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Direct Chemoselective Allylation of Inert Amide Carbonyls

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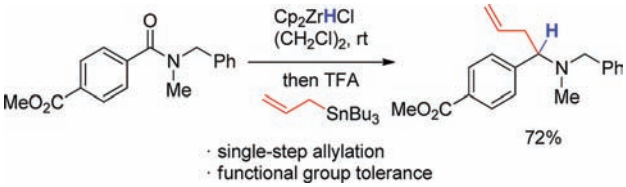
ABSTRACT



Direct allylation of inert amide carbonyls utilizing the Schwartz reagent afforded either substituted tertiary or secondary amines. A preactivation step was successfully avoided, which is generally a requisite to increase the electrophilicity of amides. The reaction exhibited remarkable functional group tolerance and proceeded even in the presence of methyl esters and nitro groups.

Nucleophilic addition to carbonyl groups, such as ketones and esters, is one of the most fundamental transformations in organic synthesis.[1] However, the reaction with amide carbonyls remains a formidable challenge because of their high stability caused by the resonance effect of the nitrogen atom. Assuming a high yielding access to amide groups,[2] direct chemoselective nucleophilic addition to the amide carbonyls would undoubtedly offer an opportunity for widespread applications in the synthesis of natural products and pharmaceuticals. However, direct nucleophilic addition to amide carbonyls requires harsh reaction conditions, which limits the substrate scope. Acyclic amides are especially challenging substrates because the intermediates readily undergo hydrolysis.[3] Thus, general approaches for the functionalization of acyclic amides currently rely on a preactivation step of the inert amide carbonyl (Scheme 1, **1**→**2**∼**4**) and use of reactive nucleophiles such as DIBAL, Grignard reagents, and organolithium reagents (**2**∼**4**→**5**). A preactivation step increases the electrophilicity by reducing the resonance effect of the amide nitrogen via imide **2** (DeNinno[4] and Suh[5]) or thioamide **3** (Murai[6]). Recently, Bélanger[7c,f] and Huang[7d,e] reported a practical one-pot

(1) For a review on functionalization of carbonyl groups in ketones, esters, and amides, see: Seebach, D. *Angew. Chem., Int. Ed.* **2011**, *50*, 96–101.

(2) For selected recent reviews on amide bond formation, see: (a) Humphrey, J. M.; Chamberlin, A. R. *Chem. Rev.* **1997**, *97*, 2243–2266. (b) Albericio, F.; Chinchilla, R.; Dodsworth, D. J.; Nájera, C. *Org. Prep. Proced. Int.* **2001**, *33*, 203–313. (c) Han, S.-Y.; Kim, Y.-A. *Tetrahedron* **2004**, *60*, 2447–2467. (d) Montalbetti, C. A. G. N.; Falque, V. *Tetrahedron* **2005**, *61*, 10827–10852. (e) Valeur, E.; Bradley, M. *Chem. Soc. Rev.* **2009**, *38*, 606–631.

(3) For selected examples on direct conversion of acyclic amides to α, α-dimethylamines, see: (a) Kuffner, F.; Polke, E. *Monatsh* **1951**, *82* 330–335. (b) Schiess, M. Diss. ETH Nr. 7935, ETH: Zürich, 1986. (c) Calderwood, D. J.; Davies, R. V.; Rafferty, P.; Twigger, H. L.; Whelan, H. M. *Tetrahedron Lett.* **1997**, *38*, 1241–1244. (d) Denton, S. M.; Wood, A. *Synlett* **1999**, 55–56. (e) Tomashenko, O.; Sokolov, V.; Tomashevskiy, A.; Buchholz, H. A.; Welz-Biermann, U.; Chaplinski, V.; de Meijere, A. *Eur. J. Org. Chem.* **2008**, 5107–5111.

(4) (a) DeNinno, M. P.; Eller, C. *Tetrahedron Lett.* **1997**, *38*, 6545–6548. (b) DeNinno, M. P.; Eller, C.; Etienne, J. B. *J. Org. Chem.* **2001**, *66*, 6988–6993.

