Published in final edited form as:
Chem Commun (Camb). 2012 August 7; 48(61): 7568–7570. doi:10.1039/c2cc33401a.

α-Amination of keto-nitrones *via* Multihetero-Cope rearrangement employing an imidoyl chloride reagent†

Justin T. Malinowski, **Ericka J. Malow**, and **Jeffrey S. Johnson**
Department of Chemistry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-3290, United States

Jeffrey S. Johnson: jsj@unc.edu

Abstract

α-Aminations of ketone-derived nitrones have been developed *via* [3,3]-rearrangement of the intermediates generated upon condensation with imidoyl chlorides. Careful reagent selection provides synthetically attractive amino protecting groups. The enediamide or α′-carbamoyl enamide products can be hydrolyzed to the desired carbonyl, or exposed to electrophiles for further α-functionalization.

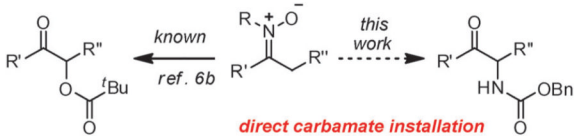
α-Amino carbonyls are ubiquitous in organic chemistry. Creation of this functional group *via* C_α–N bond construction is a central challenge in organic synthesis that has received considerable attention in the literature.[1] The electrophilic α-amination of enolates and their equivalents is in principle a direct, efficient method for α-amino carbonyl synthesis and significant work on this problem has been reported. Azodicarboxylates are especially prominent N(+)-sources that have been widely and effectively applied to this reaction, including asymmetric variants,[2] but come with several drawbacks. Atom inefficiency, explosion hazard,[3] and typically harsh or multistep deprotection protocols to reveal the amine somewhat counterbalance the favourable reactivity profile. Thus, an argument can be made that an important but often-overlooked component of the electrophilic α-amination problem lies in the "packaging" of the amine product. Previous studies by our group made use of a weak N–O bond for electrophilic amination methodology,[4] and we questioned whether this tactic could be harnessed to provide convenient nitrogen protecting groups (*e.g.* Boc, Fmoc, Cbz) concomitantly upon α-amination. The purpose of this communication is to report a [3,3]-rearrangement of imidoyl nitrones providing α-amination products with synthetically-attractive amino protecting groups.

[3,3]-Sigmatropic rearrangements are important reactions for the reliable introduction of various functionality in complex settings.[5] Multihetero-[3,3]-rearrangements, such as those of *N*-alkyl-*N*-acetoxyenamines, are an important subclass.[6] Coates and Cummins were the first to develop this rearrangement as a method for α-functionalization: treatment of *N*-^{t}Bu nitrones with acyl chlorides provide α-acyloxy carbonyls (eqn (1)).[6*b*] Extension of this strategy to achieve α-amination has been scarcely pursued. The use of an imidoyl chloride rather than an acyl chloride in the condensation with a keto-nitrone afforded α-amido ketone products in two preliminary investigations.[7] The imidoyl electrophiles used (Y, Z = Ph *or* Y

†Electronic supplementary information (ESI) available: Experimental details and characterization data for new compounds. See DOI: 10.1039/c2cc33401a

Correspondence to: Jeffrey S. Johnson, jsj@unc.edu.

= Ph, Z = Me (Scheme 1)) provided *N*-Ph/Me-benzoylamino products that would be difficult to convert to the free α-amino ketones.



(1)

In formulating a reaction design for an α-amination that proceeds with concurrent generation of synthetically-attractive protecting groups, we envisioned that a [3,3]-rearrangement involving an appropriately functionalized imidoyl chloride reagent could be useful (Scheme 1). Herein, we disclose an α-amination protocol for keto-nitrone substrates *via* [3,3]-rearrangement. The α-amino products obtained are conveniently configured as benzyl carbamates (NH–Cbz). An unexpected deprotonation event occurs with acyl migration to furnish enediamide or α′-carbamoyl enamide products dependent on the α-proton availability on the nitrone substrate (*vide infra*).

