

# Direct Conversion of Aldehydes and Ketones to Azides via Sequential Nucleophilic Addition & Substitution

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**Abstract:** This report describes the direct conversion of aldehydes and ketones to alkyl azides through the addition of common organometallic reagents and tandem conversion of the resulting alkoxide without isolation of the intermediate alcohol. A wide range of aldehydes and organometallic reagents (R-Li or R-MgX) are suitable participants in this process. Additional reaction telescoping beyond azide formation is demonstrated.

### Introduction

A major goal of modern organic synthesis is to develop methods for the conversion of readily available feedstocks into synthetic targets of interest while simultaneously minimizing both the resources used and waste generated during the synthesis. In this context, numerous formative metrics have been developed including atom, 1 step, 2 or redox economy. 3 Quantitatively, the majority of waste generated in fine chemical synthesis is solvent and water used in isolation and purification of products.<sup>4</sup> As such, one straightforward way to optimize a synthesis is to combine two or more reactions together into a single operation, an approach known colloquially as telescoping.<sup>5</sup> While conceptually appealing, practical issues arising from reagent (in)compatibility, salt precipitation, acidbase reactions, or side product formation increase the challenges of telescoping relative to traditional sequential reactions. Presented herein is a procedure to telescope the addition of organometallic reagents to carbonyl functionality with *in situ* alcohol activation and azide formation. These steps have been routinely conducted separately,<sup>6</sup> however they are not commonly combined into a single procedure.

We became interested in the synthesis of activated alkyl azides, which are valuable intermediates in the synthesis of amines and heterocycles,<sup>7</sup> and sought an efficient and reliable way to readily prepare these starting materials with the minimal input of time and resources. Alkyl azides are classically prepared by the nucleophilic displacement of alkyl halides or activated alcohols (i.e. tosylates) with sodium azide (Equation 1).<sup>7,8</sup> Additionally, various methods are known to convert alcohols directly to azides through in situ alcohol activation such as via the Mitsunobu reaction,<sup>9</sup> through the use of base and diphenylphosphoryl azide (DPPA),<sup>10</sup> or the combination of HN<sub>3</sub> or trimethylsilyl azide and an acid promoter<sup>11</sup> (Equation 1). In our initial efforts, we struggled to find a reliable method to prepare some azides because the activated alkyl halides were prone to decomposition. For example, we were unable to isolate the tertiary bromide en route to azide 46. Many other methods required multiple steps, resulted in alcohol dehydration, ether

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formation, or poor conversion. This led us to consider whether the azides of interest could be prepared directly from readily available carbonyl containing compounds through reaction telescoping, which would avoid the need to isolate potentially unstable activated intermediates. The proposed route could involve addition of an organometallic reagent (organolithium or Grignard) to the carbonyl, *in situ* trapping of the resultant alkoxide, and nucleophilc displacement to form the azide without isolation of the intermediate alcohol or alcohol derivative (Equation 2).

**Established Azide Preparations** 

This Work: Direct Synthesis from Carbonyl



### **Results and Discussion**

We began with 4-methoxy benzaldehyde (1) as a model activated substrate and investigated the addition of phenyl magnesium bromide followed by the addition of various activating agents and azide sources (Table 1). The use of tosyl chloride as an activating reagent followed by NaN<sub>3</sub> addition afforded the desired azide 2 in modest yield (81%) and the use of TMSN<sub>3</sub> did not afford appreciable levels of azide (not shown). DPPA provided the highest yield in the initial evaluation (entry 1), was the most operationally straightforward azide source, and is generally considered to have an excellent safety profile. Therefore, DPPA was selected for further optimization. The process could be conducted in a variety of solvents (entries 1 - 4) and THF was selected due to its ubiquity. Conducting the substitution reaction to proceed at slightly elevated temperature allowed the equivalents of reagents to be reduced and the concentration of the reaction to be increased (entries 5 - 8). The optimized procedure involves the addition of the carbonyl compound to 1.2 equivalents of Grignard reagent cooled in ice bath followed by the addition of 1.3 equivalents of DPPA, after which the reaction can be gradually warmed to 40 °C to facilitate nucleophilic displacement (entry 8).

Table 1. Reaction Optimization.

