Substrates

entry	substrate	product	% yield[a]
1			57
2			80
3			54
4			91[b]
5			30

[a] Reactions were conducted with 2 mol % of $Rh_2(esp)_2$, 1.65 equiv of $PhI(OAc)_2$, and 2.5 equiv of MgO in toluene at 40 °C. [b] Product formed as a single diastereomer based on ^1H NMR analysis.



Selective and efficient C−H amination of urea- and guanidine- derived substrates has been achieved with the advent of $Rh_2(esp)_2$. This catalyst in combination with an inexpensive oxidant, MgO, and toluene as solvent makes possible the facile assembly of complex 1,2-diamine derivatives in the form of imidazolidin-2-ones and 2-aminoimidazolines. Such heterocycles are ubiquitous structural elements in natural and designed compounds, thus conferring these oxidative methods with a large degree of practical value. The expanding number of substrates that are now viable for C−H amination reactions should promote further these methods as essential tools for chemical synthesis.

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Supporting Information Available: General experimental protocols and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) 2,2,2-Trichloroethylsulfamate ($TcesNH_2$) is now available from Aldrich Chemical Co. It may also be readily prepared from Cl_3CCH_2OH and $ClSO_2NCO$ in a single step. We have employed $TcesNH_2$ for Rh-catalyzed intermolecular C−H amination and alkene aziridination; see: ref 4 and Guthikonda, K.; Du Bois, J. *J. Am. Chem. Soc.* **2002**, *124*, 13672−13673, respectively.

(15) For a preparation of related *N*-arenesulfonyl imidodithionates, see: Gompper, R.; Hägele, W. *Chem. Ber.* **1966**, *99*, 2885−2899. For use of these reagents in guanidine synthesis, see: Bosin, T. R.; Hanson, R. N.; Rodricks, J. V.; Simpson, R. A.; Rapoport, H. *J. Org. Chem.* **1973**, *38*, 1591−1600.

(16) (a) Saulnier, M. G.; Frennesson, D. B.; Deshpande, M. S.; Hansel, S. B.; Vyas, D. M. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1985−1990. (b) Neidlein, R.; Haussmann, W. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 521−522.

(17) Many secondary alcohol-derived carbamates (e.g., cyclohexyl carbamate) react with $PhI(OAc)_2$ under Rh-catalysis to give ketone products (cyclohexanone). We believe that this undesired reaction is the result of either intramolecular C−H insertion or C−H abstraction at the α-center. See refs 1a and 10 for details.

(18) The analogous conditions when employed with Tces-protected imidazolidin-2-ones failed to cleave the N−S bond, thus giving the product as the *N*-sulfated cyclic urea. Preliminary investigations indicate that strongly acidic conditions (e.g., 6 M HCl) may be needed to liberate the fully deprotected urea product.