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Transnitrilation from Dimethylmalononitrile to Aryl Grignard and Lithium Reagents: A Practical Method for Aryl Nitrile Synthesis

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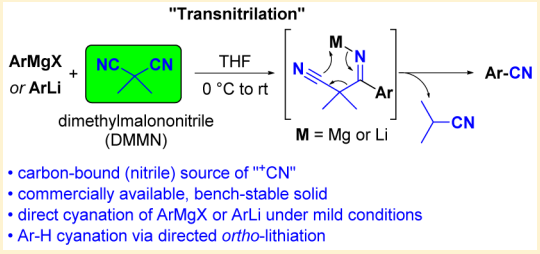
Supporting Information

ABSTRACT: An electrophilic cyanation of aryl Grignard or lithium reagents, generated *in situ* from the corresponding aryl bromides or iodides, by a transnitrilation with dimethylmalononitrile (DMMN) was developed. DMMN is a commercially available, bench-stable solid. The transnitrilation with DMMN avoids the use of toxic reagents and transition metals and occurs under mild reaction conditions, even for extremely sterically hindered substrates. The transnitrilation of aryllithium species generated by directed *ortho*-lithiation enabled a net C−H cyanation. The intermediacy of a Thorpe-type imine adduct in the reaction was supported by isolation of the corresponding ketone from the quenched reaction. Computational studies supported the energetic favorability of retro-Thorpe fragmentation of the imine adduct.



INTRODUCTION

The nitrile functional group is ubiquitous in organic synthesis. Aryl nitriles are present in numerous natural products and marketed drugs.[1] The cyanation of aryl halides is a commonly employed strategy for the preparation of aryl nitriles. Historically, this conversion has been accomplished by the reaction of stoichiometric quantities of CuCN with aryl diazonium salts[2] or aryl iodides.[3] More recent methods for cyanation of aryl halides include transition metal catalyzed processes involving a cyanide anion source,[4] or the reaction of an aryl organometallic species with an electrophilic cyanating reagent.[5]

Transition metal catalyzed cyanation has the drawback of using highly toxic cyanide salts as reagents, thus posing a significant safety concern for large scale applications. Furthermore, the strong bonding of cyanide with the metals used as catalysts makes reaction stalling due to catalyst poisoning a risk. Consequently high catalyst loadings are usually required, particularly for industrial scale reactions where a failed batch can have serious safety and economic implications.[6] While reactions employing less toxic reagents such as $K_4Fe(CN)_6$,[7] BnCN,[8] and NH_3/DMF[9] have been developed, these processes often require conditions not desirable for large scale (high temperatures, high catalyst loadings, or oxygen atmosphere). Transition metal catalyzed cyanation by C−H activation has recently emerged as an alternative method.[10] However, the substrate generality of these processes is currently limited.

The electrophilic cyanation of organometallic reagents (Figure 1) avoids the expense and catalyst poisoning issues of a transition metal catalyst and proceeds at mild temperatures.[5] The reaction was first demonstrated by Grignard in 1914 for the reaction of aryl Grignard reagents with cyanogen chloride (Figure 1A).[11] Grignard later showed the reaction also worked with cyanogen and that BrCN and ICN reacted primarily or exclusively, respectively, as halogenating rather than cyanating reagents.[12] In 1965, Martin[13] reported the use of phenyl cyanate for benzonitrile synthesis from aryl Grignard reagents, and Lee[14] described the analogous utility of 2-pyridyl cyanate in 1996 (Figure 1B). The cyanation of Grignard reagents with TsCN was reported by van Leusen in 1970.[15] Knochel extended the scope of cyanation with TsCN to functionalized organozinc reagents in 1993.[16] In 1999, Cava reported the cyanation of aryllithium reagents with 1-cyanobenzotriazole.[17] In 2010 Beller described the use of 1-cyanobenzimidazole for aryl Grignard cyanation.[18] In 2011, Beller reported *N*-cyano-*N*-phenyl *p*-toluenesulfonamide for aryl Grignard cyanation.[19] With the exception of the latter reagent, these electrophilic cyanating reagents are highly toxic (ClCN, NCCN), are prepared from highly toxic ClCN or BrCN (ArOCN, TsCN, 1-cyanobenzimidazole), are prepared from highly toxic NaCN (1-cyanobenzotriazole), or require low temperature storage to avoid decomposition (ArOCN, TsCN). Furthermore, many of the reagents are either not commercially available or available only on milligram scale at high cost. Herein we report the development of dimethylmalononitrile (DMMN), a safe, bench-stable, commercially available solid, as an effective reagent for transnitrilation with both aryl Grignard and aryllithium reagents (Figure 1C). Unlike the reagents listed in