(5) (a) Suh, Y.-G.; Shin, D.-Y.; Jung, J.-K.; Kim, S.-H. *Chem. Commun.* **2002**, 1064–1065. (b) Suh, Y.-G.; Kim, S.-H.; Jung, J.-K.; Shin, D.-Y. *Tetrahedron Lett.* **2002**, *43*, 3165–3167. (c) Jung, J.-W.; Shin, D.-Y.; Seo, S.-Y.; Kim, S.-H.; Paek, S.-M.; Jung, J.-K.; Suh, Y.-G. *Tetrahedron Lett.* **2005**, *46*, 573–575.

(6) (a) Murai, T.; Mutoh, Y.; Ohta, Y.; Murakami, M. *J. Am. Chem. Soc.* **2004**, *126*, 5968–5969. (b) Murai, T.; Asai, F. *J. Am. Chem. Soc.* **2007**, *129*, 780–781. For other selected examples on nucleophilic additions to acyclic thioamides, see: (c) Tamaru, Y.; Harada, T.; Nishi, S.; Yoshida, Z. *Tetrahedron Lett.* **1982**, *23*, 2383–2386. (d) Ishida, A.; Nakamura, T.; Irie, K.; Oh-ishi, T. *Chem. Pharm. Bull.* **1985**, *33*, 3237–3249. (e) Tominaga, Y.; Kohra, S.; Hosomi, A. *Tetrahedron Lett.* **1987**, *28*, 1529–1532. (f) Tominaga, Y.; Matsuoka, Y.; Hayashida, H.; Kohra, S.; Hosomi, A. *Tetrahedron Lett.* **1988**, *29*, 5771–5774.

(7) For selected examples on nucleophilic addition to acyclic amides via iminium triflates, see: (a) Magnus, P.; Payne, A. H.; Hobson, L. *Tetrahedron Lett.* **2000**, *41*, 2077–2081. (b) Magnus, P.; Gazzard, L.; Hobson, L.; Payne, A. H.; Rainey, T. J.; Westlund, N.; Lynch, V. *Tetrahedron* **2002**, *58*, 3423–3443. (c) Larouche-Gauthier, R.; Bélanger, G. *Org. Lett.* **2008**, *10*, 4501–4504. (d) Xiao, K.-J.; Luo, J.-M.; Ye, K.-Y.; Wang, Y.; Huang, P.-Q. *Angew. Chem., Int. Ed.* **2010**, *49*, 3037–3040. (e) Xiao, K.-J.; Wang, Y.; Ye, K.-Y.; Huang, P.-Q. *Chem. Eur. J.* **2010**, *16*, 12792–12796. (f) Bélanger, G.; O'Brien, G.; Larouche-Gauthier, R. *Org. Lett.* **2011**, *13*, 4268–4271.

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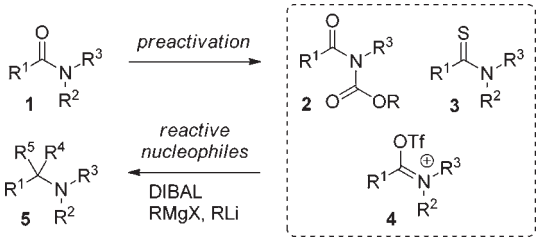
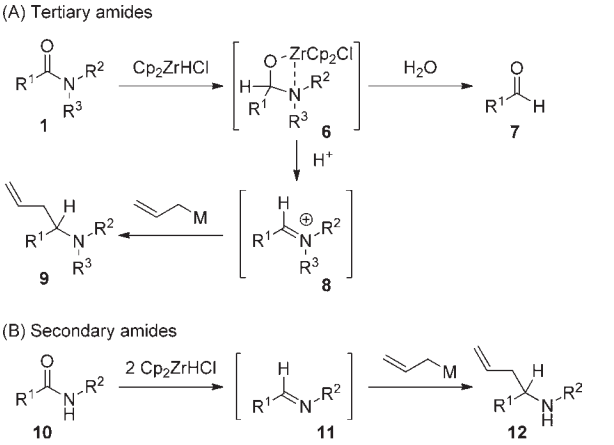
nucleophilic addition via iminium triflate **4**.[7] Although the preactivation step enhances the electrophilicity of the amide carbonyls, it costs an extra operation and still requires reactive nucleophiles, which renders the reaction conditions incompatible with sensitive functional groups.