The requisite keto-nitrones were prepared *via* hydroxylamine/ketone condensation.[8] A variety of enolizable ketones were employed with aryl, alkyl, and cyclic substrates providing varied yields (13–88%) of nitrone product.[9] These compounds are stable to SiO_2 chromatography and can be stored in a freezer indefinitely. The Cbz-protected trifluoromethyl imidoyl chloride **1** was synthesized *via* the published two step route.[10]

The reaction of cyclopentanone-derived nitrone **2** and the imidoyl chloride **1** in the presence of Et_3N at 0 °C led to rapid and complete reagent consumption. Analysis of the crude reaction mixture showed formation of an α′-carbamoyl enamide product (**3**), rather than the anticipated α-amino imine or ketone (Scheme 2). This was rationalized *ex post facto* by a 1,4-trifluoroacetyl migration/proton transfer[6a] of the initial [3,3]-imine product (**5** → **3**, Scheme 2). At this time it is unclear whether the system is under kinetic or thermodynamic control, although the formation of α′-carbamoyl enamide products (deprotonation at the less-hindered site) suggests a kinetic scenario. Equimolar quantities of nitrone and reagent **1** treated with 2.0 equiv. triethylamine provided the optimal results for this transformation when run in CH_2Cl_2 at 0 °C. The reaction was usually complete within 30 min.

A divergence in reactivity was observed when acetophenone-derived nitrone **6** was subjected to identical conditions. In the absence of an α′-enolizable proton, terminal deprotonation occurred at the α-site furnishing the enediamide product (**9** → **7**, Scheme 3).

With optimized conditions in hand and two product classes identified, we explored the scope of the [3,3]-rearrangement/α-amination. Nitrones derived from acetophenone derivatives provided moderate yields ranging from 49–66% (**7**, **10–12**, Table 1). The enediamide moiety was formed exclusively in the (*Z*)-configuration. When a propiophenone-derived nitrone was used, the product geometry was reversed (**12**), presumably due to increased $A^{1,3}$-strain introduced by the methyl substituent (*vs.* −H). Cyclic nitrones also performed well in the [3,3]-rearrangement (Table 2). Cyclopentyl and cyclohexyl substrates provided α′-carbamoyl enamides in 64–78% yields (**3**, **13–16**). The use of a 4-^{t}Bu-cyclohexanone derived nitrone decreased the yield and provided minimal diastereoselectivity (**17**).

The nitrone *N*-benzyl protecting group was varied, using the cyclopentyl core as a model. Several substituted benzyl nitrones were examined, with the tolyl group providing the

highest yield (**14**). A chiral nitrone derived from (*S*)-α-methyl benzylamine was synthesized and tested,[11] but chirality transfer was poor (**18**).

The acetone-derived nitrone provided the enediamide **19** rather than the isomeric α′-carbamoyl enamide. In this case and other examples reported with diminished yields, competing reactions producing unknown byproducts account for the mass balance. The cyclohexenone-derived nitrone displayed unique reactivity wherein the chloride byproduct was incorporated yielding *cis*-β′-chloro-α′-carbamoyl enamide **20**.

Both the enediamide and α′-carbamoyl enamide products are resistant to hydrolysis and survive acidic or basic aqueous workup; however, after extensive screening of conditions, basic hydrolysis was realized upon treatment with freshly prepared sodium benzylthiolate in MeOH. Subjecting the enamide **3** to these conditions cleanly provided the Cbz-protected α-amino ketone **21** in 85% yield (**A**, Scheme 4). Enediamide product **7** was also hydrolyzed upon thiolate exposure and subsequent acidic workup. In this case, partial tranesterification occurred providing the methoxy-carbamyl protected α-amino ketone as a minor product (**B**, Scheme 4). A one-pot procedure taking nitrone starting material directly to the Cbz-protected α-amino ketone **21** was also realized by treating the crude reaction product from the [3,3]-α-amination with NaSBn/MeOH. This sequence resulted in a yield of 69%, significantly higher than the analogous two-step process (**C**, Scheme 4).

The enamide in both product classes provides opportunities for further α-functionalization. Exposure of enamide **3** to Br_2 provided hemiaminal oxazolidinone **23** from bromination-debenzylation (**D**, Scheme 4).

In conclusion, we have developed an α-amination of keto-nitrones *via* multiheteroatom-[3,3]-rearrangement. This reaction provides enediamide or α′-carbamoyl enamide products based on the enolizable sites on the substrates employed. Upon basic hydrolysis, carbonyl functionality may be revealed providing a new method for carbonyl α-amination. Ongoing studies in our laboratory are focused on extending this method to aldo-nitrones and development of an asymmetric variant.