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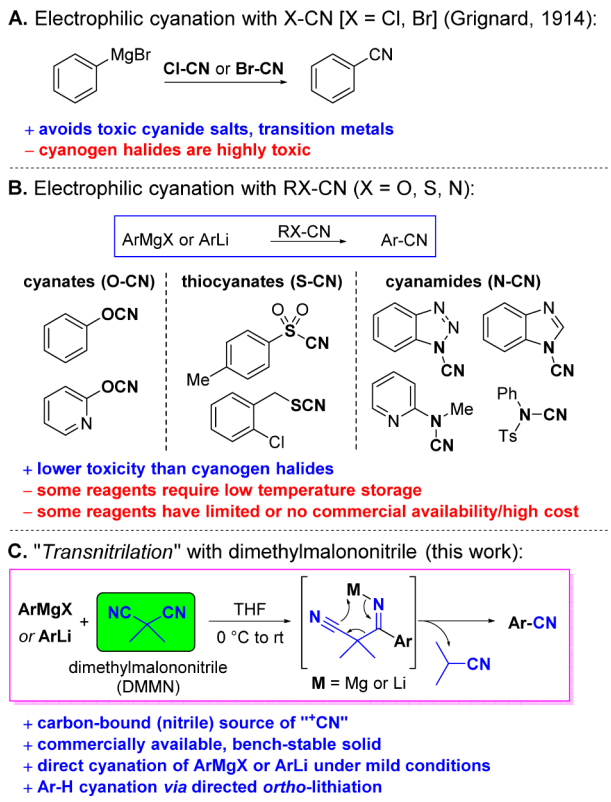


Figure 1. Methods for electrophilic cyanation and development of a transnitrilation from dimethylmalononitrile.

Figure 1A and 1B which contain a heteroatom–CN bond, DMMN is a carbon-bound electrophilic CN source, i.e., a nitrile, and as such possesses greater stability and unique reactivity compared with other reagents.

RESULTS AND DISCUSSION

In support of a drug development program, we required a safe and scalable method for conversion of aryl bromide **1** to nitrile **2** (Figure 2). Traditional Pd-catalyzed cyanation using

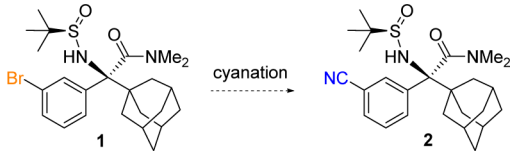
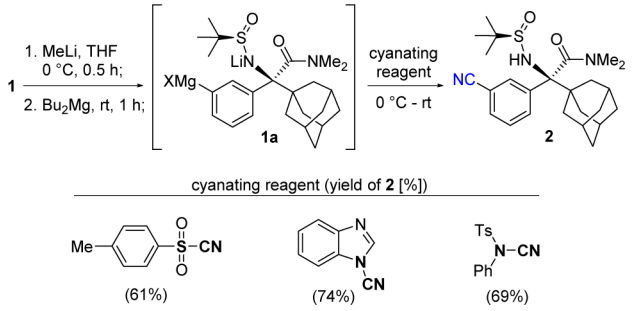


Figure 2. Cyanation of substrate **1**.

$Zn(CN)_2$ was effective for this transformation, but had the two major drawbacks noted above: (1) the reaction was prone to "stalling" presumably due to catalyst poisoning by free cyanide ions, and thus a high catalyst loading (4 mol % Pd) was necessary;[6] (2) the safety concerns for large scale use of $Zn(CN)_2$ or other cyanide sources. The possibilities of applying an electrophilic cyanation were therefore explored.

