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One-Pot Synthesis of Bicyclic β-Alkoxy Amides from Cyanohydrin Ethers

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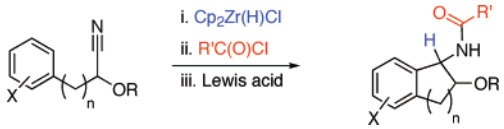
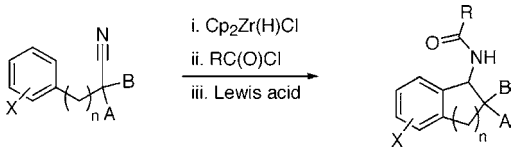
ABSTRACT



In this manuscript we report that intramolecular Friedel–Crafts alkylation reactions of aryl-substituted α-alkoxy acylimines proceed in the presence of mild Lewis acids to afford bicyclic β-alkoxy amides. The intermediate acylimines are prepared through cyanohydrin ether hydrozirconation and acylation of the resulting metalloimine, providing an operationally facile one pot protocol. A two-step variant of the procedure has also been developed to effect cyclizations from acylimines that undergo competitive tautomerization.

An important objective in developing projects for diversity oriented synthesis[1] is to devise new molecular scaffolds that uniquely orient functional groups in chemical space.[2] Reactions that rapidly increase the complexity of readily available precursors through ring formation or stereocenter introduction are quite useful for achieving this objective. We have initiated a program that exploits the capacity of electrophilic acylimines to react with a range of nucleophiles in the preparation of structurally diverse libraries of amides.[3] The acylimines are derived from easily accessible nitriles through a sequence of hydrozirconation and acylation.[4] While our previous efforts have been directed toward bimolecular nucleophilic additions that form carbon−heteroatom bonds, we envisioned that this process could also be applied to intramolecular nucleophilic additions that produce carbocyclic structures in a single operation (Scheme 1). In this manuscript we report that nitrile-derived acylimines[5] engage in Lewis acid-mediated Friedel−Crafts alkylation reactions[6] to form indanyl or tetrahydronaphthyl amides. Employing cyanohydrin ether

Scheme 1. Annulation through Nitrile Hydrozirconation, Acylation, and Friedel−Crafts Alkylation



(1) (a) Schreiber, S. L. *Science* **2000**, *287*, 1964. (b) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46. (c) Spring, D. R. *Chem. Soc. Rev.* **2005**, *34*, 472. (d) Tan, D. S. *Nat. Chem. Biol.* **2005**, *1*, 74. (e) Arya, P.; Joseph, R.; Gan, Z.; Rakic, B. *Chem. Biol.* **2005**, *12*, 163.

(2) Recent examples: (a) Brummond, K. M.; Mitasev, B. *Org. Lett.* **2004**, *6*, 2245. (b) Chen, C.; Li, X.; Neumann, C. S.; Lo, M. M.-C.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 2249. (c) Stevens, B. D.; Nelson, S. G. *J. Org. Chem.* **2005**, *70*, 4375. (d) Wipf, P.; Walczak, M. A. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 4172. (e) Mitasev, B.; Yan, B.; Brummond, K. M. *Heterocycles* **2006**, *70*, 367. (f) Dandapani, S.; Duduta, M.; Panek, J. S.; Porco, J. A., Jr. *Org. Lett.* **2007**, *9*, 3849. (g) Sunderhaus, J. D.; Dockendorff, C.; Martin, S. F. *Org. Lett.* **2007**, *9*, 4223. (h) Ng, P. Y.; Tang, Y.; Knosp, W. M.; Stadler, H. S.; Shaw, J. T. *Angew. Chem., Int. Ed.* **2007**, *46*, 5352. (i) Luo, T.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 8250. (j) Su, S.; Porco, J. A., Jr. *Org. Lett.* **2007**, *9*, 4983.

(3) Wan, S.; Green, M. E.; Park, J.-H.; Floreancig, P. E. *Org. Lett.* **2007**, *9*, 5385.

(4) Maraval, A.; Igau, A.; Donnadieu, B.; Majoral, J. P. *Eur. J. Org. Chem.* **2003**, 385.

(5) For reviews of acylimines and related species, see: (a) Petrini, M.; Torregiani, E. *Synthesis* **2007**, 159. (b) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431. (c) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817.