Scheme 1. Nucleophilic Addition to Amide Carbonyl Groups via the Preactivation Step



As part of our ongoing studies aimed at exploring direct functionalization of inert amide carbonyls, our group[8a] and that of Vincent/Kouklovsky[8b] independently reported the novel sequential nucleophilic addition to *N*-alkoxyamides via a five-membered chelated intermediate.[8] In this methodology, exclusion of the preactivation step was achieved with assistance of the *N*-alkoxy group. In this paper, we describe the development of a direct chemoselective allylation[9] of inert amide carbonyls using the Schwartz reagent (Cp_2ZrHCl),[10,11] which enables us to functionalize amide groups directly without supporting functional groups (Scheme 2). When tertiary amides such as **1** are exposed to the Schwartz reagent at room temperature, they are known to produce the zirconacycle intermediate **6**, which affords the corresponding aldehyde **7** after workup.[12] We predicted that addition of an acid to **6** in one pot would initiate the generation of iminium ion **8** instead of aldehyde **7**. The resulting iminium ion **8** could undergo subsequent allylation to give substituted tertiary amine **9** in a single step. On the other hand, reduction of the secondary amide **10** mechanistically requires 2 equiv of the Schwartz reagent, providing imine **11**.[13] We expected that imine **11** would be amenable to one-pot allylation, providing the secondary amine **12**. The reaction conditions we developed were found to be highly chemoselective, enabling the direct allylation of either tertiary or secondary amides in the presence of sensitive functional groups.

Scheme 2. (A) Direct Allylation of Tertiary Amides without the Preactivation Step; (B) Direct Allylation of Secondary Amides without the Preactivation Step.



Our direct allylation of tertiary amides was first evaluated with *N*-benzyl-*N*-methylbenzamide **1a** (Table 1).[14] Treatment of **1a** in $(CH_2Cl)_2$ with Schwartz reagent, which was freshly prepared from Red-Al and Cp_2ZrCl_2 in THF,[10b] quickly gave zirconacycle **6a**. The subsequent allylation with allyltributylstannane, in the absence of acid, provided the desired product **9a** in 9% yield, along with a significant amount of benzaldehyde **7a** (Table 1, entry 1). This result indicated that iminium ion **8a** (shown in Scheme 2) was not efficiently formed without an acid. We then investigated the effect of different acids, which could potentially mediate the formation of both iminium ion **8a** and aldehyde **7a** from the common zirconacycle **6a**. Indeed, the allylation with $Sc(OTf)_3$ produced tertiary amine **9a** in 36% yield and secondary alcohol **13a** in 34% yield (Table 1, entry 2). The selectivity depended greatly on the nature of the acid. When $BF_3 \cdot Et_2O$ was utilized, both yield and selectivity were improved to produce **9a** in 58% yield, along with **13a** in 9% yield (Table 1, entry 3). After an extensive survey of Lewis acids and Brønsted acids, TFA proved to be the best acid with **9a** isolated in 75% yield

(8) (a) Shirokane, K.; Kurosaki, Y.; Sato, T.; Chida, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 6369–6372. (b) Vincent, G.; Guillot, R.; Kouklovsky, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 1350–1353. Kibayashi reported pioneering work involving Grignard addition and subsequent hydride reduction to six-membered *N*-alkoxylactams; see: Iida, H.; Watanabe, Y.; Kibayashi, C. *J. Am. Chem. Soc.* **1985**, *107*, 5534–5535.