Generation of the requisite organomagnesium derivative of **1** was best accomplished by initial deprotonation of the sulfinamide with MeLi, followed by treatment with Bu_2Mg to generate the arylmagnesium compound **1a** (Table 1). Deprotonation of the sulfinamide with magnesium reagents (MeMgCl or Bu_2Mg) resulted in an extremely slow and incomplete subsequent bromine/magnesium exchange reac-

Table 1. Cyanation of 1 with Some Common Electrophilic Cyanating Reagents[a,b]



[a]Reaction conditions: (i) 1 equiv of **1**, 1.1 equiv of MeLi, THF, 0 °C, 0.5 h; (ii) 0.8 equiv of Bu_2Mg, rt, 1 h; (iii) 1.5 equiv of cyanating reagent, 0 °C to rt, 16 h. [b]HPLC assay yield.

tion.[20] The arylmagnesium reagent **1a** was then treated at 0 °C with three commonly used electrophilic cyanating reagents: TsCN, 1-cyanobenzimidazole, and *N*-cyano-*N*-phenyl *p*-toluenesulfonamide. The first two reagents were purchased from commercial sources, whereas the third was prepared from *N*-phenylurea as described by Beller.[19] The desired nitrile **2** was formed in good assay yields, with 1-cyanobenzimidazole giving the best result of 74%.

While the feasibility of electrophilic cyanation of **1** was successfully demonstrated, we were interested in exploring the use of more widely available and inexpensive reagents. Along these lines, we were intrigued by a report from Houben and Fischer in 1930 of the base-mediated conversion of trichloromethyl ketimines to nitriles (Figure 3A).[21] The

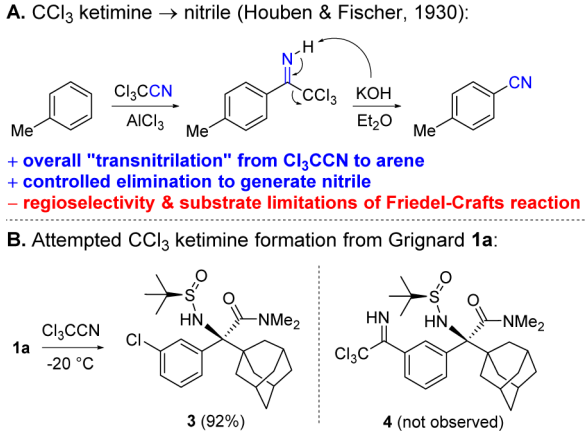


Figure 3. Houben and Fischer's transnitrilation from Cl_3CCN and attempted ketimine formation from Grignard **1a**.

requisite ketimines were prepared by a Friedel–Crafts reaction of an arene with trichloroacetonitrile. This process had the advantage of a controlled elimination to produce the nitrile product.[22] However, the requirement of electron rich arenes as substrates and regioselectivity issues for the Friedel–Crafts reaction limited the generality of the process and rendered it not directly applicable to the preparation of **2**.[23] It was reasoned that addition of aryl Grignard reagent **1a** to trichloroacetonitrile may offer an alternative regioselective route to the requisite trichloromethyl ketimine. Unfortunately, trichloroacetonitrile reacted exclusively as a chlorinating agent with **1a**, providing chloride **3** in 92% yield (Figure 3B).[24] None of the desired trichloromethyl ketimine **4** was observed. The concept of using

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a nitrile bearing an adjacent carbon leaving group for "transnitrilation" with Grignard reagents nonetheless seemed worthy of further exploration.[25]

Development of Dimethylmalononitrile (DMMN) as a Reagent for Transnitrilation. In the design of potential transnitrilation reagents, the use of a substituted pivalonitrile scaffold was explored. It was reasoned that a more hindered nitrile would be beneficial, as it would slow the addition of the organometallic reagent and potentially minimize or prevent formation of overaddition byproducts. Within this structural motif, two possible variations were envisioned with respect to leaving groups (Figure 4). In analogy with the trichloroacetonitrile example above, a nitrile with a suitable electron withdrawing group attached to the α-carbon would, after initial addition of the aryl Grignard reagent, fragment to expel an isopropyl anion stabilized by the electron withdrawing group (Figure 4A). A nitrile with a leaving group at the β-position (Figure 4B) would, after adduct formation, fragment as shown to expel isobutylene and the leaving group and yield the aryl nitrile product.

