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# Multicomponent Synthesis of α-Branched Amides

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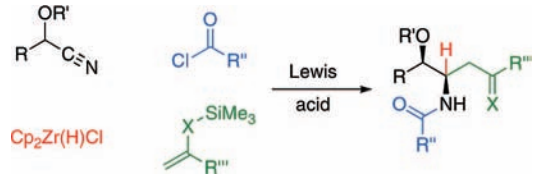
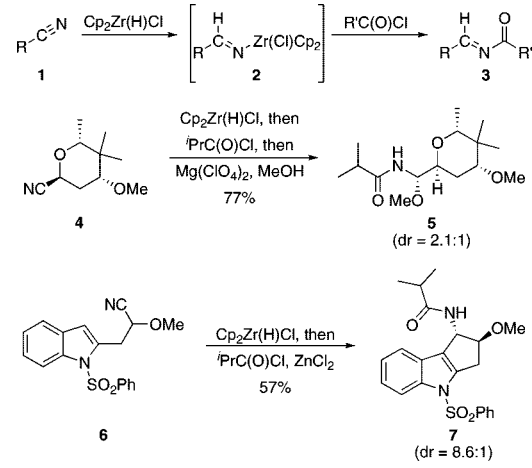
## ABSTRACT




**α-Branched amides are prepared by multicomponent reactions in which nitriles undergo hydrozirconation to form metalloimines that react with acyl chlorides. The resulting acylimines react with a variety of π-nucleophiles in the presence of Lewis acids to form the desired amides.**

Multicomponent reactions[1] have emerged as attractive processes for rapidly increasing molecular complexity and structural diversity.[2] Nitriles are well-suited to be substrates in multicomponent reactions because their polarization and multiple π-bonds create numerous opportunities for sequential addition processes. We have demonstrated[3] the viability of using nitriles in this capacity through the sequences that are shown in Scheme 1. Nitriles (**1**) react readily[4] with the Schwartz reagent ($Cp_2Zr(H)Cl$)[5] to form metalloimines (**2**) that add into acyl chlorides[6] to yield acylimines[7] (**3**). These acylimines are useful electrophiles for the formation of a wide range of amide-containing structures.[8] Specifically, we have shown that tetrahydropyranyl nitrile **4** can be transformed into acyl aminal **5** through hydrozirconation, acylation, and MeOH addition,[3a] and nitrile **6** can be converted to tricyclic amide **7** by employing an intramolecular Friedel−Crafts reaction as the nucleophilic addition step.[3b] In this paper, we show that this method can be applied to multicomponent syntheses of α-branched amides through

**Scheme 1.** Amide Formation from Nitrile Hydrozirconation




(1) (a) Dömling, A. *Chem. Rev.* **2006**, *106*, 17. (b) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602. (c) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem.—Eur. J.* **2000**, *6*, 3321.

(2) (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.

(3) (a) Wan, S.; Green, M. E.; Park, J.-H.; Floreancig, P. E. *Org. Lett.* **2007**, *9*, 5385. (b) Xiao, Q.; Floreancig, P. E. *Org. Lett.* **2008**, *10*, 1139.

(4) (a) Erker, G.; Frömberg, W.; Atwood, J. L.; Hunter, W. E. *Angew. Chem., Int. Ed.* **1984**, *23*, 68. (b) Frömberg, W.; Erker, G. *J. Organomet. Chem.* **1985**, *280*, 343. (c) Anbhaikar, N. B.; Herold, M.; Liotta, D. C. *Heterocycles* **2004**, *62*, 217.

(5) $Cp_2Zr(H)Cl$ is commercially available, but we prefer to prepare it from $Cp_2ZrCl_2$. (a) Hart, D. W.; Schwartz, J. *J. Am. Chem. Soc.* **1974**, *96*, 8115. (b) Buchwald, S. L.; LaMaire, S. J.; Nielsen, R. B.; Watson, B. T.; King, S. M. *Org. Synth.* **1993**, *71*, 77.

