Organic Syntheses

Discussion Addendum for:

Mild Conversion of Tertiary Amides to Aldehydes Using $Cp_2Zr(H)Cl$ (Schwartz's Reagent)

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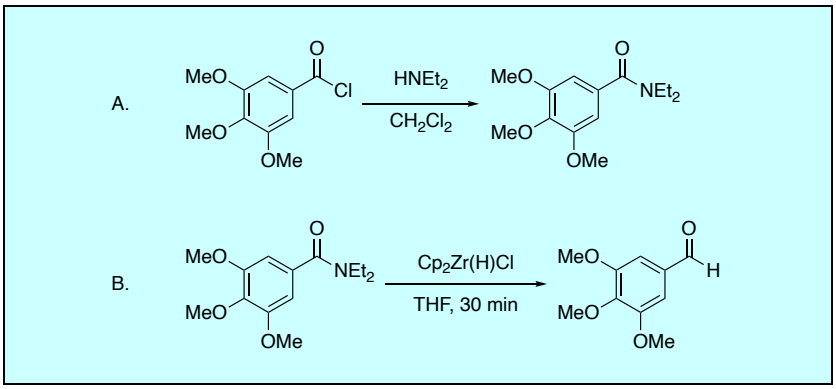

Extending the Utility and Scope of the Reaction

Inspired by our chemoselective reduction protocol for converting amides to aldehydes,[2-4] sparing esters, and other functional groups prone to reduction, subsequent publications reported improved protocols for this transformation, including catalytic methods. Multiple groups extended the utility of the chemistry, including the formation of amines from acetamides, phenols from N,N-diethyl aryl O-carbamates, and the reductive cleavage reaction of heterocyclic carbamates. Many groups used the initially formed

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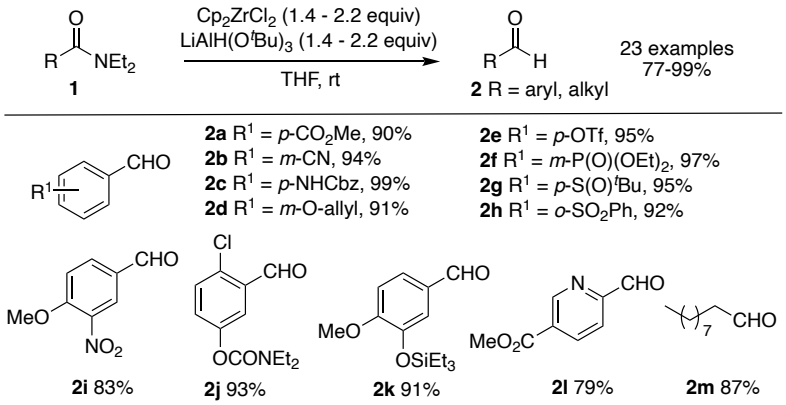
reduced intermediates to add amines, carbon nucleophiles, and phosphonates. The intermediates were also employed in Ugi and Mannich/Michael tandem reactions. Many of the reaction products are complex structures that are otherwise difficult to prepare.

In situ Generation of $Cp_2Zr(H)Cl$

Zhao and Snieckus reported in 2014 a practical method for the *in situ* generation of $Cp_2Zr(H)Cl$ (Schwartz's reagent) from Cp_2ZrCl_2 and $LiAlH(O^tBu)_3$ to address the limitations associated with previously reported *in situ* protocols and the limited shelf-life of the commercial reagent (Scheme 1).[5] In a comparative study against commercial $Cp_2Zr(H)Cl$ they showed that the *in situ* procedure proceeded with overall better reaction times and yields in the conversion of amides **1** to aldehydes **2**. Representative examples **2a-2m** demonstrate again the excellent chemoselectivity of this reaction.

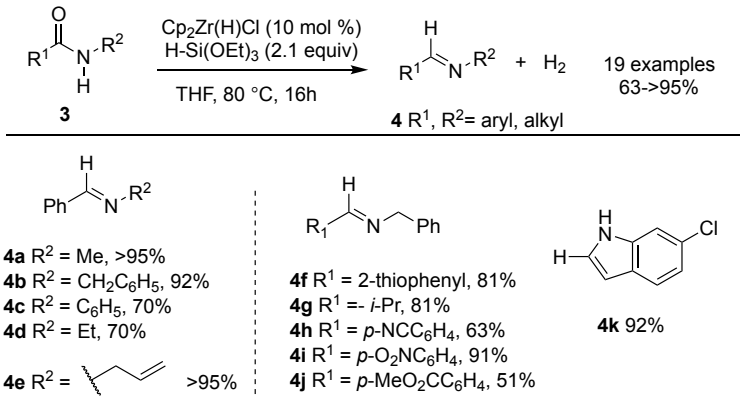


Scheme 1. Reduction of N,N-diethylamides to aldehydes using an in situ generated Schwartz reagent

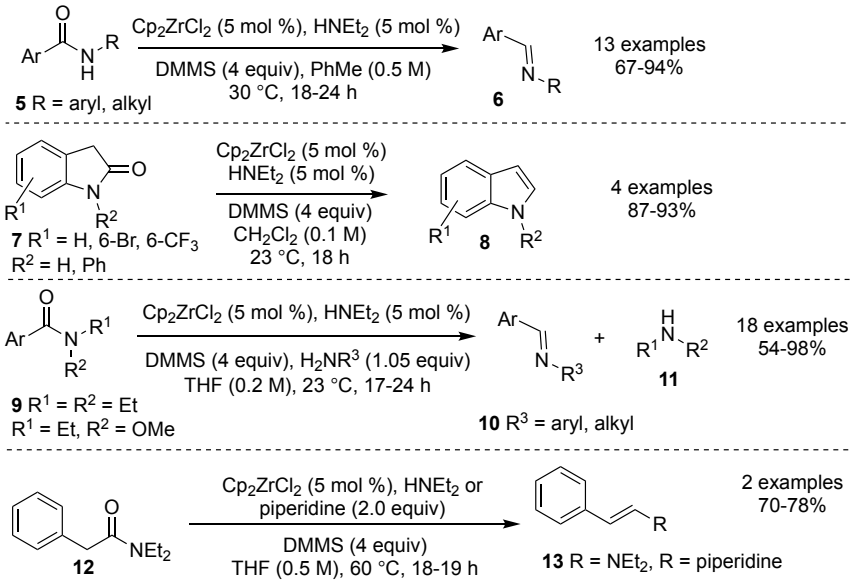
Catalytic Amide Reductions with the Schwartz Reagent

To address the limited stability of the reagent, Donnelly et al. developed a catalytic version by using triethoxysilane ($(EtO)_3SiH$) as a mild stoichiometric reductant (Scheme 2).[6] This approach enables the efficient transformation of secondary amides **3** to imines **4** and tolerates a variety of functional groups. Under these conditions, 6-chloro-2-oxindole formed

deoxygenated **4k** after tautomerization of the initially formed imine. Mechanistic studies suggest that the turnover of the active [Zr]-H species is achieved through the metathesis of the Si-H and Zr-OR σ-bonds.