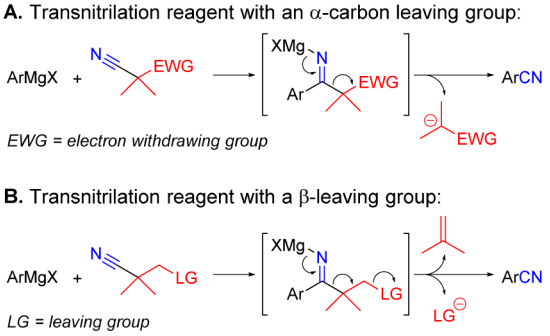
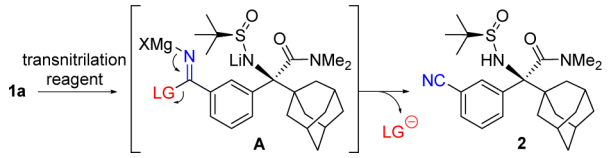
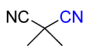
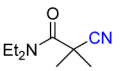
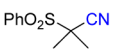
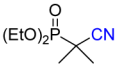
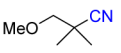
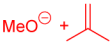
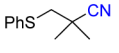
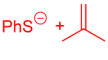
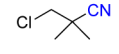


Figure 4. Concepts for transnitrilation reagents with α-carbon (A) and β- (B) leaving groups.

Several transnitrilation reagents were screened in the cyanation of Grignard **1a** (Table 2). Nitriles with α-carbon leaving groups are shown in entries 1–4. The symmetrical dimethylmalononitrile (DMMN, entry 1) gave clean conversion to **2** after 4 h at rt (91% assay yield, 85% isolated yield). In this case, the leaving group is the isobutyronitrile anion. After workup, the liquid isobutyronitrile byproduct was easily removed during the crystallization of **2**.[26] The collapse of adduct **A** to product **2** when DMMN is used as the nitrile transfer reagent is the reverse of a Thorpe reaction (the addition of an α-metalated nitrile to a nitrile).[27] The mild conditions for the reaction of **1a** with DMMN are remarkable compared to the harsh conditions reported in the literature for addition of Grignard reagents to the monocyanated congener of DMMN, *t*-BuCN. For example, Hall and Weiberth have shown that the addition of cyclohexylmagnesium chloride to *t*-BuCN proceeds to only 4% conversion after 24 h at reflux in THF.[28] Presumably the electron withdrawing effect of the second cyano group renders the electrophilicity of DMMN very high and facilitates the addition of **1a** at low temperatures. Transfer of a nitrile group to a Grignard or organolithium reagent has been observed from di- or triaryl acetonitriles.[29] In addition, the reductive decyanation of malononitriles has been reported.[30] DMMN is a commercially available, bench stable solid. It has a health rating of 2 in both the HMIS and NFPA rating systems according to the Sigma-Aldrich MSDS. It has been employed often in the synthesis of bis-oxazoline ligands

Table 2. Survey of Transnitrilation Reagents[a]



entry	transnitrilation reagent	leaving group (LG)	conditions	yield of **2**[b]
1			0-23 °C, 4 h	91%[c]
2			0-23 °C, 4 h	81%
3			0-23 °C, 4 h	<5%
4			0-23 °C, 4 h	0%
5			120 °C, 24 h	63%
6			120 °C, 24 h	0%[d]
7			120 °C, 24 h	<5%

[a]Reaction conditions: 1 equiv of **1a**, THF, 1.5 equiv of transnitrilation reagent. [b]HPLC assay yield. [c]Isolated yield: 85%. [d]The adduct **A** was formed but failed to collapse to **2**.

by condensation with amino alcohols.[31] 2-Cyano-*N*,*N*-diethyl-2-methylpropanamide (entry 2) also worked well as a nitrile transfer reagent, giving **2** in 81% assay yield. The use of a phenylsulfonyl (entry 3) or diethylphosphoryl (entry 4) group was unsuccessful, giving little to no product. Nitriles bearing a β-leaving group are shown in entries 5–7.