(6) For recent examples of intermolecular Friedel-Crafts reactions with acylimines and related species, see: (a) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 11804. (b) Wang, Y.-Q.; Song, J.; Hong, R.; Li, H.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 8156. (c) Ballini, R.; Palmieri, A.; Petrini, M.; Torregiani, E. *Org. Lett.* **2006**, *8*, 4093. (d) Terada, M.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 292. (e) Kang, Q.; Zhao, Z.-A.; You, S.-L. *J. Am. Chem. Soc.* **2007**, *129*, 1484. (f) Rowland, G. B.; Rowland, E. B.; Liang, Y.; Perman, J. A.; Antilla, J. C. *Org. Lett.* **2007**, *9*, 2609. (g) Tussetschläger, S.; Baro, A.; Laschat, S.; Frey, W. *Eur. J. Org. Chem.* **2007**, 5590.

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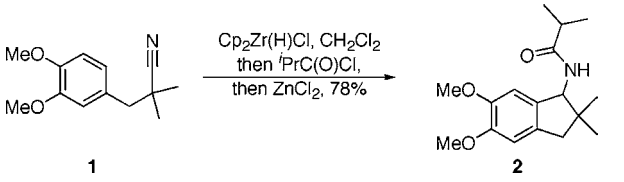
substrates leads to the formation of bicyclic β-alkoxy amides with good to excellent levels of diastereocontrol. We also report a two step variation of this method that can be applied to acylimines that undergo tautomerization faster than nucleophilic addition in the one-step protocol.

To test the viability of this protocol, we prepared nitrile **1** and subjected it to hydrozirconation, acylation with isobutyroyl chloride, and activation with $ZnCl_2$ (Scheme 2). This

Scheme 2. Annulation through Nitrile Hydrozirconation and Acylation

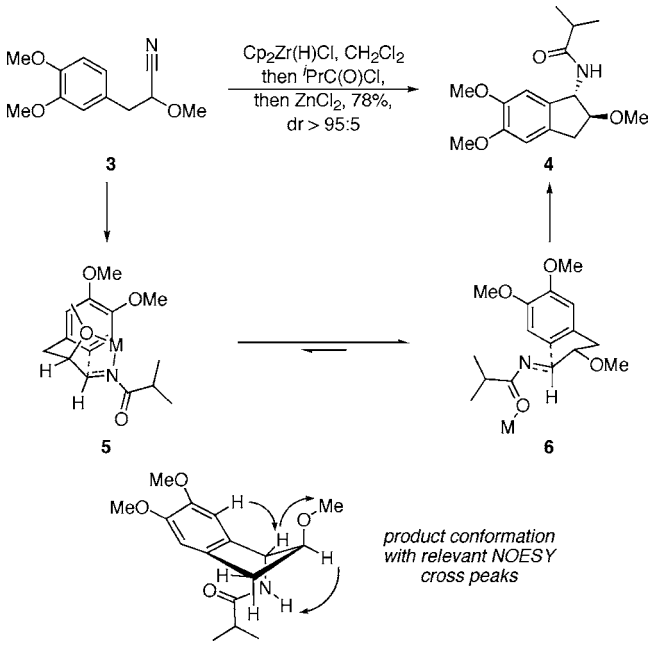


1 **2**

reaction provided indanyl amide **2** in 78% yield. Optimal yields were observed when CH_2Cl_2 was employed as the solvent, and the activating methoxy group and Lewis acid were required to promote cyclization.

Nitrile **3**, which lacks the geminal methyl groups that facilitate cyclization through the gem-dialkyl effect, was subjected to the sequence (Scheme 3) to provide β-alkoxy