Scheme 2. Catalytic reduction of secondary amides with Schwartz's reagent



Scheme 3. Applications for the Cp_2ZrCl_2/DMMS catalytic system

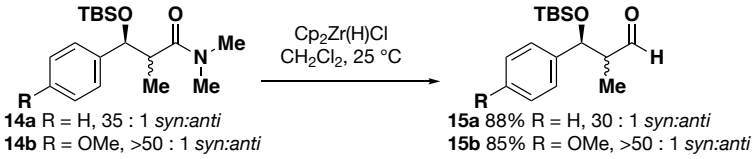
In their 2023 study, Kehner et al. advanced another catalytic approach by employing the more stable Cp_2ZrCl_2 as a precursor for the zirconocene hydride catalyst, thereby circumventing the direct handling of the air- and moisture-sensitive Schwartz's reagent (Scheme 3).[7] Their method reduces secondary and tertiary amides using 5 mol% of Cp_2ZrCl_2 at room temperature. Dimethoxymethylsilane (DMMS) was utilized as a reductant in place of $(EtO)_3SiH$, to avoid the formation of the pyrophoric and toxic byproduct SiH_4. For secondary amides **5**, this approach proved efficacious with aromatic amides, while the dialkyl amide N-benzylpentanamide gave a lower yield (41%). The chemistry was also applied to synthesizing indoles **8** from 2-indolinones **7**. Notably, tertiary amides **9** could be reduced to imines **10** under these conditions through reductive transamination, adding an extra equivalent of a primary amine. In the case of aliphatic amide **12**, the addition of secondary amines gave the corresponding enamines **13**.

Conversion of α-Substituted Amides to Aldehydes with no or Minimal Erosion of Stereochemistry

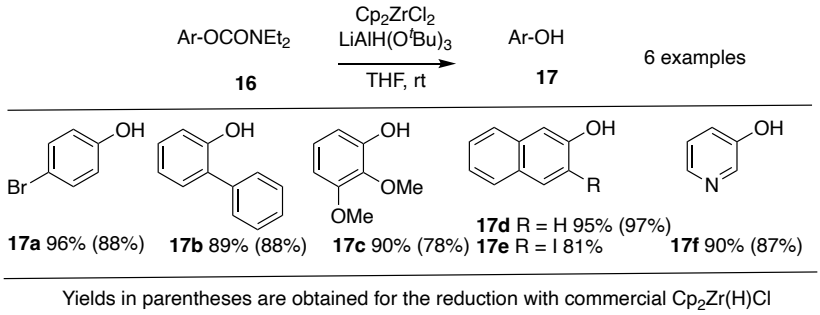
In 2006, McGilvra et al. prepared β-hydroxy amides **14** employing a hydrogen bonding-catalyzed Mukaiyama aldol reaction.[8] The authors then used $Cp_2Zr(H)Cl$ to convert amides **14** into aldehydes **15** with minimal erosion of the alpha stereocenter gained in the previous step. Key to the optimized conversion was the solvent change from THF to CH_2Cl_2 (Scheme 4), which significantly increased the reaction rate and prevented isomerization. The reduced diastereomeric ratio (dr) was attributed to the iminium intermediate, which can isomerize to an enamine when the reaction rate is slow.

Reductive Cleavage of Aryl O-Carbamates and Reductive Cleavage of Heterocyclic N-Carbamides

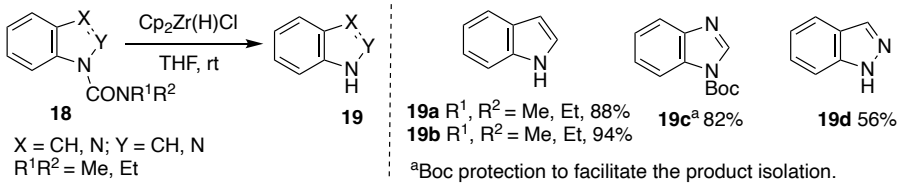
In 2013, Morin et al. reported a mild reductive cleavage method for conversion of aryl O-carbamates **16** to phenols **17** using Schwartz's reagent (Scheme 5).[9] Substituted phenol O-carbamates containing halogens, electron-withdrawing, and donating groups were studied. Reductive cleavages with the commercial and the in situ generated $Cp_2Zr(H)Cl$ were equally efficient. The authors extended the scope of this reductive cleavage reaction to heterocyclic carbamates **18**, which provided moderate to good yields for cleavage products **19** (Scheme 6).



Scheme 4. Conversion of amides to aldehydes with $Cp_2Zr(H)Cl$ with minimal erosion of stereochemistry



Scheme 5. Reductive cleavage of N,N-diethyl aryl O-carbamates to phenols using the *in situ* generated Schwartz reagent

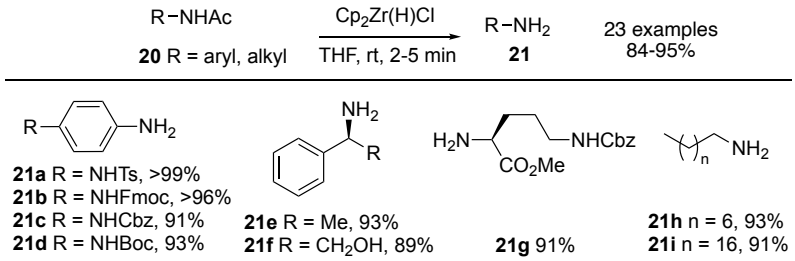


Scheme 6. Reductive cleavage of heterocyclic carbamides using the Schwartz reagent

Chemoselective Conversion of Acetamides to Amines with $Cp_2Zr(H)Cl$

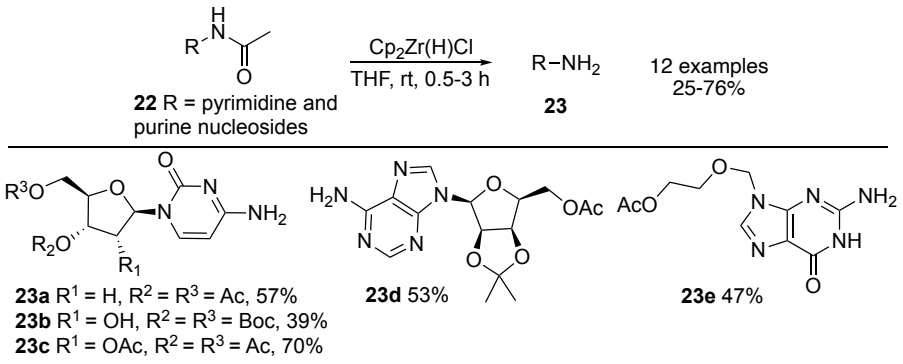
While our original report focused on generating aldehydes from amides, the other species released in this reaction is the amine portion of the amide. Thus, Sultane et al. described in 2014 the selective N-deacetylation of

acetamides **20** using the Schwartz reagent under mild conditions and with high chemoselectivity (Scheme 7).[10] This strategy demonstrated that N-deacetylation of aliphatic and heteroaromatic substrates is efficient and rapid, providing amines **21** in high yields from amide substrates with diverse electronic and steric properties. Epimerization was not observed during the synthesis of chiral amines **21e**, **21f,** and **21g**.. Since Ts, Fmoc, Cbz, and Boc protection of amines was retained, this reductive procedure can be used in an orthogonal protection/deprotection strategy.