Supplementary Material

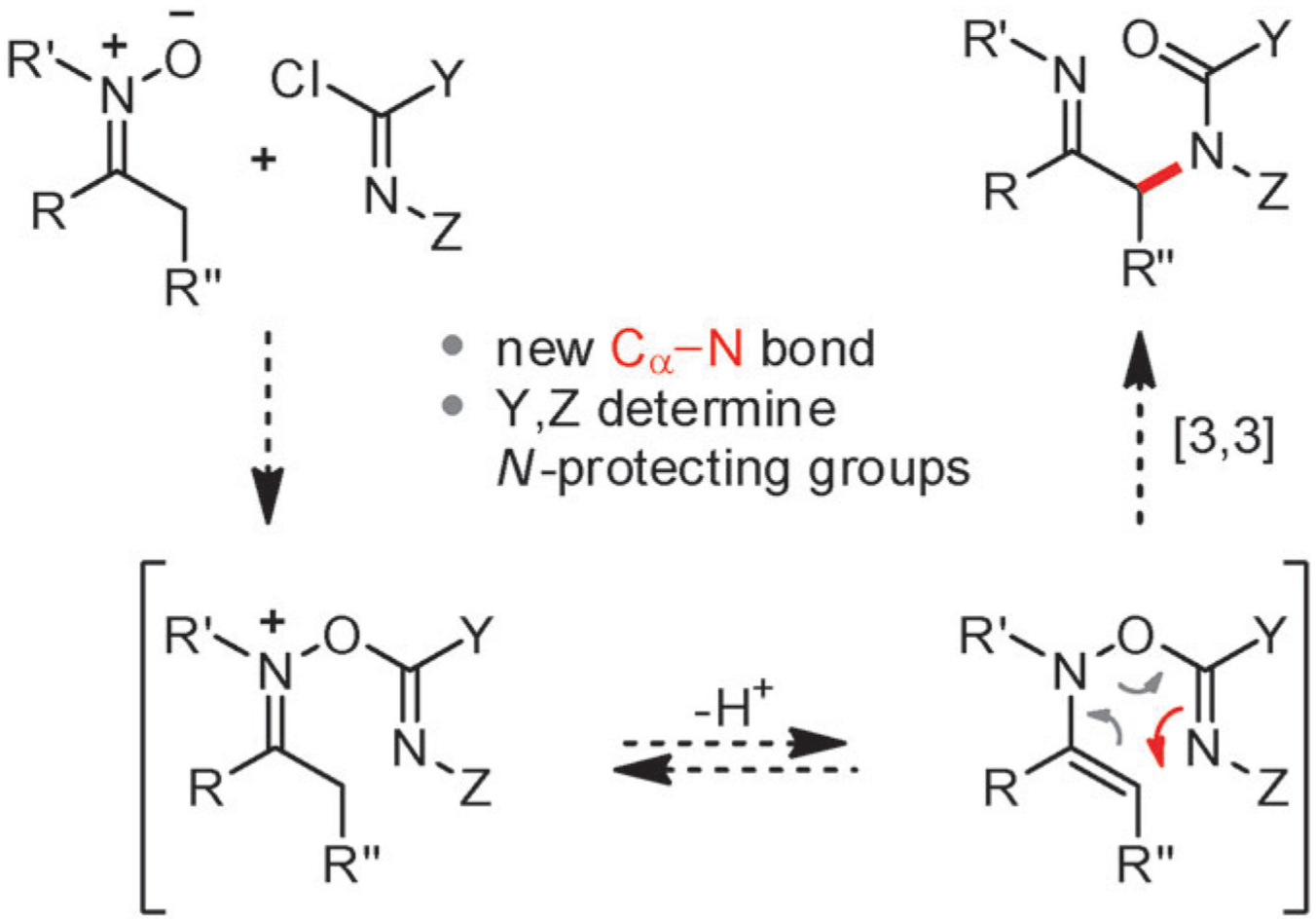
Refer to Web version on PubMed Central for supplementary material.