Scheme 3. Cyclization of a Cyanohydrin Ether and Product Conformation



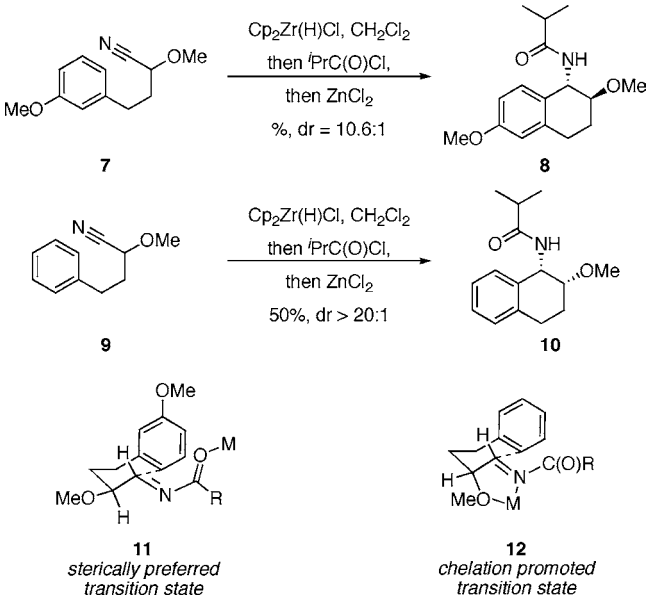
3 **4** **5** **6**

product conformation with relevant NOESY cross peaks

amide **4** in 78% yield and with nearly complete diastereocontrol. The *trans*-orientation of the amido group and the methoxy group were confirmed through NOESY studies (key cross-peaks are shown in Scheme 3) and through coupling constant and chemical shift analogy with a related structure that was prepared from commercially available *trans*-1-amino-2-indanol. This stereochemical outcome is consistent with cyclization through conformer **6** rather than chelated conformer **5**. This outcome can also be explained through the methoxy and acylimine groups adapting pseudoaxial orientations in the transition state (not shown).[7] The trans-diaxial geometry in the transition state would be consistent with the Cornforth model,[8] which has generated a revived interest.[9] The surprising preference for reaction through the nonchelated structure[10] can be rationalized by the untoward steric interactions in **5**. Notably, as indicated by $^1H-^1H$ coupling constants, the amido and alkoxy groups in **4** are aligned in pseudoaxial orientations to alleviate allylic strain.

Cyclization reactions that yield tetrahydronaphthyl amides proceed much more readily than those that form indanyl amides. As shown in Scheme 4, nitrile **7**, which contains an

Scheme 4. Tetrahydronaphthyl Amide Preparation



7 **8** **9** **10**

11 *sterically preferred transition state*

12 *chelation promoted transition state*

electron rich arene nucleophile, reacts instantaneously in the presence of $ZnCl_2$ and can cyclize in the absence of a Lewis acid, albeit less efficiently. Arenes that lack an electron dontating group at the *para*-position, such as **9**, can be used as nucleophiles with $ZnCl_2$ acylimine activation. The stereochemical outcomes in these reactions is critically dependent upon the cyclization rate. Rapid cyclizations proceed through the sterically favored conformation **11**. Slower cyclizations occur through Cram chelate-like conformer **12**. While chelation is disfavored in the construction of indanyl

(7) We thank an anonymous referee for bringing this possibility to our attention.

(8) Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K. *J. Chem. Soc.* **1959**, 112.

(9) (a) Evans, D. A.; Siska, S. J.; Cee, V. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 1761. (b) Marco, J. A.; Carda, M.; Díaz-Oltra, S.; Murga, J.; Falomir, E.; Roeper, H. *J. Org. Chem.* **2003**, *68*, 8577. (c) Cee, V. J.; Cramer, C. J.; Evans, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 2920.

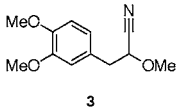
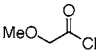
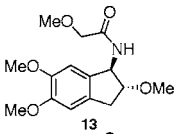
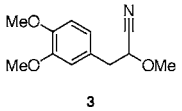
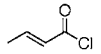
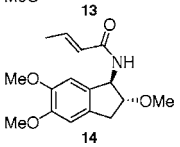
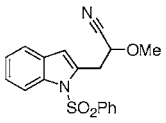
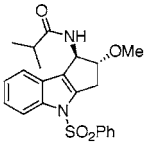
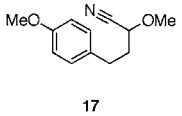
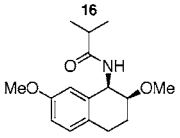
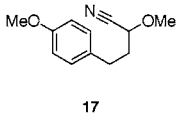
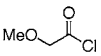
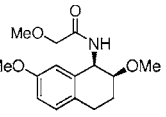
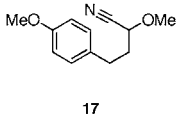
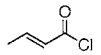
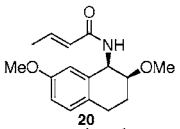
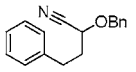
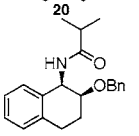
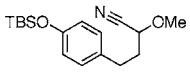
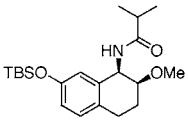
(10) Activation by Lewis acid coordination to the nitrogen of the acylimine in **6** is also reasonable.

amides, the higher homologs react smoothly because the additional methylene group eliminates the steric interations that are present in conformer **5**.