The use of β-methoxypivalonitrile (entry 5) resulted in smooth formation of the adduct **A** upon heating at high temperature (120 °C), with slow collapse of **A** to generate **2** in 63% assay yield. While this reagent was conceptually interesting, the high temperature and extended reaction time were not ideal. It was thought that the use of a leaving group better than methoxide could facilitate the reaction under milder conditions. Along these lines, the sulfur analog β-phenylthiopivalonitrile (entry 6) was investigated. Interestingly, this reagent failed to yield any product **2**; the imine adduct **A** was stable and did not convert further. The use of β-chloropivalonitrile (entry 7) gave a complex mixture of products with only trace amounts of **2**. Given the high yield obtained with DMMN under mild reaction conditions, its commercial availability, and its ease of handling and storage, we chose this reagent for evaluation of the scope of the transnitrilation reaction.

Reaction of DMMN with Aryl Grignard Reagents. The scope of the reaction of DMMN with various commercially available aryl Grignard reagents was investigated first (Table 3). The reaction of DMMN with these simple substrates proceeded in good to excellent yields (78–96%). Notably, more sterically hindered aryl Grignard substrates bearing one or two *ortho* methyl groups reacted to give the corresponding nitriles **8** and **9** in the highest yields. The adventitious effect of increased steric hindrance proved to be a salient feature of reactions with DMMN (*vide infra*). The reactions are operationally simple: the Grignard solution is treated with a

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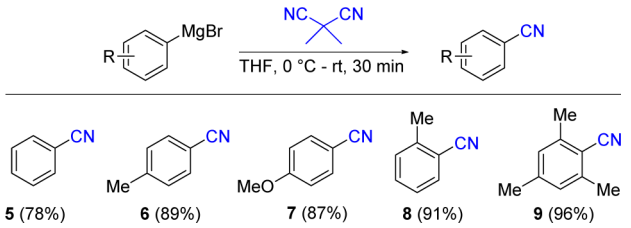
Table 3. Transnitrilation of Aryl Grignard Reagents[a,b]

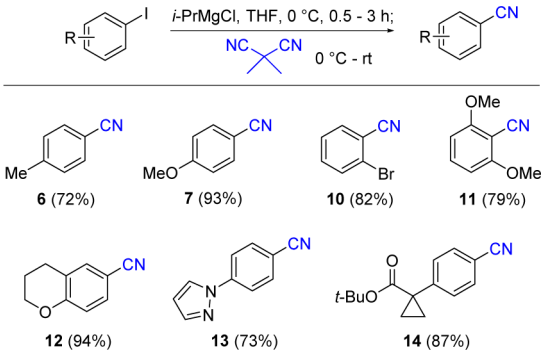


[a]Reaction conditions: 1 equiv of ArMgBr, 1.5 equiv of DMMN, THF, 0 °C–rt. [b]Isolated yield.

THF solution of DMMN (1.5 equiv) at 0 °C, and after the addition is complete the reaction mixture is allowed to warm to rt. The reactions were complete as determined by HPLC analysis after 30 min. The use of a lower stoichiometry of DMMN was possible, but optimal yields were obtained when 1.5 equiv of the reagent was employed.

Knochel's iodine/magnesium or bromine/magnesium exchange procedures offer a convenient method for *in situ* generation of aryl Grignard reagents from the corresponding aryl iodides or bromides.[32] The reaction of aryl Grignard reagents, generated *in situ* from aryl iodides and *i*-PrMgCl according to Knochel's protocol,[33] with DMMN was explored next (Table 4). Simple aryl iodides bearing *para* substituents

Table 4. Transnitrilation of Grignard Reagents Generated *in Situ* from Aryl Iodides[a,b]

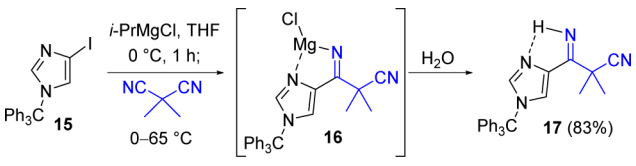


[a]Reaction conditions: 1 equiv of ArI, 1.1 equiv of *i*-PrMgCl, THF, 0 °C; 1.5 equiv of DMMN, THF, 0 °C–rt. [b]Isolated yield.