Scheme 7. Deacetylation of N-acetamides by the Schwartz reagent

Similarly, the application of Schwartz's reagent for the selective removal of acetyl groups from N-acetyl purine and pyrimidine nucleoside analogs **22** was explored by Ferrari et al. in 2015 with 12 examples, resulting in yields of 25-76% for amines **23** (Scheme 8).[11] The compatibility of the Schwartz reagent with different protecting groups was investigated. Amide cleavage was

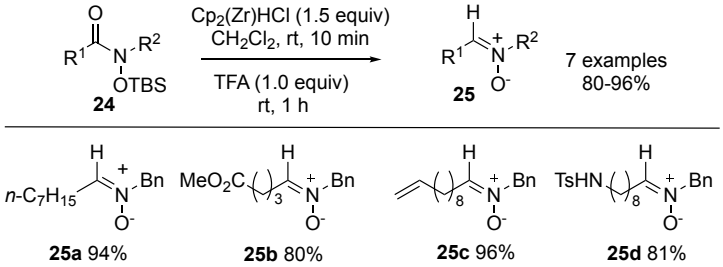


Scheme 8. Deacetylation of protected pyrimidines and purine nucleosides

successful for both purine and pyrimidine nucleoside analogs that had various protecting groups, such as OAc (**23a**, **23c**, **23d**, and **23e**), OTBDMS, OTHP, OBoc (**23b**), OBz, O-trityl and O-isopropylidene groups (**23d**). This scope underscores the method's utility in the selective removal of N-acetyl groups in the production of nucleoside-based compounds.

Nitrone Synthesis from N-Siloxyamides with the Schwartz Reagent

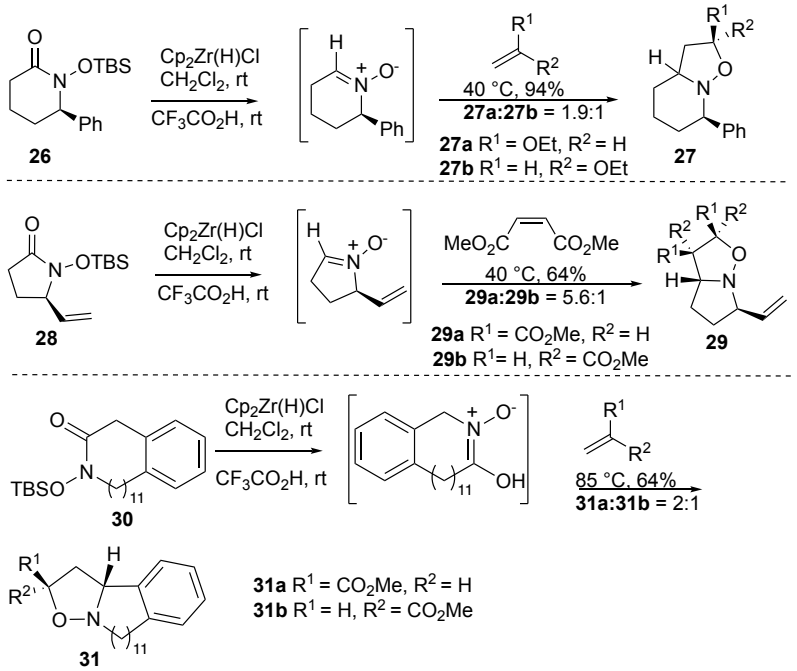
Katahara et al. reported 2017 a reductive methodology for nitrone synthesis, commencing from N-siloxyamides **24** using Schwartz's reagent. Subsequent acid addition yielded functionalized nitrones **25** (Scheme 9).[12] This reaction again exhibited the remarkable chemoselectivity in the presence of a diverse array of sensitive functional groups prone to reduction, such as esters, nitro groups, and olefins. The utility of this methodology was demonstrated in the synthesis and application of functionalized cyclic and macrocyclic nitrones, which were employed for the synthesis of bicyclic isoxazolidines **27**, **29**, and **31** (Scheme 10) through [3+2] cycloaddition reactions.



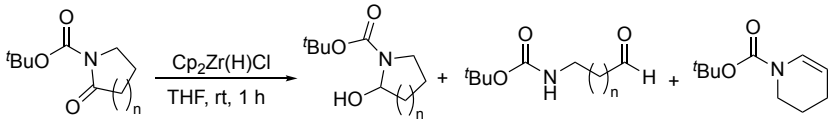
Scheme 9. Reductive formation of nitrones from N-siloxyamides

Reduction of Lactams with the Schwartz Reagent

In 2011, Piperno et al. demonstrated the efficacy of the Schwartz reagent for reducing N-alkoxy carbonyl lactams **32**, ranging from four to seven-membered rings (Scheme 11).[13] The selective reduction of γ-lactam **32** (n = 1) to lactamol **33** marked a significant advancement in synthetic methodologies. δ-Lactam **32** (n = 2) provided a 4:1 mixture of **33** and enamine **35**. β-Lactam **32** (n = 0) and ε-lactam **32** (n = 3) yielded 1:1 mixture of lactamols **33** and aldehydes **34**.