MeO	H <u>condi</u>		MeO		Ph <b>2</b>	
Entry	Equiv. PhMgBr	Equiv. DPPA	[1]/M	Solvent	°C <sup>[a]</sup>	Yield(%) <sup>[b]</sup>
1	1.5	2.0	0.2	PhMe	rt	90
2	1.5	2.0	0.2	Et <sub>2</sub> O	rt	28
3	1.5	2.0	0.2	DME	rt	93
4	1.5	2.0	0.2	THF	rt	92
5	1.5	2.0	0.2	THF	40	94
6	2.0	3.0	0.7	THF	40	89
7	1.0	1.1	0.7	THF	40	77
8	1.2	1.3	0.7	THF	40	94

With optimized conditions in hand, we investigated the nucleophilic reagent. The scope of the organometallic reagent that participated in this process was quite broad (Table 2).<sup>12</sup> Organolithium and Grignard reagents provided comparable yields (entries 1, 3, and 5 vs. entries 2, 4, and 6 respectively) providing the user flexibility. Furthermore, aryl (entries 1, 2 and 10), alkyl (entries 3-6), vinyl (entries 7 and 8),<sup>12</sup> cycloalkyl (entry 9), and heteroaryl (entry 10) reagents all afforded excellent yields in this process.

We next investigated the scope of reaction with respect to the aldehyde (Table 3). Other electron rich (entry 1), neutral (entry 2), or deficient (entries 3 and 4) benzaldehydes afforded the azide in high yield. It is worth noting that in the less activated cases (entry 2-4), the nucleophilic displacement with azide was slow and required longer reaction times, higher temperatures, and/or the addition of exogenous azide (tetrabutylammonium azide) to increase the yield. Heterocycle carboxaldehydes (entries 5 and 6) as well as enals (entries 7 and 8)<sup>13</sup> also participated in this tandem process. Fully saturated aldehydes (entry 9) provided trace elimination products (5% - 10%) in addition to the azide. Chemoselective addition was possible (enty 10). An aromatic nitro group was compatible with these conditions and vinyl Grignard over Bartoli reaction (entry 11). The use of *m*-formyl-benzoic acid did not lead to a high yield of the desired azide due to competing acyl azide formation and further reaction(s).<sup>14</sup> When taken together, these data reflect a wide scope of participating aldehydes and illustrate that this method is of practical utility. To further illustrate the utility, the reaction was conducted on a gram scale (Scheme 1) and the model azide was obtained in excellent yield.



To further test the limits of this telescoped process, other carbonyl compounds were investigated (Table 4). Several activated ketones were compatible with the conditions.

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Benzophenone (entry 1) and 4-methoxy acetophenone (entry 2) afforded the target azide in modest yield. Enones (entries 3 and 4) were also compatible. Unactivated ketones (entry 5), were less reactive to substitution of the putative tertiary phosphate and larger quantities of elimination product(s) were observed. Finally, phenyl benzoate (entry 6) was subjected to the reaction conditions and a modest yield of trityl azide was obtained.



General conditions: 0.4 mmol substrate, 4.8 mmol PhMgBr, 5.2 mmol DPPA, 0.7 M in THF, 0 °C to 40 °C, 18 – 24h [a] Isolated yields after column chromatography. Yields are reported as the average of duplicate trials.

The increased efficiency of this method is exemplified by comparison to the published synthesis of azide **46** (Scheme 2). Previously, a three step procedure involving Horner-Wadsworth-Emmons condensation, selective reduction, and azide formation has been reported in an overall yield of about 5%.<sup>11e,15,16</sup> Starting from the same initial precursor, the method reported here allows a direct synthesis, increases the overall

yield by >10 fold, and reduces the step count from 3 steps to 1 step.

#### Table 3. Scope of Aldehyde.



General conditions: 0.4 mmol substrate, 4.8 mmol PhMgBr, 5.2 mmol DPPA, 0.7 M in THF, 0 °C to 40 °C, 18 – 24h [a] Isolated yields after column chromatography. Yields are reported as the average of duplicate trials. [b] 1 equiv. of TBAN<sub>3</sub> was added and the reaction was conducted at 60 °C. [c] PhLi was used instead of PhMgBr [d] CH<sub>2</sub>CHMgBr was used instead of PhMgBr.





Table 4. Use of Ketones.



General conditions: 0.4 mmol substrate, 4.8 mmol PhMgBr, 5.2 mmol DPPA, 0.7 M in THF, 0 °C to 40 °C, 18 – 24h [a] Isolated yields after column chromatography. Yields are reported as the average of duplicate trials.