(products **6** and **7**) provided products in good yields, comparable to those obtained with the commercial Grignard solutions. The hindered 2,6-dimethoxybenzonitrile **11** was produced in good yield (79%). Functional groups such as bromo (product **10**), benzopyranyl (product **12**), pyrazolyl (product **13**), and ester (product **14**) were tolerated.

Notably, the reaction of iodoimidazole **15** resulted not in cyanation but rather formation of the imine **17** in 83% isolated yield (Scheme 1). Presumably the intermediate adduct **16** is stabilized by formation of a magnesium chelate, which renders

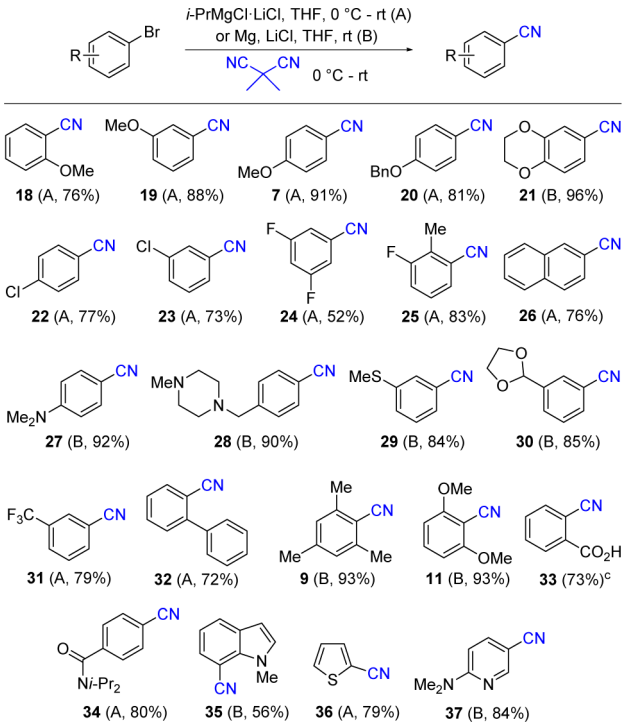
Scheme 1. Imine 17 from the Reaction of Imidazole 15



the retro-Thorpe fragmentation reaction unfavorable. The imine N–H signal in the ^{1}H NMR spectrum of **17** is a single sharp peak and occurs at an unusually low field (10.7 ppm) compared to other N–H ketimines,[28] suggesting an intramolecular hydrogen bond with the imidazole.

The transnitrilation of aryl Grignard reagents generated *in situ* from aryl bromides was examined next (Table 5). In this

Table 5. Transnitrilation of Grignard Reagents Generated *in Situ* from Aryl Bromides[a,b]



[a]Reaction conditions: (A): 1 equiv of ArBr, 1.1 equiv of *i*-PrMgCl·LiCl, THF, 0 °C–rt; 1.5 equiv of DMMN, THF, 0 °C–rt. (B): 1 equiv of ArBr, 1.2 equiv of Mg, 1.2 equiv of LiCl, THF, rt; 1.5 equiv of DMMN, THF, 0 °C–rt. [b]Isolated yield. [c]Grignard formation: 0.55 equiv of Bu_2Mg followed by 1.2 equiv of *n*-BuLi.