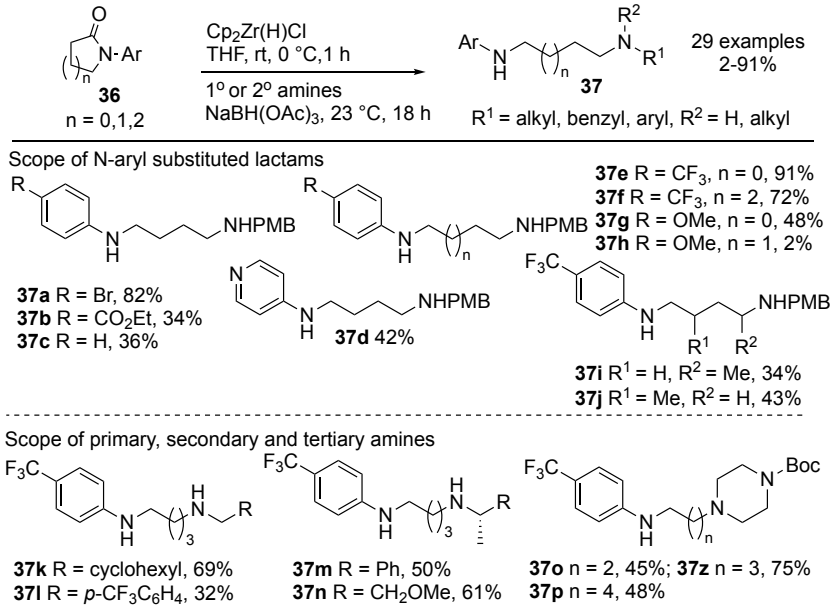
Scheme 10. Synthesis of bicyclic isoxazolidines from cyclic nitrones



Scheme 11. Reduction of β, γ, δ, and ε-lactams with the Schwartz reagent

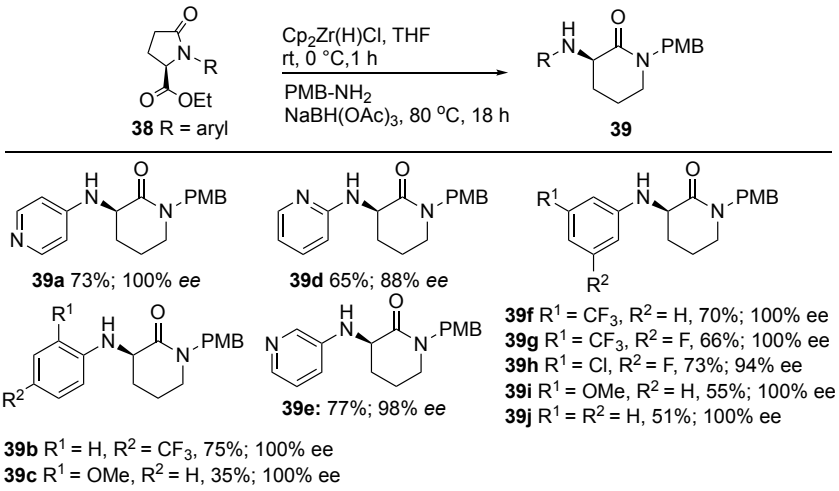
Reduction of Lactams with $Cp_2Zr(H)Cl$ Followed by the Addition of Amines and Reductive Amination

In 2019, Prince et al. reported a novel and operationally simple protocol for coupling primary or secondary amines with N-aryl-substituted lactams to produce differentiated diamines with moderate to high yields (Schemes 12 and 13).[14] The process initially involves the reduction of lactams **36** using Schwartz's reagent followed by reductive amination of the aldehyde



Scheme 12. Aryl-substituted lactams and amines in the one-pot reductive coupling reaction

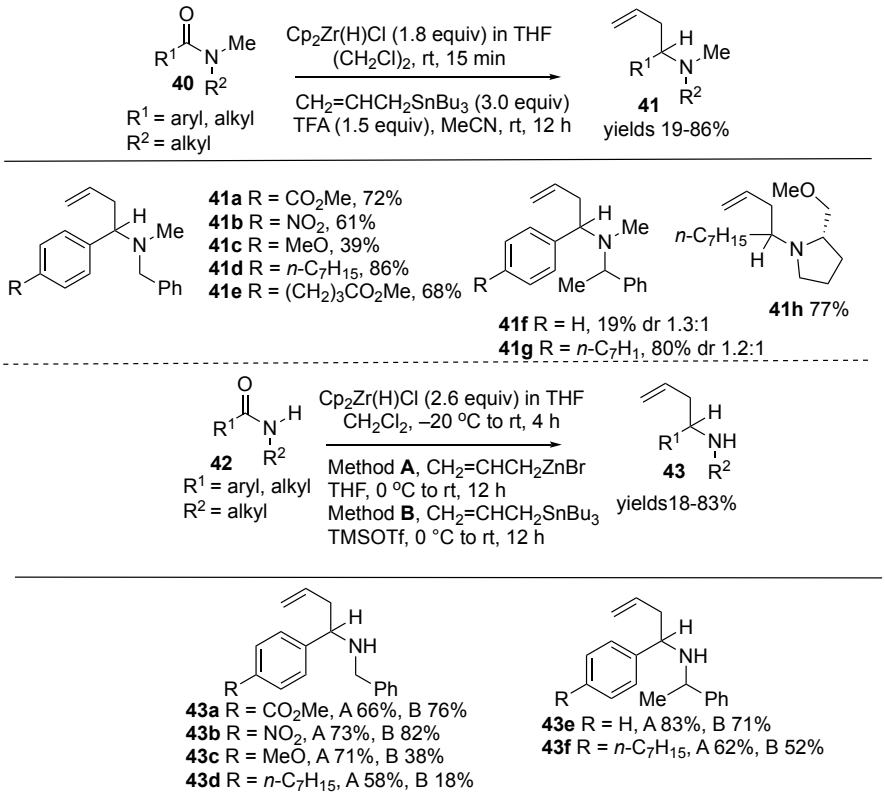
intermediate with the amine nucleophiles to generate diamines **37**. These steps can be combined into a one-pot reaction to streamline the procedure. The methodology's scope was demonstrated with different substituted lactams of various ring sizes to form the desired diamine products, yielding **37a-37j** and various primary and secondary amines **37k-37n**. The utility of the reaction was validated by performing gram-scale syntheses. The methodology was extended to include N-aryl pyrrolidinones **38** with enantiopure ester groups, resulting in the formation of α-amino piperidinones **39a-39j** with complete retention of stereochemistry (Scheme 13). The study highlights the utility of lactams as synthons for the synthesis of complex molecules and offers a practical approach to accessing diverse diamine structures. The proposed mechanistic pathway involves a zirconium complex as a masked aldehyde intermediate that, upon reductive amination, is followed by cyclization while retaining stereochemistry. This work opens new avenues for using lactams in organic synthesis and demonstrates the value of innovative reaction strategies for creating complex molecules.