Notes and references

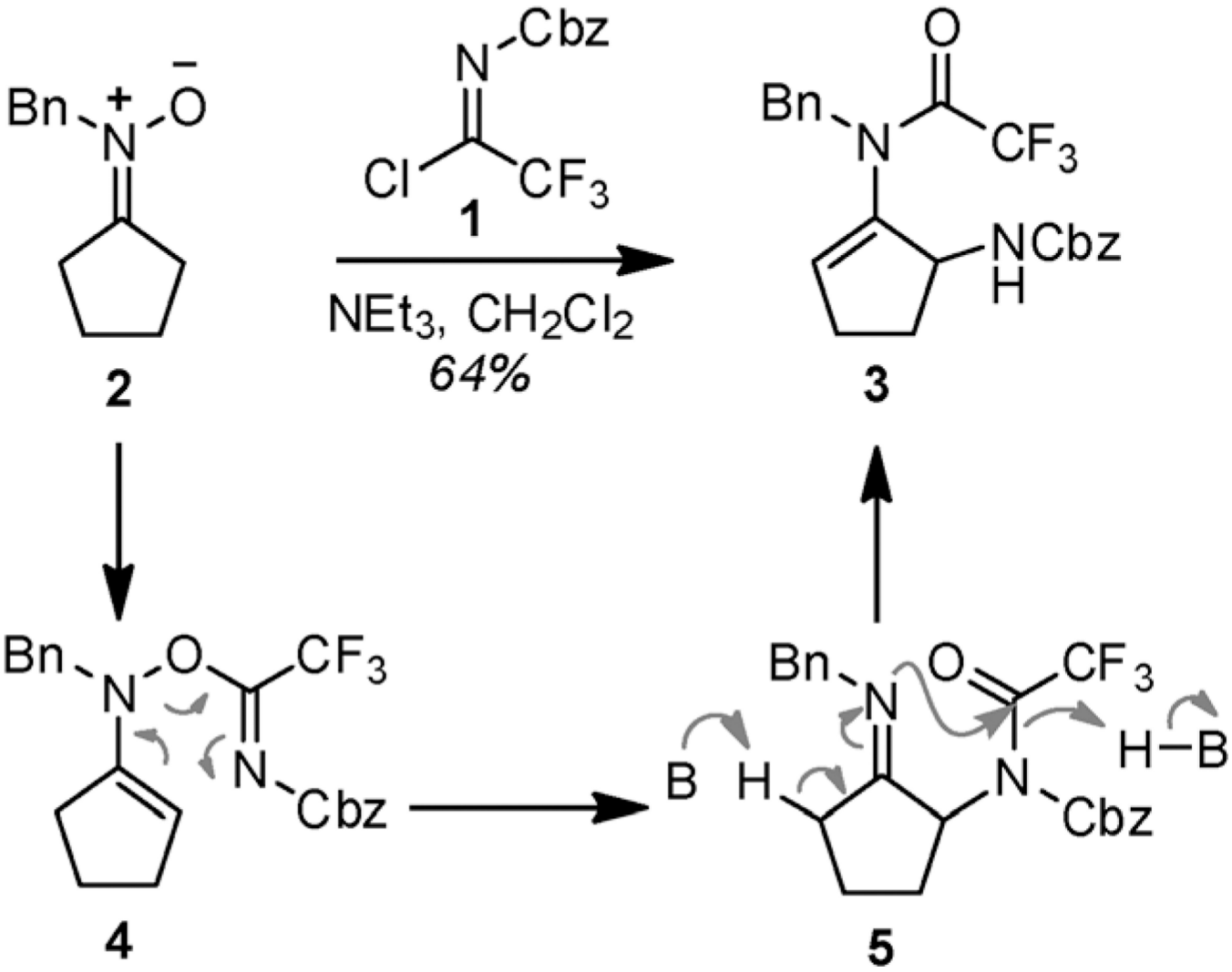
1. For reviews on electrophilic α-amination see: Boche G. Helmchen G, Hoffmann RW, Mulzer J, Schaumann E. Stereoselective Synthesis. 1996; vol. 9StuttgartThieme:5133–5157. Greck C, Genet JP. Synlett. 1997:741. Ciganek E. Org. React. 2009:1–36. Genet JP, Greck C, Lavergne D. Ricci A. Modern Amination Methods. 2000; ch. 3Weinheim, GermanyWiley-VCH Janey JM. Angew. Chem. 2005; 117:4364. (*Angew. Chem., Int. Ed.*, 2005, **44**, 4292).
2. (a) Evans DA, Johnson DS. Org. Lett. 1999; 1:595. [PubMed: 10823188] (b) Juhl K, Jørgensen KA. J. Am. Chem. Soc. 2002; 124:2420. [PubMed: 11890774] (c) Marigo M, Jørgensen KA. Chem. Commun. 2006:2001.(d) Bøgevig A, Juhl K, Kumaragurubaran N, Zhuang W, Jørgensen KA. Angew. Chem. 2002; 114:1868. (*Angew. Chem., Int. Ed.*, 2002, **41**, 1790); (e) Hayashi Y, Aratake S, Imai Y, Hibino K, Chen Q-Y, Yamaguchi J, Uchimaru T. Chem.–Asian J. 2008; 3:225. [PubMed: 18165948] (f) Yamashita Y, Ishitani H, Kobayashi S. Can. J. Chem. 2000; 78:666.(g) Evans DA, Nelson SG. J. Am. Chem. Soc. 1997; 119:6452.(h) List B. J. Am. Chem. Soc. 2002; 124:5656. [PubMed: 12010036] (i) Mouri S, Chen Z, Mitsunuma H, Furutachi M, Matsunaga S, Shibasaki M. J. Am. Chem. Soc. 2010; 132:1255. [PubMed: 20055386] (j) Kumaragurubaran N, Juhl K, Zhuang W, Bøgevig A, Jørgensen KA. J. Am. Chem. Soc. 2002; 124:6254. [PubMed: 12033850] (k) Bui T, Hernandez-Torres G, Milite C, Barbas CF III. Org. Lett. 2010; 12:5696. [PubMed: 21070065] (l) Bui T, Borregan M, Barbas CF III. J. Org. Chem. 2009; 74:8935.