Further studies on the scope of the process are summarized in Table 1. Oxygen-containing (entries 1 and 5) and unsaturated (entries 2 and 6) acid chlorides are tolerated in the scheme. Sulfonyl indoles are suitable nucleophiles for the reaction (entry 3), demonstrating that the scope of products that are available through the protocol includes electron rich heterocyclic structures. Functionalized arenes can engage in the chelation-promoted tetrahydronaphthyl amide formation when the group is *meta* to the forming bond (entries 4−6 and 8). Cyanohydrin benzyl ethers are effective substrates (entry 7), thereby demonstrating the capacity for alkoxy group variation in library syntheses. The diminished stereoselectivity that results from the use of a benzyl ether rather than a methyl ether is consistent with Keck's observations[11] that benzyl ethers are less likely than methyl ethers to engage in chelation. A silylated phenol can be used as the nucleophilic group (entry 8). Given the capacity to convert aryl silyl ethers to aryl triflates and the versatility of aryl triflates in transition metal-mediated bond-forming processes,[12] this substrate class is well-suited for further library development.

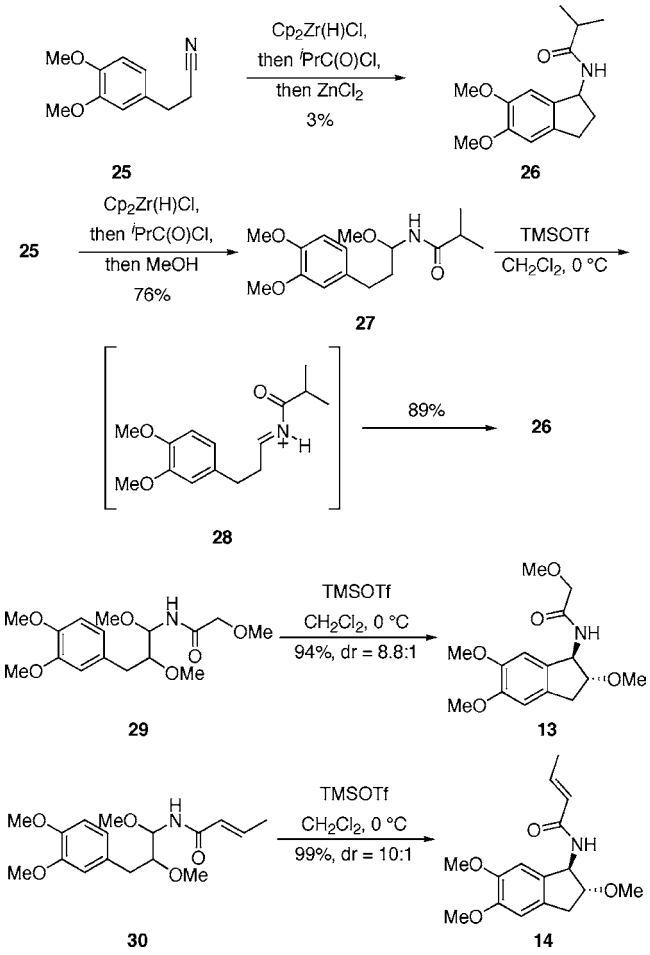
Nitriles that do not have a substituent at the α-position are poor substrates for the process, as observed in the attempted conversion of **25** to **26** (Scheme 5). This can be attributed to the intermediate acylimine undergoing tautomerization and subsequent decomposition faster than nucleophilic addition under these reaction conditions. To promote cyclization reactions from nitriles that lack substitution at the α-position, we devised a two-step variant of the method. In this sequence, the nitrile is converted to a stable, isolable acyl aminal through our recently reported method[3]