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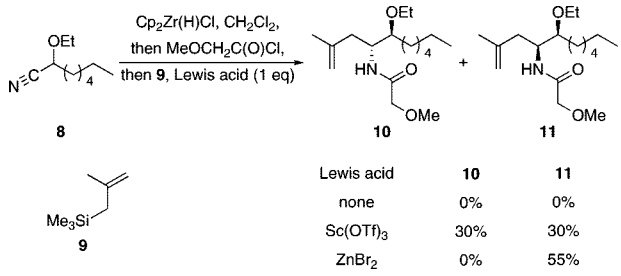
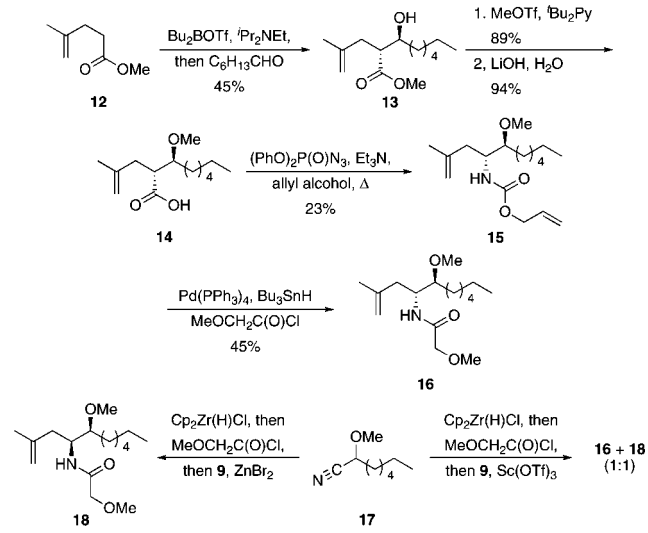
diastereoselective bimolecular additions of $\pi$-nucleophiles into nitrile-derived acylimines. We also report that acylimines that lack branching at the α-position can be tautomerized to form *E*-enamides.

We chose to investigate additions of $\pi$-nucleophiles into acylimines that are formed from cyanohydrin ether **8** (Scheme 2) in consideration of our observation[3b] that

**Scheme 2.** Bimolecular Carbon−carbon Bond Formation




**Scheme 3.** Stereochemical Determination




intramolecular carbon−carbon bond forming reactions were inefficient for substrates in which acylimine tautomerization is facile. This substrate is readily prepared from the diethyl acetal of heptanal through $BiBr_3$-mediated ionization and TMSCN addition.[9] Our initial studies focused on the use of methallyl trimethylsilane (**9**) as the nucleophile. Subjecting **8** to hydrozirconation and acylation with methoxyacetyl chloride followed by adding **9** did not provide the desired amide, with the acyl hemiaminal that forms from water addition during the workup being the only isolable product. We postulated that, in contrast to alcohols and thiols, weakly reactive $\pi$-nucleophiles require acylimine activation by a Lewis acid to promote addition. Adding $Sc(OTf)_3$ to the reaction mixture indeed resulted in addition to form amides **10** and **11** as a 1:1 mixture in 60% combined yield (see below for the stereochemical determination). Changing the Lewis acid to $ZnBr_2$ provided a 55% yield of **11** while completely suppressing the formation of **10**.

We devised an independent pathway for product synthesis to assign the stereochemical relationship of the products (Scheme 3). The sequence commenced with a Masamune *syn*-aldol reaction[10] between the (*E*)-dibutylboron enolate of ester **12** and heptanal to provide **13** as a single stereoisomer. Methylation of the hydroxyl group and ester cleavage formed acid **14**, which was converted to carbamate **15** through a Curtius reaction under Shioiri's conditions.[11] The methyl ether was prepared rather than the ethyl ether because it could be formed under milder conditions. Cleaving the Alloc-group with $Pd(PPh_3)_4$ and $Bu_3SnH$ in the presence of methoxyacetyl chloride[12] led to the formation of **16**. While **16** showed several spectral features that were essentially identical to those of **10**, assigning the structures unambiguously required that we prepare methoxy nitrile **17** and subject it to the multicomponent amide synthesis protocol with catalysis by of $Sc(OTf)_3$ and $ZnBr_2$. In the presence of $ZnBr_2$ we observed the formation of a single stereoisomer with spectroscopic properties that did not match those of **16**, allowing us to assign this structure as *syn*-isomer **18**. In the presence of $Sc(OTf)_3$ we observed the formation of a 1:1 mixture of **16** and **18**, thereby establishing the structural assignment. The formation of the *syn*-isomer through $ZnBr_2$ catalysis is consistent with the reaction proceeding through a transition state in which the alkoxy group and the nitrogen of the acylimine chelate the Lewis acid.[13]