Scheme 13. Reductive coupling/cyclization sequence of enantiopure N-arylated pyrrolidinones

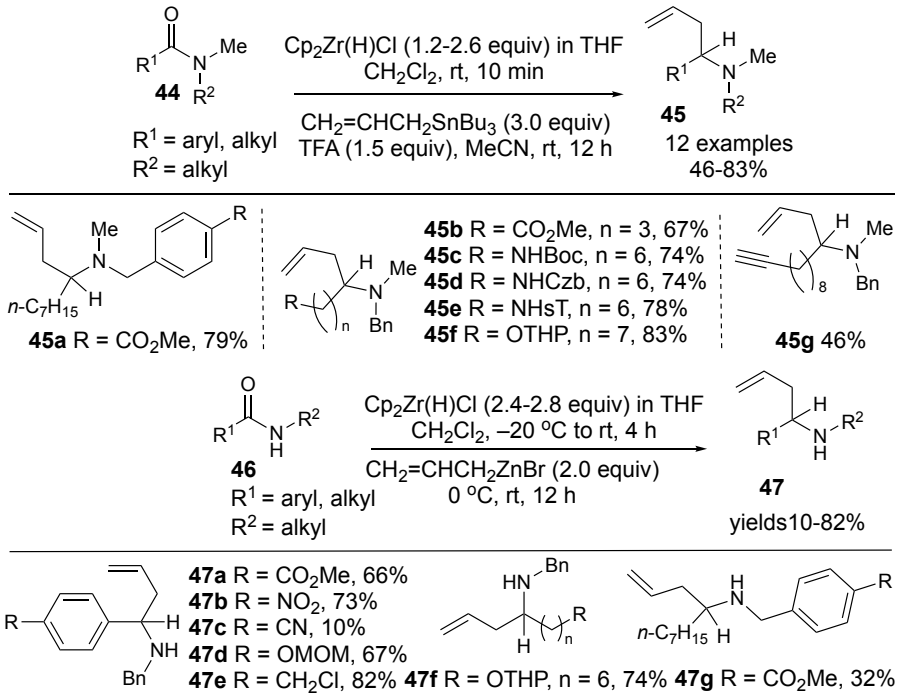
Chemoselective Reductive Alkylation of Amides and N-Methoxy Amides to Form α-Substituted Amines

Oda et al. reported in 2012 the direct allylation of amides **40** and **42** with allyltributylstannane, resulting in the formation of either substituted tertiary amines **41** or secondary amines **43** using Schwartz's reagent (Scheme 14).[15] Notably, the need for a pre-activation step, typically required to enhance the electrophilicity of amides, was avoided. This method facilitates the direct functionalization of amide groups without additional functional group support. This reaction displayed significant tolerance towards various functional groups, proceeding smoothly even in the presence of electrophilic

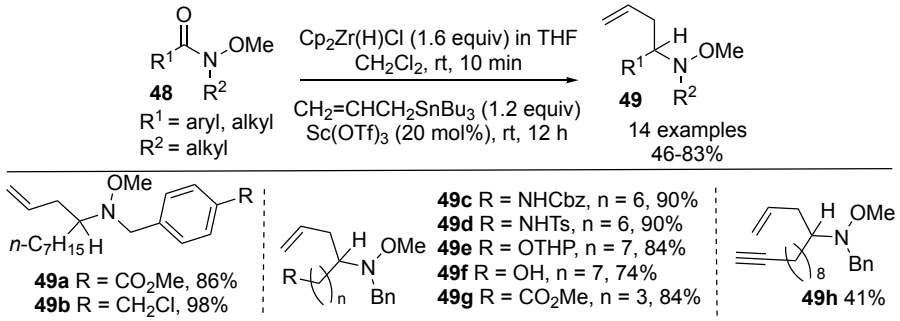


Scheme 14. Reductive allylation of tertiary and secondary amides with allyltributylstannane

and other sensitive groups. Tertiary amides formed allylated tertiary amines **41a-41h,** and secondary amides formed allylated secondary amines **43a-43f**. In 2014, Nakajima et al. extended the direct allylation chemistry to tertiary amides **44** to form tertiary α-allyl amines **45** (Scheme 15).[16] Having established chemoselective reductive nucleophilic addition to tertiary amides, their focus shifted to secondary amides **46**, which after reaction with allylzinc bromide yielded secondary amines **47a-47g**. In this report,[16] they further extended their work to N-methoxy amides **48**, significantly broadening the scope of their work, which yielded significantly improved

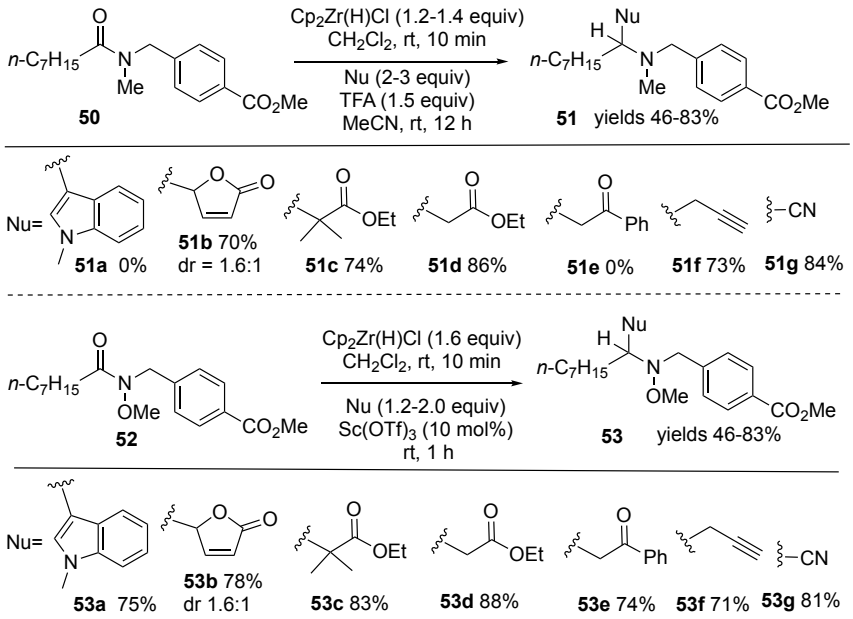


Scheme 15. Reductive allylation of tertiary and secondary amides with allyltributylstannane and allylzinc bromide



Scheme 16. Reductive allylation of N-methoxy amides with allyltributylstannane

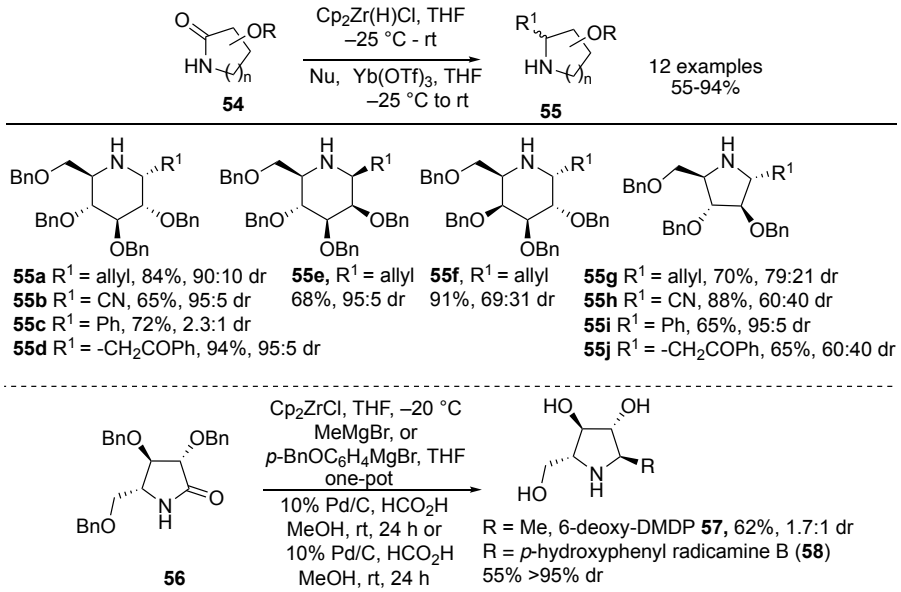
outcomes compared to tertiary and secondary amides in both yield and chemoselectivity when utilizing a catalytic amount of $Sc(OTf)_3$ for the synthesis of **49a-49h** (Scheme 16). The reaction allowed them to use different nucleophiles, such as indole, enol ethers, TMSCN, and tributyl(propa-1,2-dien-1-yl)stannane, while maintaining the high chemoselectivity for both tertiary amides **50** to generate amines **51a-51g** and N-methoxy amides **52** to generate N-methoxy amines **53a-53g** (Scheme 17).