We next sought to expand the process beyond azide formation. Gratifyingly, the azide could be reduced to the benzhydrylamine derivative **47** without prior isolation (Scheme 3). This provides a direct synthesis of non-symmetric benzhydrylamine derivatives from readily available precursors in a single process. Benzhydrylamine derivatives are the key pharmacophore present in pharmaceuticals such as Letrozole, Cetirizine, Agispor, and Flunarizine.

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#### Conclusions

The addition of common organometallic reagents to aldehydes can be telescoped with azide formation. This procedure avoids the need to isolate the intermediate alcohol and is compatible with a wide range of aldehydes. A variety of common organometallic reagents are suitable. Preliminary results indicate that both ketones and esters can participate in this cascade and further reaction telescoping is possible even beyond azide formation.

#### **Experimental Section**

Azide Safety: Azides are known to be high energy materials and explosions have been reported when working with azides. In the course of this work, no issues were encountered. All of the azides synthesized in this report have C/N ratios equal to or above the recommended guideline of 3. Precautionary blast shields were used for all reaction using or producing more than 1 mmol of azide. Blast shields were used both in the fume hood and during rotary evaporation. All waste and aqueous solution which could be contaminated with azide were kept in individually labeled containers and were kept STRICTLY free of acid to avoid the accidental production of HN<sub>3</sub> – DO NOT use aqueous HCl during work up of any of the reactions reported herein. Please read further before repeating these experiments.<sup>17</sup>

Azide synthesis. Procedure I: A magnetic stir bar was added to a 50 mL or 100 mL 2- or 3-neck oven dried round bottom flask. The flask was fitted with rubber septa, gas inlet, and connected to a Schlenk line. The flask was evacuated and backfilled with argon (3 cycles), placed under a positive pressure of argon, and partially submerged into an ice bath. To the flask, THF (6 mL) and phenylmagnesium bromide (1.5 mL, 3M in Et<sub>2</sub>O, 4.5 mmol, 1.2 equiv.) were sequentially transferred via syringe. After 5 min in the ice bath, 4-methoxybenzaldehyde (0.48 mL, 3.7 mmol, 1 equiv.) was added dropwise via syringe. After addition of the benzaldehyde was complete, the ice bath was removed. After an additional 10 min, the flask was reintroduced into the ice bath and diphenylphosphoryl azide (1.1 mL, 4.8 mmol, 1.3 equiv.) was added dropwise. After an additional 10 min in the ice bath, the ice bath was removed and the solution was heated to 40 °C. The temperature was maintained at 40 °C for 18 h - 24 h. After this time, the reaction was quenched by addition of water. The resulting solution was extracted with DCM (3 x 20 mL) and the combined organic phases were dried (MgSO<sub>4</sub>), filtered, and concentrated under reduced pressure. Final purification by column chromatography (40 g cartridge, gradient elution 0% - 30%EtOAc in hexanes) afforded the final product (795 mg, 90%) as a faintly yellow oil. Deactivated aryl aldehydes, including compounds 6, 8, and 10, needed higher temperature and exogenous azide to complete the nucleophilic substitution. A modified procedure was used in these cases:

Procedure II: A magnetic stir bar was added to a 50 mL or 100 mL 2- or 3-neck oven dried round bottom flask. The flask was fitted with rubber septa, gas inlet, and connected to a Schlenk line. The flask was evacuated and backfilled with argon (3 cycles), placed under a positive pressure of argon, and partially submerged into an ice bath. To the flask, THF (3 mL) and phenylmagnesium bromide (0.80 mL, 3M in Et<sub>2</sub>O, 2.4 mmol, 1.2 equiv.) were sequentially transferred via syringe. After 5 min in the ice bath, 4-fluorobenzaldehyde (0.22 mL, 2.0 mmol, 1 equiv.) was added dropwise via syringe. After addition of the benzaldehyde was complete, the ice bath was removed. After an additional 10 min, the flask was reintroduced in the ice bath and diphenylphosphoryl azide (0.57 mL, 2.6 mmol, 1.3 equiv.) was added dropwise. After an additional 10 min in the ice bath, the ice bath was removed and the solution was heated to 60 °C. After 4h, the solution was allowed to cool to room temperature and solid tetrabutylammonium azide (573 mg, 2.0 mmol, 1.0 equiv.) was added to the flask. The flask was then heated to 60 °C. After 18 - 24 h at 60 °C, the reaction was guenched by addition of water. The resulting solution was extracted with DCM (3 x 20 mL) and the combined organic phases were dried (MgSO<sub>4</sub>), filtered, and concentrated under reduced pressure. Final purification by column chromatography (40 g cartridge, gradient elution 0% - 30% EtOAc in hexanes) afforded the final product (245 mg, 81%) as a faintly yellow oil.