A sampling of the scope of nucleophiles and electrophiles that can be employed in this reaction is shown in Table 1. Allyl trimethylsilane provided amide **19** (entry 1), though the process was significantly less efficient than the reaction with methallyl trimethylsilane. Enolsilanes derived from acetone (entry 2) and acetophenone (entry 3) added into the acylimine smoothly to form $\beta$-amido ketones **20** and **21**, respectively. Indole was a suitable nucleophile for the formation of amide **22** (entry 4), indicating that bimolecular Friedel−Crafts additions are possible with appropriately nucleophilic arenes. The reactivity trends in this series generally followed the Mayr nucleophilicity table,[14] with methallyl trimethylsilane proving to be the least nucleophilic species to afford smooth reactivity. Notably allyltin reagents,

(7) 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.

(8) For other examples of nucleophilic additions into nitriles followed by acylation, see: (a) Savarin, C. G.; Boice, G. N.; Murry, J. A.; Corley, E.; DiMichele, L.; Hughes, D. *Org. Lett.* **2006**, *8*, 3903. (b) Fleming, F. F.; Wei, G.; Zhang, Z.; Steward, O. W. *Org. Lett.* **2006**, *8*, 4903.

(9) Komatsu, N.; Uda, M.; Suzuki, H.; Takahashi, T.; Domae, T.; Wada, M. *Tetrahedron Lett.* **1997**, *38*, 7215.

(10) Abiko, A.; Liu, J.; Masamune, S. *J. Org. Chem.* **1996**, *61*, 2590.

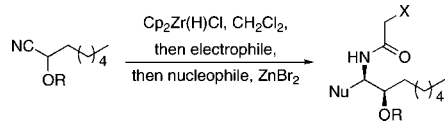
(11) Ninomiya, K.; Shioiri, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151.

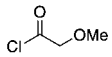
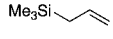
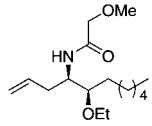
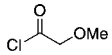
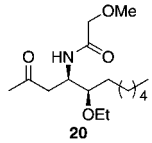
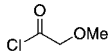
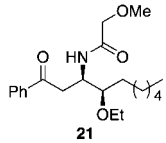
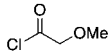
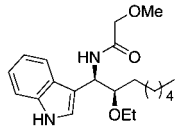
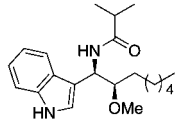
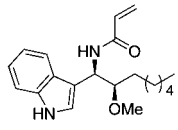
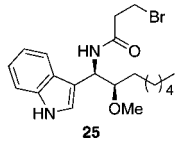
(12) Roos, E.; Bernabe, P.; Hiemstra, H.; Speckamp, N.; Kaptein, B.; Boesten, W. H. J. *J. Org. Chem.* **1995**, *60*, 1733.

(13) For related stereochemical discussions, see: (a) Sugiura, M.; Hagio, H.; Hirabayashi, R.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 12510. (b) Ella-Menye, J.-R.; Dobbs, W.; Billet, M.; Klotz, P.; Mann, A. *Tetrahedron Lett.* **2005**, *46*, 1897.

(14) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66.

**Table 1.** Nucleophile and Electrophile Variations




| entry | nitrile | electrophile | nucleophile | product | yield (%) |
|---|---|---|---|---|---|
| 1 | **8** |  |  |  **19** | 18 |
| 2 | **8** |  |  |  **20** | 56 |
| 3[b] | **8** |  |  |  **21** | 55 |
| 4 | **8** |  |  |  **22** | 60 |
| 5[c] | **17** |  |  |  **23** | 47 |
| 6[d] | **17** |  |  |  **24** | 42 |
| 7[e] | **17** |  |  |  **25** | 46 |

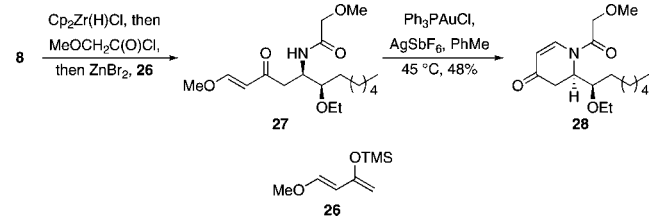
[a] Representative procedure: $Cp_2Zr(H)Cl$ (1.2 equiv) was added to a solution of the substrate in the solvent (0.1 M). The mixture was stirred for 10 min at rt and then was cooled to 0 °C. The electrophile (1.2−1.5 equiv) was added and stirred for 10 min. The nucleophile (4 equiv) and the $ZnBr_2$ (1 equiv) were added at a suitable temperature (see the Supporting Information for details), and the reaction was stirred until the acyl hemiaminal was not observed by TLC. [b] Reaction provided a 5.2:1 ratio of diastereomeric products. [c] Reaction provided a 4.2:1 ratio of diastereomers. [d] Reaction provided a 4.9:1 ratio of diastereomers. [e] Reaction provided a 4.5:1 ratio of diastereomers.

though more nucleophilic than allylsilanes, did not provide the desired addition products, suggesting an incompatibility of these nucleophiles with the reaction conditions.