[PubMed: 19950878] (m) Cheng L, Liu L, Wang D, Chen Y-J. Org. Lett. 2009; 11:3874. [PubMed: 19708700] (n) Qian Z-Q, Zhou F, Du T-P, Wang B-L, Zhou J. Chem. Commun. 2009:6753.

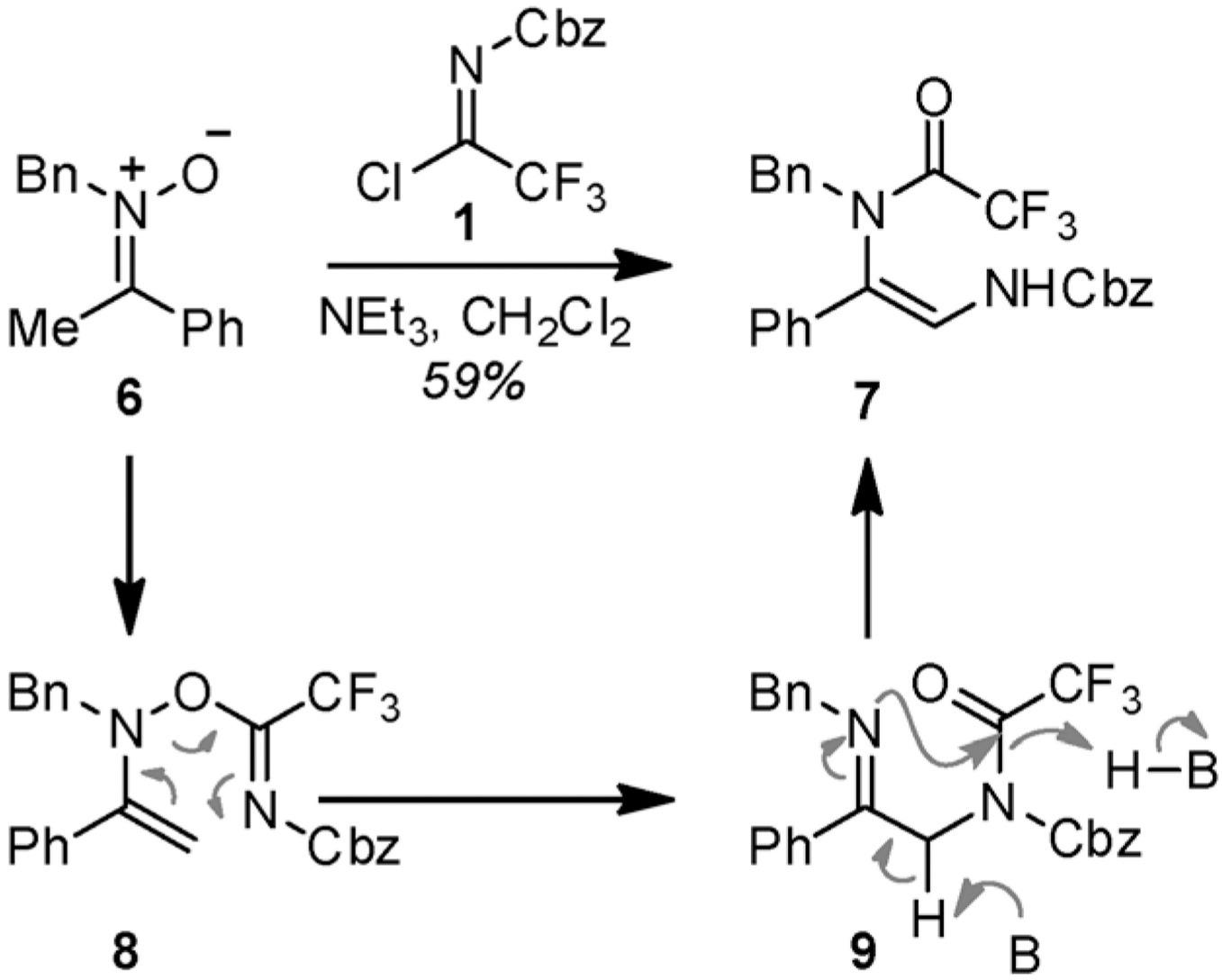
3. Berger A, Wehrstedt KD. J. Loss Prev. Process Ind. 2010; 23:734.
4. (a) Berman AM, Johnson JS. J. Am. Chem. Soc. 2004; 126:5680. [PubMed: 15125656] (b) Berman AM, Johnson JS. J. Org. Chem. 2006; 71:219. [PubMed: 16388639]
5. (a) Ilardi EA, Stivala CE, Zakarian A. Chem. Soc. Rev. 2009; 38:3133. [PubMed: 19847347] (b) Nubbemeyer U. Synthesis. 2003:961.
6. (a) House HO, Richey FA. J. Org. Chem. 1969; 34:1430.(b) Cummins CH, Coates RM. J. Org. Chem. 1983; 48:2070.(c) Beshara CS, Hall A, Jenkins RL, Jones KL, Jones TC, Killeen NM, Taylor PH, Thomas SP, Tomkinson NCO. Org. Lett. 2005; 7:5729. [PubMed: 16321033] (d) Hall A, Hugent EP, Jones KL, Jones TC, Killeen NM, Yau SC, Tomkinson NCO. Synlett. 