(9) For selected reviews on allylation to iminium intermediates, see: (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207–2293. (b) Puentes, C. O.; Kouznetsov, V. *J. Heterocycl. Chem.* **2002**, *39*, 595–614.

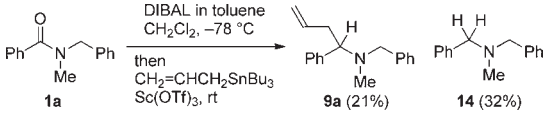
(10) (a) Wailes, P. C.; Weigold, H. *J. Organomet. Chem.* **1970**, *24*, 405–411. (b) Hart, D. W.; Schwartz, J. *J. Am. Chem. Soc.* **1974**, *96*, 8115–8116.

(11) For selected reviews on the Schwartz reagent, see: (a) Negishi, E.; Takahashi, T. *Synthesis* **1988**, 1–19. (b) Hoveyda, A. H.; Morken, J. P. *Angew. Chem., Int. Ed.* **1996**, *35*, 1262–1284. (c) Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *52*, 12853–12910. (d) Wipf, P.; Nunes, R. L. *Tetrahedron* **2004**, *60*, 1269–1279.

(12) (a) White, J. M.; Tunoori, A. R.; Georg, G. I. *J. Am. Chem. Soc.* **2000**, *122*, 11995–11996. (b) Spletstoser, J. T.; White, J. M.; Tunoori, A. R.; Georg, G. I. *J. Am. Chem. Soc.* **2007**, *129*, 3408–3419.

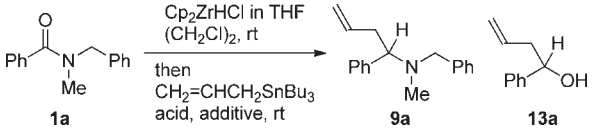
(13) (a) Schedler, D. J. A.; Godfrey, A. G.; Ganem, B. *Tetrahedron Lett.* **1993**, *34*, 5035–5038. (b) Schedler, D. J. A.; Li, J.; Ganem, B. *J. Org. Chem.* **1996**, *61*, 4115–4119.

(14) As a control experiment, tertiary amide **1a** was reduced with DIBAL (1.3 equiv) at −78 °C, and subsequent treatment with $Sc(OTf)_3$ (1.3 equiv) and allyltributylstannane (3 equiv) at room temperature afforded **9a** in 21% yield, along with overreduced byproduct **14** in 32% yield. These results indicated that the *N*,*O*-acetal after DIBAL reduction was quickly converted to the iminium ion, which underwent extra DIBAL reduction to provide **14**.



(Table 1, entry 4). Addition of MeCN prior to the allylation gave a slightly better yield (Table 1, entry 5).

Table 1. Optimization of the Reaction Conditions in the Direct Allylation of Tertiary Amides **1a**[a]



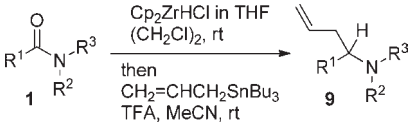
			yield (%)[b]	
entry	acid	additive	**9a**	**13a**
1	none	none	9	0
2	$Sc(OTf)_3$	none	36	34
3	$BF_3 \cdot Et_2O$	none	56	9
4	TFA	none	75	15
5	TFA	MeCN	77	6