Methoxyacetyl chloride proved to be the best acylating agent that we tested with respect to product yield and diastereocontrol, but other acid chlorides can also be employed. Isobutyryl chloride (entry 5), acryloyl chloride (entry 6), and $\beta$-bromopropionyl chloride (entry 7) provided amides **23**−**25** when indole was utilized as the nucleophile. While the yields for these reactions were moderate the capacity to prepare useful amounts of a range of amides will prove useful for applications to library synthesis. No other structures, such as the products of inverse-electron-demand hetero Diels−Alder reactions,[15] could be isolated from these reactions. This indicates that the moderate yields result from the competitive formation of chromatographically immobile products.

When the Danishefsky diene[16] (**26**) was used as the nucleophile (Scheme 4), the vinylogous Mannich product

**Scheme 4.** Stereoselective Dihydropyridone Synthesis




**27** was isolated rather than the hetero-Diels−Alder product.[17] This reaction appears to be quite efficient when monitored by TLC, though only low and variable yields of slightly impure product could be isolated. Subsequent studies showed that **27** is highly unstable toward acids, including silica gel, and readily undergoes fragmentation through a retro-Mannich reaction. We directed our efforts toward devising a transition metal mediated cyclization to circumvent the need for Brønsted acids in an effort to convert **27** to dihydropyridone **28** without promoting fragmentation. Our recently developed protocol for adding oxygen and nitrogen nucleophiles into $\alpha,\beta$-unsaturated ketones in the presence of $Ph_3PAuCl$ and $AgSbF_6$ was well suited for this application.[18] When we subjected partially purified **27** to these conditions, we isolated **28** as a single stereoisomer in 48% yield, suggesting that this sequence can be effective for preparing dihydropyridones if superior isolation methods for the Mannich adducts can be developed.

Efforts to conduct these reactions with nonbranched nitriles were not fruitful, in accord with prior studies,[3b] with dimers and higher oligomers of the acylimine intermediates being formed as the major products. We reasoned that these

(15) (a) Scola, P. M.; Weinreb, S. M. *J. Org. Chem.* **1986**, *51*, 3248. (b) Chao, W.; Weinreb, S. M. *Tetrahedron Lett.* **2000**, *41*, 9199. Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807.

(16) For examples of hetero Diels−Alder reactions between Danishefsky's diene and aryl imines, see: (a) Badorrey, R.; Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A. *Tetrahedron* **1999**, *55*, 7601. (b) Akiyama, T.; Takaya, J.; Kagoshima, H. *Tetrahedron Lett.* **1999**, *40*, 7831. (c) Yuan, Y.; Li, X.; Ding, K. *Org. Lett.* **2002**, *4*, 3309. (d) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 4018.

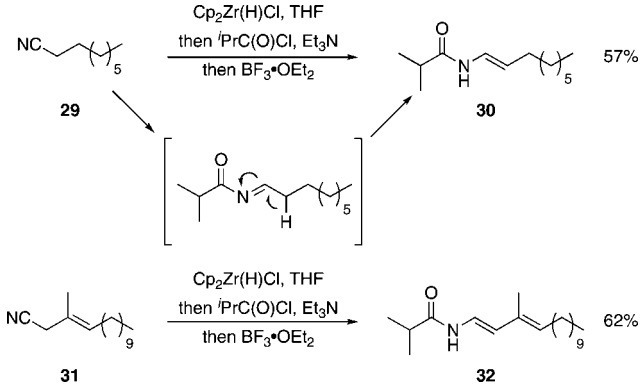
(17) Jung, H. H.; Floreancig, P. E. *J. Org. Chem.* **2007**, *72*, 7359.