2007:293.(e) Reis LV, Lobo AM, Prahhakar S, Duarte MP. Eur. J. Org. Chem. 2003:190.(f) Hofelmeier R, Blechert S. Angew. Chem., Int. Ed. Engl. 1982; 21:370.(g) Almeida PS, Lobo AM, Prabhakar S. Heterocycles. 1989; 28:653.(h) Porzelle A, Woodrow MD, Tomkinson NCO. Org. Lett. 2010; 12:1492. [PubMed: 20199033]
7. (a) Abramovitch DA, Abramovitch RA, Benecke H. Heterocycles. 1985; 23:25.(b) Lantos I, Zhang W-Y. Tetrahedron Lett. 1994; 35:5977.
8. Pfeiffer JY, Beauchemin AM. J. Org. Chem. 2009; 74:8381. [PubMed: 19791735]
9. See Supporting Information for nitrone scope and characterization data.
10. (a) Osipov S, Artyushin O, Kolomiets A, Bruneau C, Dixneuf P. Synlett. 2000:1031.(b) Karimova N, Vorobyeva D, Shchetnikov G, Osipov S. Russ. Chem. Bull. 2010; 59:107.
11. Breuning M, Hauser T, Tanzer E-M. Org. Lett. 2009; 11:4032. [PubMed: 19691351]