Gram Scale reaction: A magnetic stir bar was added to a 250 mL 3-neck oven dried round bottom flask. The flask was fitted with rubber septa, gas inlet, and connected to a Schlenk line. The flask was evacuated and backfilled with argon (3 cycles), placed under a positive pressure of argon, and partially submerged into an ice bath. To the flask, THF (18 mL) and phenylmagnesium bromide (4.8 mL, 3M in Et<sub>2</sub>O, 4.5 mmol, 1.2 equiv.) were sequentially transferred via syringe. After 5 min in the ice bath, 4-methoxybenzaldehyde (1.5 mL, 12 mmol, 1 equiv.) was added dropwise via syringe. After addition of the benzaldehyde was complete, the ice bath was removed. After an additional 10 min, the flask was reintroduced into the ice bath and diphenylphosphoryl azide (3.4 mL, 16 mmol, 1.3 equiv.) was added dropwise. After an additional 10 min in the ice bath, the ice bath was removed and the solution was heated to 40 °C. The temperature was maintained at 40 °C for 18 h. After this time, the reaction was quenched by addition of water. The resulting solution was extracted with DCM (3 x 20 mL) and the combined organic phases were dried (MgSO<sub>4</sub>), filtered, and concentrated under reduced pressure. Final purification by column chromatography (80 g cartridge, gradient elution 0% - 30% EtOAc in hexanes) afforded the final product (2.57 g, 90%) as a faintly yellow oil.

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**Keywords:** azides • green chemistry • organic chemistry: methodology and reactions

## **Entry for the Table of Contents** COMMUNICATION

then N<sub>3</sub>-P(O)(OPh)<sub>2</sub> 30% - 98% >25 examples

R, R', R" = Aryl, Alkyl, Alkenyl, OPh, or H

Described herein is the direct conversion of aldehydes and ketones to alkyl azides through the addition of common organometallic reagents and tandem conversion of the resulting alkoxide. A wide range of aldehydes and organometallic reagents are suitable in this process. Additional reaction telescoping beyond azide formation is demonstrated.

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- <sup>4</sup> C. Jimenez-Gonzalez, C. S. Ponder, Q. B. Broxterman, J. B. Manley, Org. Process Res. Dev. 2011, 15, 912.
- <sup>5</sup> A. A. Desai, E. J. Molitor, J. E. Anderson, Org. Process Res. Dev. 2012, 16, 160.

a) S. Bräse, Organic Azides: Syntheses and Applications. In Organic Azides John Wiley & Sons, Ltd: 2009; 2010; b) E. F. V. Scriven, K. Turnbull, Chem. Rev. 1988. 88, 297.

a) S. Murahashi, Y. Taniguchi, Y. Imada, Y. Tanigawa, J. Org. Chem. 1989, 54, 3292; b) C. A. VanderWerf, V. L. Heasley, J. Org. Chem. 1966, 31, 3534. <sup>9</sup> H. Loibner, E. Zbiral, Helv. Chim. Acta 1977, 60, 417.

<sup>10</sup> A. S. Thompson, G. R. Humphrey, A. M. DeMarco, D. J. Mathre, E. J. J. Grabowski, J. Org. Chem. **1993**, 58, 5886.

<sup>11</sup> a) M. Dryzhakov, M. Hellal, E. Wolf, F. C. Falk, J. Moran, J. Am. Chem. Soc. 2015, 137, 9555; b) M. A. Tandiary, Y. Masui, M. Onaka, RCS Adv. 2015, 5, 15736; c) B. V. Rokade, K. Gadde, K. R. Prabhu, Eur. J. Org. Chem. 2015, 2015, 2706; d) P. Khedar, K. Pericherla, A. Kumar, Synlett. 2014, 25, 515; e) M. Rueping, C. Vila, U. Uria, Org. Lett. 2012, 14, 768; f) A. V. Malkov, P. Spoor, V. Vinader, P. Kocovsky, J. Org. Chem. 1999, 64, 5308; g) H. M. Sampath Kumar, B. V. Subba Reddy, S. Anjaneyulu, J. S. Yadav, Tetrahedron Lett. 1998, 39, 7385; h) A. Hassner, R. Fibiger, D. Andisik, J. Org. Chem. **1984**, *49*, 4237.