Scheme 17. Reductive addition of carbon nucleophiles to tert-amides and *tert*-N-methoxamides

In 2014, Szcześniak et al. introduced a procedure involving using Schwartz's reagent to treat sugar-derived lactams **54**, forming the corresponding imines in excellent yields.[17] However, the isolation and purification of these cyclic imines were found to be challenging due to their inherent instability. To address the instability issue, a one-pot protocol was developed, by treating the crude imine solution with $Yb(OTf)_3$ followed by the addition of allyl tributylstannane (Scheme 18). This approach yielded a mixture of diastereomeric homoallylic amines **55a**, and **55e-55g** in good yields (55-91%) and moderate to good stereoselectivity. The allyl tributyltin

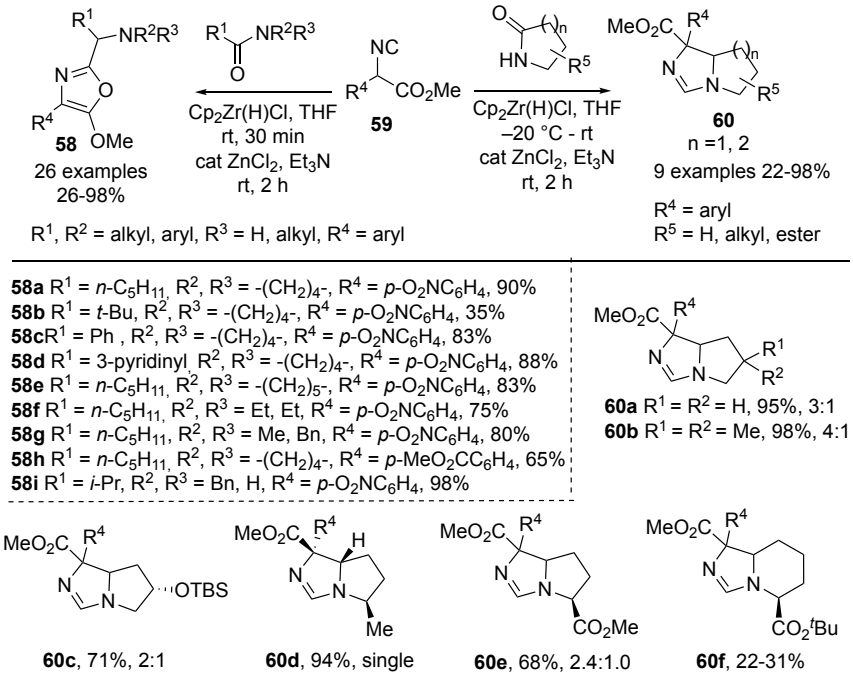
addition occurred syn to the BnO substituent at the C3 position for six-membered imines. In contrast, steric effects controlled the nucleophile addition for five-membered imines, leading to an anti-arrangement of the BnO at C3 and the allyl group at C2. Further exploration included testing other nucleophiles, TMSCN (**55b** and **55h**), PhMgBr (**55c** and **55i**), and the TMS-enol ether of acetophenone (**55d** and **55j**) yielding cyclic amines in moderate to good yields and selectivities.[17] This versatile protocol was applied to γ-lactam **56** to synthesize two pyrrolidine derivatives, 6-deoxy-DMDP (**57**) and radicamine B (**58**).[17] Overall, this method enables direct nucleophile addition to *in situ* generated cyclic imines, offering opportunities for synthesizing various polyhydroxylated pyrrolidines and piperidines, valuable in natural product synthesis and biosynthetic pathways.



Scheme 18. One-pot reduction of sugar-derived lactams with Schwartz's reagent followed by nucleophilic addition of carbon nucleophiles

In 2017, Zheng et al. reported an effective chemoselective C-C bond method for the one-pot transformations of amides into different compound classes (Scheme 19).[18] They demonstrated that the reductive addition of isocyanoacetates **59** to amides and lactams yields 5-methoxyoxazoles **58** and bicyclic imidazolines **60**. This procedure involves partial reduction of amides with Schwartz's reagent, followed by selective addition of the carbon from

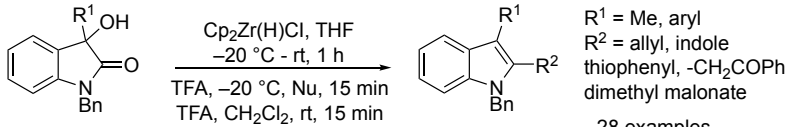
isocyanide **59**. The method was efficient for synthesizing 5-methoxyoxazoles such as **58a-58b** from tertiary amides with various alkyl groups. The reaction was also extended to heteroaromatic amides, yielding the corresponding oxazoles such as **58d**. The authors also investigated secondary lactams, discovering that 2.2 equiv of Schwartz's reagent were needed in the reaction with isocyanoacetates to produce oxazoles such as **58i**. The reaction of isocyanoacetates with 2-pyrrolidines gave separable diastereomeric mixtures of bicyclic imidazolines **60a-60e** in excellent yields. However, six-membered lactams provided low yields of compounds such as **60f**.



Scheme 19. One-pot reductive nucleophilic addition of methyl-2-isocyanoacetates 59

Ulikowski and Furman reported in 2016 the synthesis of 2,3-disubstituted indoles **62** starting from 3-substituted oxindoles **61** (Scheme 20).[19] The approach leveraged the unique reactivity of Schwartz's reagent, specifically its ability to selectively activate amide carbonyls. The reactive iminium intermediate enabled the addition of diverse nucleophiles, followed by partial reduction, all in a one-pot process, resulting in the

formation of 2,3-disubstituted indoles **62**. The reaction with nucleophiles such as allyl tributyl stannane (**62a-62b**), acetophenone enol TMS ethers (**62c-62d**), and indole (**62e-62f**) provided the desired products in good yields. One equivalent of the thiophenol is sufficient to form **62g-62h** and to avoid over-reduction. An activating group such as TMSOTf is required for dimethyl malonates to provide the desired indoles **62i-62j** in good to excellent yields. This method holds promise for synthesizing indole derivatives with pharmacological and synthetic relevance.