Table 1. Scope of the Annulation Reaction[a]

entry	nitrile	electrophile	major product	yield (dr)
1	 **3**		 **13**	60% (5:1)
2	 **3**		 **14**	53% (5.6:1)
3	 **15**		 **16**	57% (8.7:1)
4	 **17**		 **18**	56% (>19:1)
5	 **17**		 **19**	58% (4.8:1)
6	 **17**		 **20**	52% (3.4:1)
7	 **21**		 **22**	58% (3.7:1)
8	 **23**		 **24**	50% (9.1:1)

[a] Representative procedure: $Cp_2Zr(H)Cl$ (1.2 equiv) is added to a solution of the nitrile (1 eq) in CH_2Cl_2. After stirring for 10 min at rt, the electrophile (1.5 equiv) and $ZnCl_2$ (1.5 equiv) are added and the mixture stirs for several hours. See the Supporting Information for details.

Scheme 5. Cyclization through a Two-Step Protocol



(11) (a) Keck, G. E.; Castellino, S.; Wiley, M. R. *J. Org. Chem.* **1986**, *51*, 5478. (b) Keck, G. E.; Wager, C. A. *Org. Lett.* **2000**, *2*, 2307.

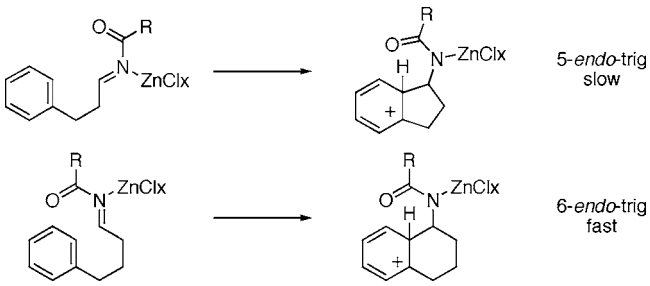
(12) Ritter, K. *Synthesis* **1993**, 735.

in which MeOH acylimine addition proceeds faster than decomposition. The acyl aminal is then ionized to form an acyliminium ion by treatment with TMSOTf, in accord with Kobayashi's studies.[13] Through this sequence, nitrile **25** was converted to acyl aminal **27**. Exposing **27** to TMSOTf led to the formation of acyliminium ion **28** and cyclization to yield indanyl amide **26** in 89% yield. This method is also effective for promoting cyclizations from acyl aminals that are accessed from cyanohydrin ethers, with indanyl amides **13** and **14** being formed in >90% yields from acyl aminals **29** and **30**. These reactions proceed with somewhat higher diastereocontrol than those that utilize the one-pot protocol.

A final noteworthy issue in this study concerns the relative cyclization rates in the formation of the indanyl and tetrahydronaphthyl ring systems. From the perspective of the acylimine addition, these processes are 5-*exo*-trig and 6-*exo*-trig cyclizations,[14] repectively. Therefore, the substantially faster cyclization to form the tetrahydronaphthyl system appears to be somewhat unexpected. However, from the perspective of the arene, initial cyclization step (Scheme 6) to form the indanyl ring system is a 5-*endo*-trig cyclization and thus would be expected to be slower than the 6-*endo*-trig cyclization that forms the tetrahydronaphthyl system.

We have reported a one step protocol for the conversion of cyanohydrin ethers to bicyclic β-alkoxy amides through a sequence of cyanohydrin ether hydrozirconation, acylation, and intramolecular Friedel−Crafts alkylation. The reactions generally proceed efficiently and with good to excellent levels of diastereocontrol. These reactions proceed in a reasonable time frame at ambient temperature. For substrates in which cyclization is not kinetically competitive with intermediate acylimine decomposition through tautomerization, the bicyclic product can be formed by a two step sequence. In this sequence, the acylimine is trapped through a rapid reaction with MeOH and acyliminium ion formation is effected by treating the resulting acyl aminal with TMSOTf. The ability to vary functional groups on the arene, the acyl group, and the alkoxy group and the capacity to form five- and six-membered rings make this route highly ammenable to applications in diversity oriented synthesis.

Scheme 6. Relative Cyclization Rates as a Function of the Initial Intermediate



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Supporting Information Available: Schemes for substrate preparation, experimental procedures for all reactions and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL8000409

(13) (a) Sugiura, M.; Kobayashi, S. *Org. Lett.* **2001**, *3*, 477. (b) Sugiura, M.; Hagio, H.; Hirabayashi, R.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 12510. For a related procedure, see: Fleming, J. J.; Williams, K.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 2028.

(14) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 738.