(18) (a) Bhattacharjee, A.; Seguil, O. R.; De Brabander, J. K. *Tetrahedron Lett.* **2001**, *42*, 1217. (b) Wu, Y.; Liao, X.; Wang, R.; Xie, X.-S.; De Brabander, J. K. *J. Am. Chem. Soc.* **2002**, *124*, 3245. (c) Nicolaou, K. C.; Kim, D. W.; Baati, R.; O'Brate, A.; Giannakakou, P. *Chem.—Eur. J.* **2003**, *9*, 6177. (d) Petri, A. F.; Sasse, F.; Maier, M. E. *Eur. J. Org. Chem.* **2005**, 1865.

products were derived from the tautomerization of a portion of the acylimines to form enamides. The nucleophilic enamides can add into the residual acylimines to initiate the oligomerization reaction. In consideration of the important role of enamides in promoting the biological activity of several natural products[19] and the growing number of reactions that employ enamides as nucleophiles,[20] we examined the possibility of deliberately tautomerizing the acylimine intermediates from the nitrile hydrozirconation/acylation sequence. Conversions of putative acylimine intermediates into enamides have previously been reported,[21] though low levels of geometrical control were observed in these processes.

Our studies on enamide formation initially utilized nonfunctionalized nitrile **29** as the substrate (Scheme 5). Hydrozirconation and acylation formed the acylimine, which was then subjected to a variety of amine bases to promote tautomerization. These reactions resulted in the slow formation of complex product mixtures that contained *cis*- and *trans*-enamides along with dimerization and oligomerization products. Successful enamide formation was effected by forming the intermediate acylimine in the presence of $Et_3N$ and quickly adding $BF_3{\cdot}OEt_2$. The use of THF as the solvent in this reaction was critical, since oligomerizaton occurred rapidly in $CH_2Cl_2$. Through this method, **29** could be converted to *trans*-enamide **30** in 57% yield. Negligible amounts of *cis*-isomer and dimerization products were formed in this reaction. The reaction requires the presence of $Et_3N$. $BF_3{\cdot}OEt_2$ promotes substantial decomposition in the absence of $Et_3N$. The formation of dienamides is also possible through this method. Allylic nitrile **31** was subjected to hydrozirconation, acylation, and tautomerization to form **32** in 62% yield. Conjugation enhances the tautomerization rate, with the formation of **32** being complete in less than 2 h and the formation of **30** requiring >6 h. Thus, while tautomerization prevents unbranched nitriles from undergoing efficient addition reactions, appropriate reaction conditions have been developed for effecting a facile enamide synthesis.

**Scheme 5.** Selective Enamide Synthesis through Tautomerization




We have devised a general multicomponent approach to α-branched amide synthesis from nitriles through a sequence of hydrozirconation, acylation, and nucleophile addition. Allylsilanes, enolsilanes, and indole were shown to react with acylimines in the presence of a Lewis acid, provided that adjacent branching was present to inhibit decomposition through tautomerization. Reactions that employ cyanohydrin ethers as substrates proceed with good to excellent levels of chelation control when $ZnBr_2$ is used as the Lewis acid. Acylimines that lack adjacent branching undergo selective tautomerization to form *E*-enamides when subjected to a mixture of $Et_3N$ and $BF_3{\cdot}OEt_2$, making the protocol applicable to the synthesis of enamide-containing cytotoxins. The range of nitriles, electrophiles, and nucleophiles that are compatible with the reaction conditions indicates that the method is well suited for the preparation of structurally diverse libraries of amides from easily accessible precursors, and the capacity to control the stereochemical outcome of the process by changing the Lewis acid suggests a potential for utilizing chiral catalysts to prepare enantiomerically enriched products.

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**Supporting Information Available:** Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) (a) Mecozzi, T.; Petrini, M. *Synlett* **2000**, 73. (b) Bayer, A.; Maier, M. E. *Tetrahedron* **2004**, *60*, 6665. For a report of an effective tautomerization process that does not explicitly address product geometry, see: (c) Shono, T.; Matsumura, Y.; Tsubata, K.; Sugihara, Y.; Yamane, S.-i.; Kanazawa, T.; Aoki, T. *J. Am. Chem. Soc.* **1982**, *104*, 6697.

(21) For representative examples of other recently reported methods for enamide synthesis, see: (a) Goossen, L. J.; Salih, K. S. M.; Blanchot, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 8492. (b) Bolshan, Y.; Batey, R. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 2109. (c) Pan, X.; Cui, Q.; Ma, D. *Org. Lett.* **2004**, *6*, 1809. (d) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667.