case one of Knochel's two methods for Grignard generation was employed: bromine/magnesium exchange with *i*-PrMgCl·LiCl (method A)[34] or magnesium insertion with Mg metal and LiCl (method B).[35] A broad selection of aryl bromides were cyanated under these conditions. Electron rich aryl bromides with *ortho*, *meta*, or *para* substitution gave high yields of nitriles **18**, **19**, **7**, **20**, and **21**. Chloro (products **22** and **23**) and fluoro (products **24** and **25**) substitution of the aryl bromide was tolerated. Nitriles containing aryl amines (**27**) and alkyl amines (**28**) were produced in high yields. Functional groups such as thioether (**29**), dioxolane (**30**), and trifluoromethyl (**31**) were compatible with the cyanation reaction. Sterically hindered bromides were converted smoothly to nitriles **32**, **9**, and **11** in good yields. Nitriles containing electrophilic functional groups such as a carboxylate (**33**) and a tertiary amide (**34**) were prepared in good yields. The cyanation with DMMN was also amenable to the synthesis of heterocyclic nitriles **35**, **36**, and **37**.

Reaction of DMMN with Aryllithium Reagents. The use of aryllithium reagents in the transnitrilation with DMMN was explored. The aryllithium species were generated *in situ* from aryl bromides by bromine/lithium exchange using *n*-BuLi at

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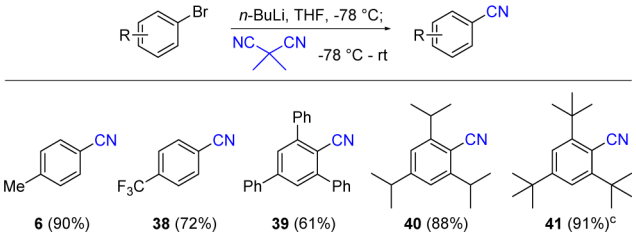
−78 °C (Table 6).[36] Subsequent addition of DMMN to the aryllithium solution resulted in rapid nitrile transfer to provide

Table 6. Transnitrilation of Aryllithiums Generated *in Situ* from Aryl Bromides[a,b]

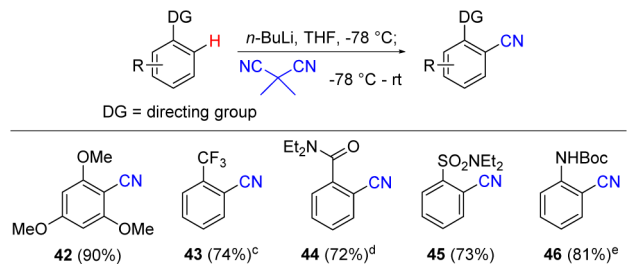


[a]Typical reaction conditions: 1 equiv of ArBr, 1.1 equiv of *n*-BuLi, THF, −78 °C; 1.5 equiv of DMMN, THF, −78 °C−rt. [b]Isolated yield. [c]Toluene/TMEDA (7:1 v/v) used as solvent. Reaction temperature of 0 °C−rt.

the products. *p*-Methyl and *p*-trifluoromethyl benzonitriles (**6** and **38**) were formed in good yields. Highly sterically hindered benzonitriles **39**-**41** were also generated smoothly. The syntheses of **40** and **41** under such mild conditions and in high yields (88% and 91%, respectively) compares well with the reported Cu-catalyzed cyanation procedure to make these compounds (**40**: 160 °C, 16 h, 85% GC yield; **41**: 180 °C, 16 h, 63% GC yield)[37] as well as a report in which **41** was prepared by electrophilic cyanation of the aryllithium reagent using TsCN (34% yield).[38] It was critical to use toluene/TMEDA (7:1 v/v) as the solvent for the reaction to generate **41**. When THF was used as solvent, the majority of the aryllithium was proto-quenched, presumably due to deprotonation of the solvent by the highly basic anion on warming.[39] Lithium/bromine exchange was equally fast in the toluene/TMEDA solvent system (15 min at 0 °C), and the reaction with DMMN took place smoothly within 1 h upon warming gradually to rt.