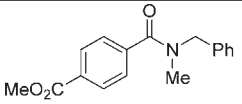
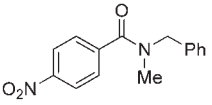
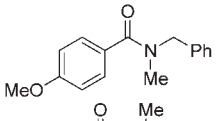
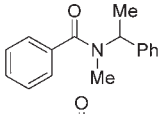
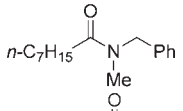
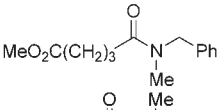
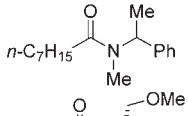
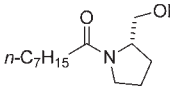
[a] Conditions: **1a** (150 μmol), Cp_2ZrHCl (1.8 equiv in THF), $(CH_2Cl)_2$, rt, 15 min, then $CH_2{=}CHCH_2SnBu_3$ (3.0 equiv), acid (1.5 equiv), additive, rt, overnight. [b] Yield of isolated product after purification by column chromatography on silica gel.

The scope of the direct allylation with various acyclic tertiary amides revealed remarkable functional group tolerance (Table 2).[15] We succeeded in chemoselective allylation of the inert amide carbonyls without affecting the more electrophilic methyl ester to afford **9b** in 72% yield (Table 2, entry 1). The reaction was also compatible with **1c** bearing the sensitive nitro group (Table 2, entry 2). Electron-rich 4-methoxybenzamide **1d** and sterically hindered amide **1e** led to a decrease in product yield with the corresponding benzyl alcohols isolated as byproduct (24% and 17%, respectively), likely because zirconacycle **6** was not stable during the reduction, and over-reduction to aldehyde **7** took place (Table 2, entries 3 and 4). The reaction of aliphatic amides gave rise to better results than aromatic amides. Allylation of aliphatic amides with, or without, the methyl ester proceeded in good yield (Table 2, entries 5 and 6). In contrast to aromatic amides, a variation in steric bulk on the amine side was possible without a loss in yield (Table 2, entries 7 and 8). While the reaction with **1h** provided a 1.2:1 mixture of diastereomers in 80% yield, proline-derived amide **1i** gave the product in 77% yield as a single diastereomer.[16]

Our next challenge was direct access to secondary amines from the corresponding secondary amides (Table 3). Because the reduction of secondary amides with the Schwartz reagent proceeds in a different manner from that of tertiary amides as shown in Scheme 2, we needed to develop different optimized conditions. We first investigated the reaction using *N*-benzylbenzamide **10a**. After treatment of **10a** with the Schwartz reagent, a variety of allylation reagents were added to the resulting imine **11a** in one pot. The nature of the allylation reagents was found to be critical in determining the selectivity between the secondary amine **12a** and secondary alcohol **13a**. While the use of allylboronicacid pinacol ester gave **13a** exclusively, allylindium bromide afforded secondary amide **12a** as the major product (Table 3, entries 1 and 2). We found that the best result in terms of both selectivity and yield was obtained when using allylzinc bromide (Table 3, entry 3: method A). As alternative conditions, TMSOTf-mediated allylation using allyltributylstannane showed complete selectivity and good yield (Table 3, entry 4: method B).

Table 2. Substrate Scope in the Direct Allylation of Tertiary Amide **1**[a]



entry	**1**		yield (%)[b]
1	**1b**		72
2	**1c**		61
3	**1d**		39
4	**1e**		19 (dr = 1.3:1)
5	**1f**		86
6	**1g**		68
7	**1h**		80 (dr = 1.2:1)
8	**1i**		77 (single)

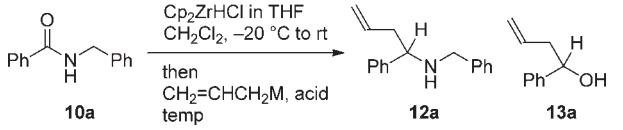
[a] Conditions: **1**, Cp_2ZrHCl in THF, $(CH_2Cl)_2$, rt, 15 min, then $CH_2{=}CHCH_2SnBu_3$, TFA, MeCN, rt, overnight. [b] Yield of isolated product after purification by column chromatography on silica gel.