61 R^1 = Me, aryl

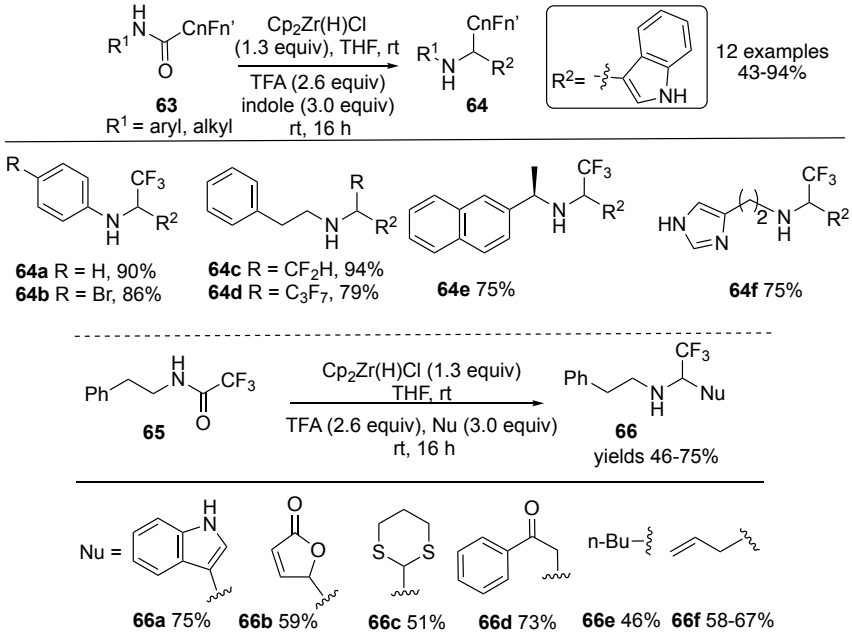
62

62a R^1 = Me, R^2 = allyl, 99%
62b R^1 = *p*-$EtO_2CC_6H_4$, R^2 = allyl, 84%
62c R^1 = Me, R^2 = -CH_2COPh, 82%
62d R^1 = *p*-$MeOC_6H_4$, R^2 = -CH_2COPh, 78%
62e R^1 = Me, R^2 = 3-indole, 80%
62f R^1 = Ph, R^2 = 3-indole, 70%
62g R^1 = Me, R^2 = SPh, 49%
62h R^1 = Ph, R^2 = SPh, 84%
62i R^1 = Me, R^2 = -$CH(CO_2Me)_2$, 51%
62j R^1 = Ph, R^2 = -$CH(CO_2Me)_2$, 55%

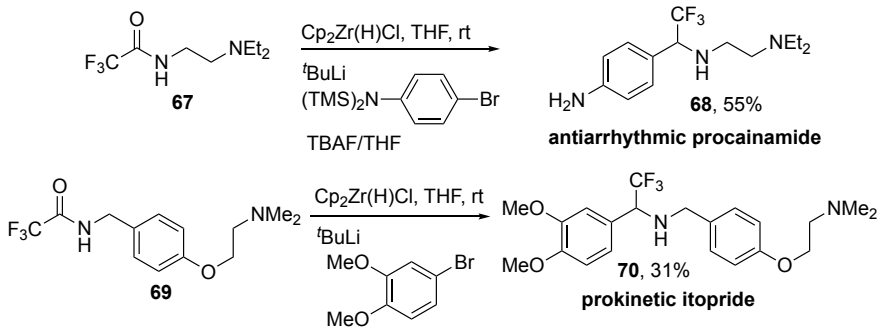
Scheme 20. Synthesis of indoles from oxindoles

Synthesis of 2-Fluoroalkyl Amines from Fluoroacetamides

In 2019, Czerwinski and Furman reported the reductive addition of nucleophiles to fluoroacetamides **63** to synthesize functionalized amines **64** using secondary fluoroamides as a replacement for fluorinated aldehydes (Scheme 21).[20] Model studies involving 2,2,2-trifluoro-N-phenylacetamide and indole as the nucleophile identified the Schwartz reagent as the only reducing agent that would produce the intended functionalized secondary amines **64** in good to moderate yields. The methodology was applied to synthesize the difluoromethyl analog **64c** and the heptafluoropropyl analog **64d** in satisfactory yields. The functionalization of the intermediate imines by reaction with a diverse range of nucleophiles was performed using the established conditions to synthesize compounds **66a-66f** from **65** as depicted in Scheme 21. The methodology provided access to trifluoromethyl bioisosteres of important drugs, namely the antiarrhythmic procainamide **68** from **67** and prokinetic itopride **70** from **69**, as shown in Scheme 22.



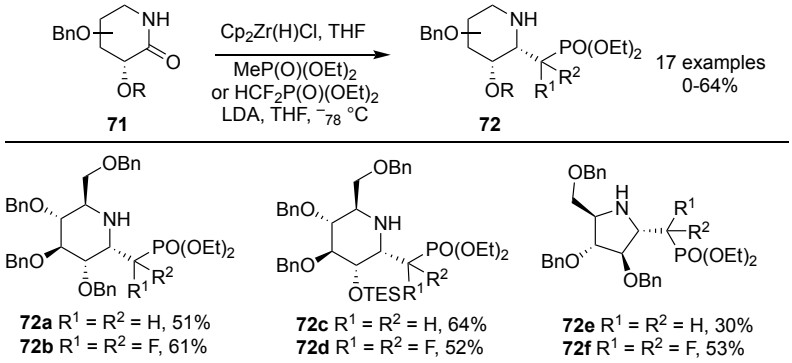
Scheme 21. Directed functionalization of fluoroacetic acid-derived amides



Scheme 22. Synthesis of trifluoromethyl bioisosteres of antiarrhythmic procainamide and prokinetic itopride

In their 2022 study, Tran et al. described an efficient method for synthesizing 1-C-phosphonomethyl and 1-C-phosphonodifluoromethyl iminosugars **72** using sugar-derived lactams **71** (Scheme 23).[21] Using Schwartz's reagent, this process employs a one-pot reaction, forming imines

from iminosugars, after which $LiCH_2P(O)(OEt)_2$ and $LiCF_2P(O)(OEt)_2$ were added to produce glycosyl phosphonates **72**. The yield of this reaction, which was as high a 64%, is influenced by the configuration and the protecting groups present in the sugar lactams, and the reaction proceeds with notable stereoselectivity. The iminosugars synthesized via this method exhibit promising characteristics as transition state inhibitors of glycosyltransferases. Their potential arises from the more stable P-C bond, offering an advantage over the naturally occurring, more hydrolysable P-O bond.