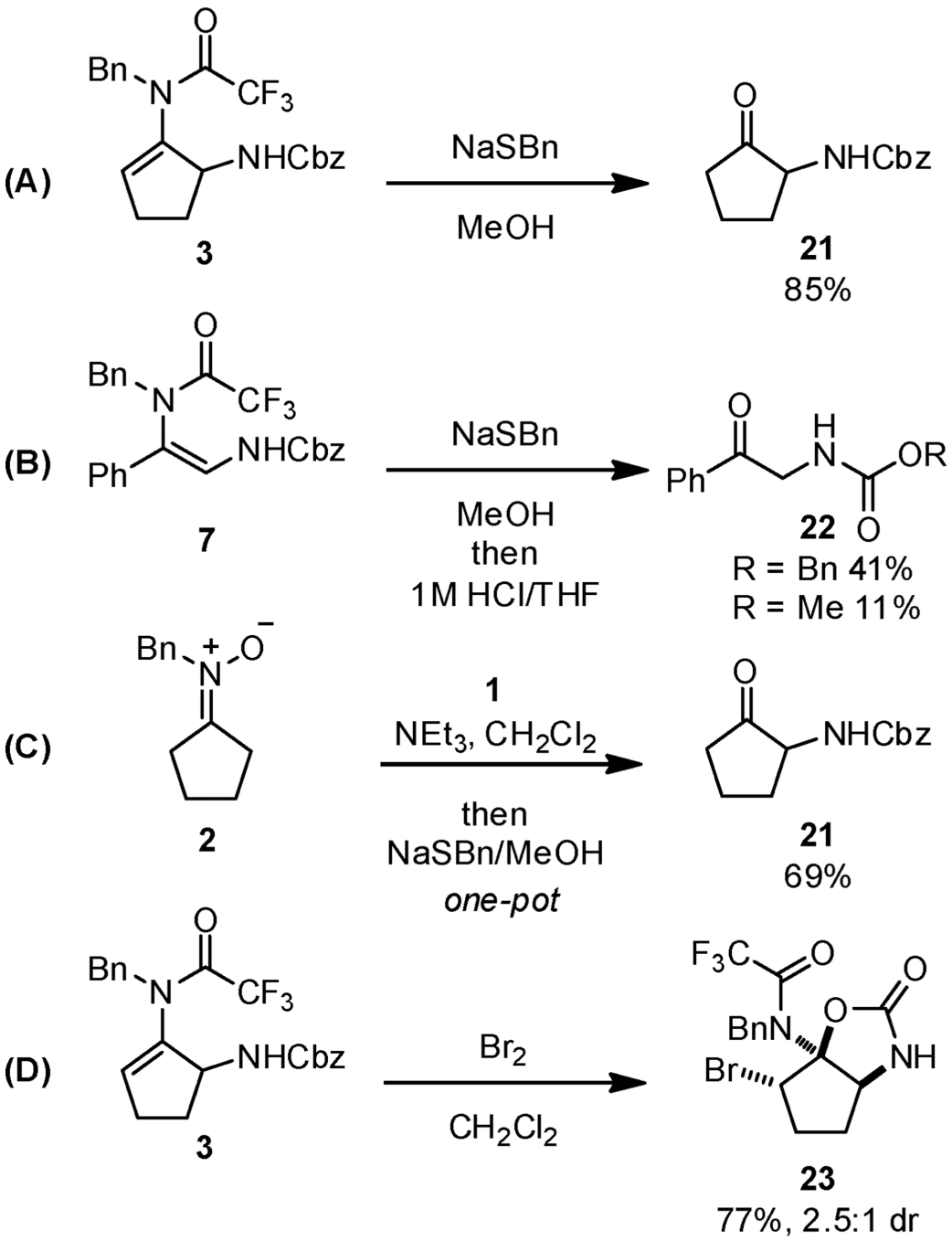
Scheme 1.
α-Amination *via* multiheteroatom [3,3]-rearrangement.



Scheme 2.
Initial result and proposed mechanism.



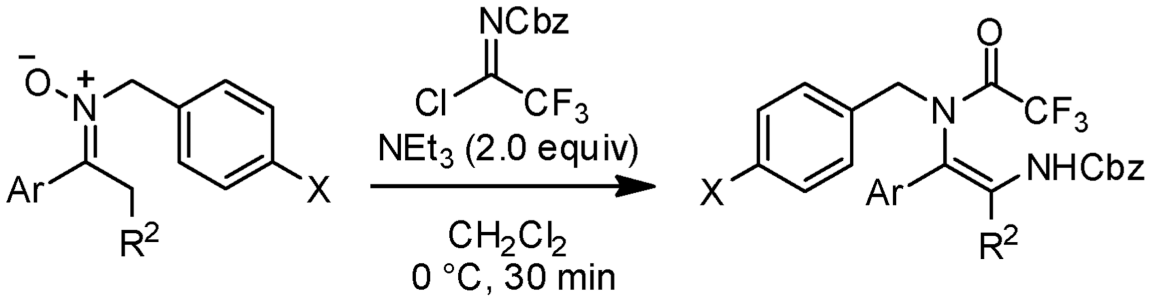
Scheme 3.
Divergent reactivity with aryl nitrone.