As summarized in Table 4, two useful methods were applied to each of the secondary amides **10**. The high functional selectivity was also observed for secondary amides bearing the methyl ester and nitro groups (Table 4, entries 1 and 2). In these situations, allyltributylstannane (method B) was superior to allylzinc bromide (method A) because of its

(15) Calderwood reported α-dimethylation of primary amides in the presence of a nitrile group; see: ref 3c.

(16) Although **9i** was obtained as a single diastereomer, the relative stereochemistry of **9i** was not determined.

Table 3. Optimization of the Reaction Conditions in the Direct Allylation of Secondary Amides **10a**[a]



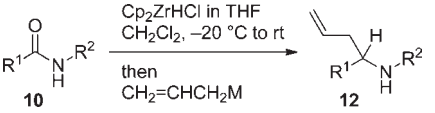
				yield (%)[b]	
entry	M	acid	temp (°C)	**12a**	**13a**
1	B(pinacol)	none	none	0	73
2	InBr	none	−78 to rt	56	7
3	ZnBr	none	0 to rt	81	0
4	$SnBu_3$	TMSOTf	rt	74	0

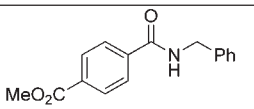
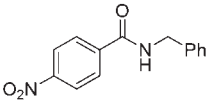
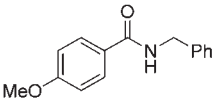
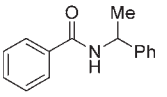
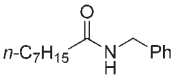
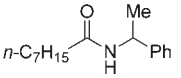
[a] Conditions: **10a** (150 μmol), Cp_2ZrHCl (2.6 equiv in THF), CH_2Cl_2, rt, 15 min, then $CH_2{=}CHCH_2M$ (2.0 equiv), acid (2.0 equiv), rt, overnight. [b] Yield of isolated product after purification by column chromatography on silica gel.

milder nucleophilicity. Method A was found to be more effective on electron-rich *p*-methoxybenzamide **10d** and sterically hindered amide **10e** (Table 4, entries 3 and 4). In contrast to the tertiary amides shown in Table 2, aliphatic secondary amides tended to give relatively lower yields than aromatic secondary amides (Table 4, entries 5 and 6). Method A was preferable for aliphatic amide **10f** (Table 4, entry 5). Variation in the steric bulk on the amine side was possible without detrimental effects on yield (Table 4, entry 6).

In conclusion, we have developed a direct allylation reaction of inert amide carbonyls by taking advantage of the properties of the Schwartz reagent. The methodology afforded either substituted tertiary amines or secondary amines from the corresponding amides without a preactivation step, which is generally required to increase the electrophilicity of amide carbonyls. A conspicuous feature of the direct allylation was its high chemoselectivity. The reaction conditions allowed us to perform functionalization of inert amides even in the presence of more electrophilic esters or sensitive nitro groups. Studies in which a carbon nucleophile is introduced in the first step, instead of the hydride, as well as the introduction of a variety of nucleophiles in the second step, will be forthcoming.

Table 4. Substrate Scope in the Direct Allylation of Secondary Amides **10**[a]



entry	**10**		method	yield (%)[b]
1	**10b**		A	66
			B	76
2	**10c**		A	73
			B	82
3	**10d**		A	71
			B	38
4	**10e**		A	83 (dr = 2.4:1)
			B	71 (dr = 1.6:1)
5	**10f**		A	58
			B	18
6	**10g**		A	62 (dr = 1.5:1)
			B	52 (dr = 1.5:1)

[a] Conditions: **10**, Cp_2ZrHCl in THF, CH_2Cl_2, −20 °C to rt, 4 h, then <method A> $CH_2{=}CHCH_2ZnBr$, THF, 0 °C to rt, overnight or <method B> $CH_2{=}CHCH_2SnBu_3$, TMSOTf, rt, overnight. [b] Yield of isolated product after purification by column chromatography on silica gel.

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Supporting Information Available. Experimental procedures; copies of ^1H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org

The authors declare no competing financial interest.