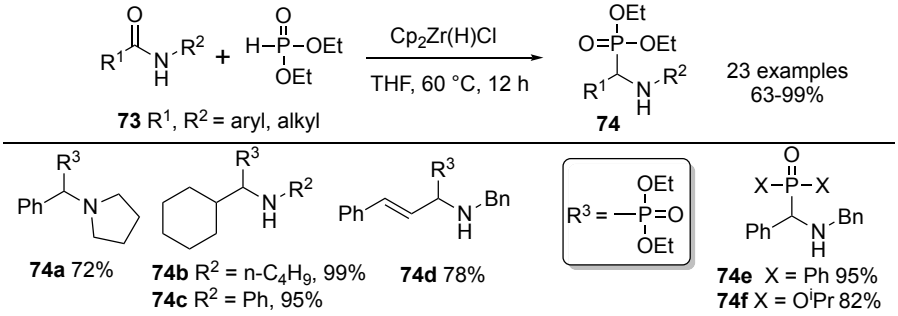


Scheme 23. Reductive alkylative synthesis of 1-C-phosphonomethyl and 1-C-difluoromethyl iminosugars from sugar-derived lactams using the Schwartz reagent

Synthesis of α-Amino Phosphonates from Amides

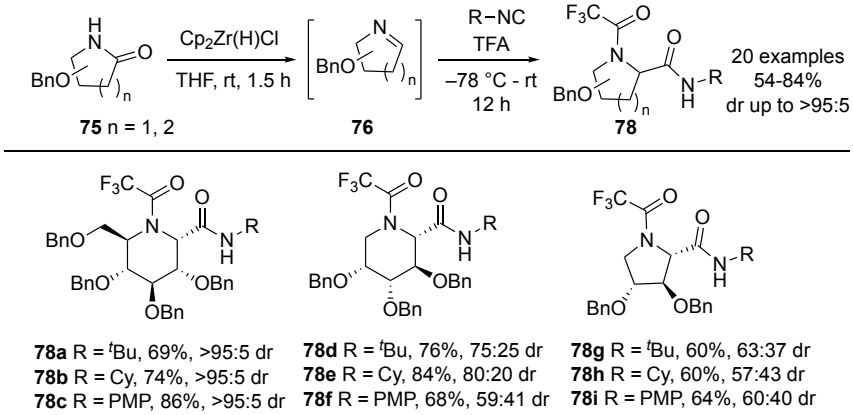
In 2013, Gao *et al.* reported the first method for the reductive phosphination of amides **73** using Schwartz's reagent in a single step (Scheme 24).[22] This reaction method introduces an innovative pathway to obtain α-amino phosphonates **74** after the reaction of amides **73** with the Schwartz reagent and diethylphosphonate, with yields ranging from good to excellent. These reactions operate effectively under mild conditions with a many substrates, including secondary and tertiary amides. Various secondary amides, such as aryl, alkyl, and alkenyl amides were converted into the corresponding α-amino phosphonates **74** in yields ranging from good to excellent. They observed that amides with a hydroxyl group were not converted to product. This could be attributed to the deactivation of $Cp_2Zr(H)Cl$ by the available hydrogen species. The reductive phosphorylation of tertiary amides led to the formation of tertiary α–aminophosphonates such as **74a**. H-phosphonates starting materials

containing diphenyl, diisopropyl, dimethyl, and acetal groups were used to this reductive phosphination reaction to furnish analogs such as **74e** and **74f**. The reactivity of the dialkyl phosphonates remained largely unaffected by the specific alkyl moieties.



Scheme 24. Transformation of secondary and tertiary amides into α–amino phosphonates

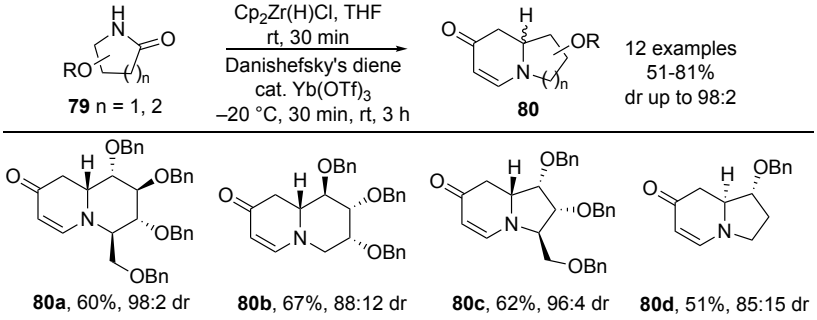
In 2015, Szcześniak et al. reported a direct and efficient approach for synthesizing polyhydroxylated piperidine and pyrrolidine peptidomimetics as outlined in Scheme 25.[23] This strategy involves a one-pot reduction of sugar-derived lactams **75** using Schwartz's reagent, followed by a multicomponent Ugi-Joullié reaction. Chiral lactams **75** were treated with $Cp_2Zr(H)Cl$, yielding the corresponding imine **76**, which was then subjected



Scheme 25. Sequential lactam reduction/Joullié–Ugi three-component reaction

to a Joullié-Ugi reaction by adding TFA and isocyanide. This process proceeds smoothly with aliphatic (^{t}Bu, Cy) and aromatic (PMP) isocyanides, providing products **78** with up to 95:5 dr. This approach facilitates not only the synthesis of proline amides but also pipecolic acid amides in a one-pot method, enhancing the overall scope of this synthetic method.

In 2014, Szcześniak et al. introduced a direct and efficient method for synthesizing quinolizidine such as **80a** and **80b** and indolizidine such as **80c** and **80d** from iminosugars **79** (Scheme 26).[24] This innovative approach involves a one-pot reduction of sugar-derived lactams **79** using Schwartz's reagent, followed by a diastereoselective Mannich/Michael tandem reaction with Danishefsky's diene. Initially, lactams are treated with $Cp_2Zr(H)Cl$ (1.6 equiv) in THF, forming the corresponding imine. The resulting imine is then subjected to cyclocondensation with the diene and $Yb(OTf)_3$ within the same reaction vessel. This process provided good yields (51-81%) of bicyclic enaminones **80** and good to high diastereoselectivities of up to 98:2 dr, making this method a valuable tool for efficiently synthesizing these complex natural product scaffolds.



Scheme 26. Synthesis of indolizidines and quinolizidines via one-pot reduction/Mannich/Michael tandem reaction

Applications of the Chemoselective Conversion of Amides to Aldehydes

Summary: In addition to the methodology development described above, chemoselective conversion of amides to aldehydes using Schwartz's reagent was used to generate intermediates within methodology studies[25–27] and also employed to generate aldehydes during the total synthesis of natural products.[29–39] The impressive breadth of application demonstrates that the method is an important tool for synthetic organic chemistry.

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