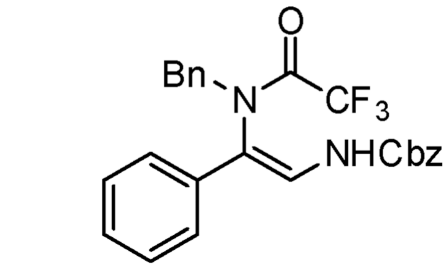


Scheme 4.
Secondary transformations.

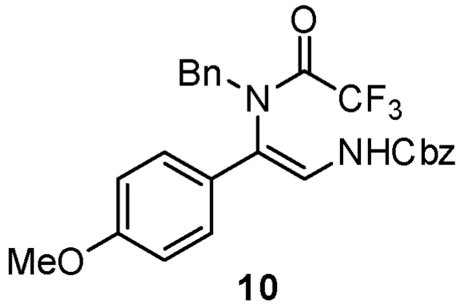
Table 1

Aryl nitrone scope[a,b,c]

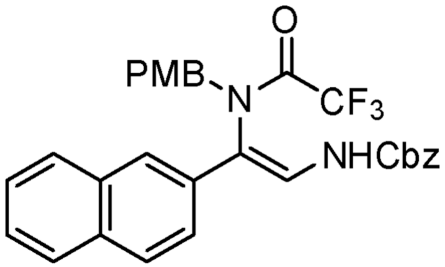




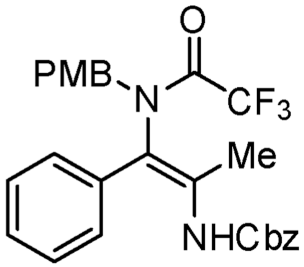
7
59%



10
66%



11
49%



12
68%

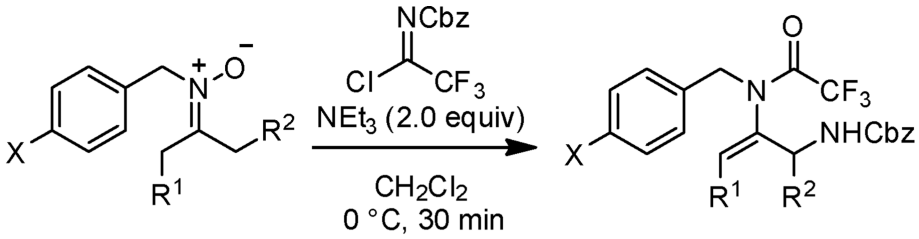
[a] All reactions: [**1**]$_0$ = 0.1 M.

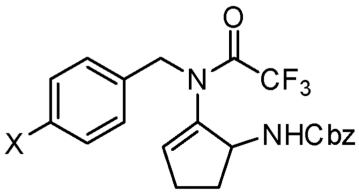
[b] Yields of isolated products.

[c] See Supporting Information for more details.

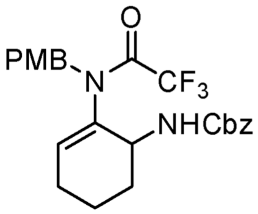
Table 2

Cyclic/alkyl nitrone scope[a,b,c]

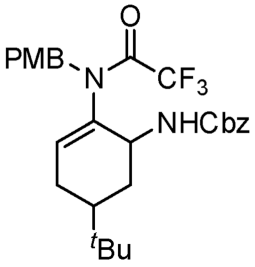




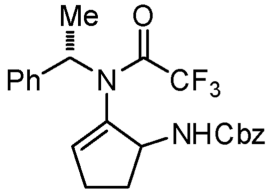
X = H **3** 64%
OMe **13** 64%
Me **14** 78%
Cl **15** 66%



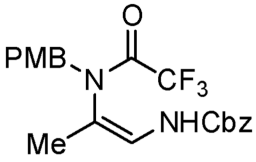
16
66%



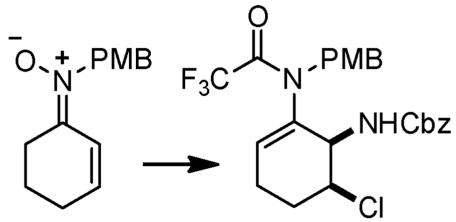
17
46%, 1.5:1 dr



18
45%, 1:1 dr



19
43%



20
80%

[a]All reactions: [**1**]$_0$ = 0.1 M.

[b]Yields of isolated products; dr determined by ^{1}H NMR spectroscopy.

[c] See Supporting Information for more details.