<sup>12</sup> The use of metal hydrides to generate the azide by tandem reduction and subsequent azide formation was not successful in preliminary experiments. Both DPPA and the azide product are sensitive to reduction. In attempts at using DIBAL-H and 4-methoxy acetophenone, only trace azide 4 was obtained.

 $^{13}$  In the case of allylic azides, which could be formed from addition into enals or by vinyl addition, the product observed could from via either an  $S_N 2^2$ mechanism or by direct S<sub>N</sub>2 followed by Winstein rearrangement. In either case, the product observed upon isolation is the conjugated isomer. For seminal reports on the Winstein rearrangement: a) A. Gagneux, S. Winstein, W. G. Young, J. Am. Chem. Soc. 1960, 82, 5956; b) A. K. Feldman, B. Colasson, K. B. Sharpless, V. V. Fokin, J. Am. Chem. Soc. 2005, 127, 13444.

<sup>14</sup> T. Shiori, K. Ninomiya, S. Yamada, J. Am. Chem. Soc. **1972**, 94, 6203.

<sup>15</sup> M. Bernasconi, V. Ramella, P. Tosatti, A. Pfaltz, Chem. Eur. J. 2014, 20, 2440.

<sup>16</sup> The azide obtained here was isolated as a 4:1 E:Z mixture. These isomers could be separated by chromatography. These isomers are in equilibrium via the Winstein rearrangement.

17 a) H. C. Kolb, M. G. Finn, K. B. Sharpless, Angew. Chem Int. Ed. 2001, 40, 2004; b) S. Bräse, C. Gil, K. Knepper, V. Zimmermann, Angew. Chem. Int. Ed. 2005, 44, 5188.

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a) B. M. Trost, Science 1991, 254, 1471; b) B. M. Trost, Angew. Chem. Int. Ed. 1995, 34, 259.

<sup>&</sup>lt;sup>2</sup> P. A. Wender, V. A. Verma, T. J. Paxton, T. H. Pillow, Acc. Chem. Res. 2008, 41, 40.

<sup>&</sup>lt;sup>3</sup> N. Z. Burns, P. S. Baran, R. W. Hoffmann, Angew. Chem. Int. Ed. 2009, 48, 2854.

<sup>&</sup>lt;sup>6</sup> a) S. Kang, W. Tang, H. Li, G. Chreifi, P. Martasek, L. J. Roman, T. L. Poulos, R. B. Silverman, J. Med. Chem. 2014, 57, 4382; b) S. C. K. Rotte, A. G. Chittiboyina, I. A. Khan, Eur. J. Org. Chem. 2013, 2013, 6355; c) C. Zhong, Y. Wang, A. W. Hung, S. L. Schreiber, D. W. Young, Org. Lett. 2011, 13, 5556; d) M. Asada, T. Obitsu, T. Nagase, M. Tanaka, Y. Yamaura, H. Takizawa, K. Yoshikawa, K. Sato, M. Narita, S. Ohuchida, H. Nakai, M. Toda, Bioorg. Med. Chem. 2010, 18, 80; e) H. Tsou, X. Liu, G. Birnberg, J. Kaplan, M. Otteng, T. Tran, K. Kutterer, Z. Tang, R. Suayan, A. Zask, M. Ravi, A. Bretz, M. Grillo, J. P. McGinnis, S. K. Rabindran, S. Ayral-Kaloustian, T. S. Mansour, J. Med. Chem. 2009, 52, 2289; f) J. Doyon, E. Coesemans, S. Boeckx, M. Buntinx, B. Hermans, J. P. Van Wauwe, R. A. H. J. Gilissen, A. H. J. De Groot, D. Corens, G. Van Lommen, ChemMedChem 2008, 3, 660; g) J.-U. Chung, S. Y. Kim, J.-O. Lim, H.-K. Choi, S.-U. Kang, H.-S. Yoon, H. C. Ryu, D. W. Kang, J. Lee, B. Kang, S. Choi, A. Toth, L. V. Pearce, V. A. Pavlyukovets, D. J. Lundberg, P. M. Blumberg, Bioorg. Med. Chem. 2007, 15, 6043; h) S. Chandrasekhara, M. Seenaiaha, A. Kumara, C. R. Reddya, S. K. Mamidyalab, C. G. Kumarb, S. Balasubramanianc, Tetrahedron Lett. 2001, 52, 806.