Given the facility of the aryllithium transnitrilation with DMMN, we explored extension of the reaction to a net C−H cyanation via directed *ortho*-lithiation. Snieckus and co-workers have extensively developed the directed *ortho*-lithiation of arenes for a broad assortment of directing groups.[40] This strategy was found to be effective for cyanation using DMMN as shown in Table 7. Lithiation of 1,3,5-trimethoxybenzene and trapping with DMMN provided nitrile **42** in excellent yield (90%). Regioselective lithiation of benzotrifluoride was accomplished using conditions reported by Schlosser (*n*-BuLi,

Table 7. C−H Cyanation by Directed Lithiation and Transnitrilation[a,b]

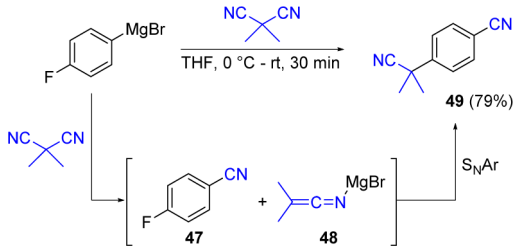


[a]Reaction conditions: 1 equiv of ArH, 1.1 equiv of *n*-BuLi, THF, −78 °C; 1.5 equiv of DMMN, THF, −78 °C−rt. [b]Isolated yield. [c]Lithiation with *n*-BuLi (1.1 equiv) and KO*t*-Bu (1.1 equiv). [d]Lithiation with *s*-BuLi (1.2 equiv) and TMEDA. [e]Lithiation with *t*-BuLi (2.2 equiv).

KO*t*-Bu, THF, −78 °C),[41] and after trapping the anion with DMMN the nitrile **43** was isolated in 74% yield. *N*,*N*-Diethylbenzamide was *ortho*-lithiated with *s*-BuLi and TMEDA and furnished the 2-cyanobenzamide **44** in 72% yield. The *N*,*N*-diethylsulfonamide and *N*-lithio-*N*-Boc directing groups were also effective in the cyanation, providing nitriles **45** (73%) and **46** (81%) respectively.

Tandem Transnitrilation/S_NAr Reaction. The reaction of 4-fluorophenylmagnesium bromide with DMMN occurred in an anomalous manner (Scheme 2). Instead of the expected

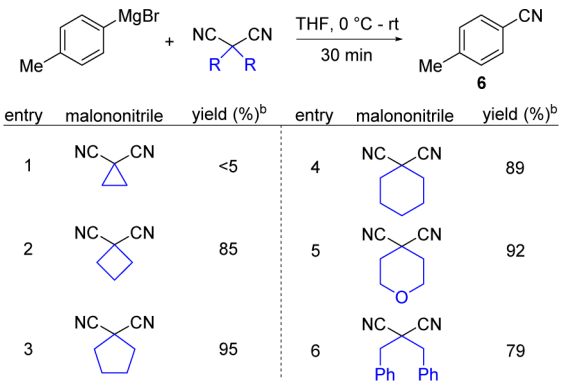
Scheme 2. Transnitrilation/S_NAr Reaction of 4-Fluorophenylmagnesium Bromide



product 4-fluorobenzonitrile (**47**), clean and rapid formation of the 1,4-difunctionalized arene **49** was observed (79% yield). This product derives from S_NAr reaction of isobutyronitrile anion **48** with the electronically activated 4-fluorobenzonitrile **47**. This reaction appears limited to 4-fluorophenyl Grignard reagents, as substrates with 3-fluoro or 4-chloro substituents (Table 5, products **22**, **24**, and **25**) were not observed to undergo S_NAr reaction. While S_NAr reactions of metalated nitriles with aryl fluorides have been reported,[42] the facility and mild conditions, along with the use of a magnesiated nitrile as opposed to a group I counterion, are unique features of this net difunctionalization reaction.[43]

Transnitrilation with Structural Variants of DMMN. The effect of altering the structure of dimethylmalononitrile on the transnitrilation reaction with *p*-tolylmagnesium bromide was explored (Table 8). Cyclic malononitriles bearing three- to six-membered rings were tested (entries 1−5) along with dibenzylmalononitrile (entry 6). 1,1-Dicyanocyclopropane (entry 1) reacted to give only trace amounts of nitrile product **6**, along with several unidentified impurities. In this case, the dinitrile may react with the Grignard reagent not only at a

Table 8. Effect of Variation of Dinitrile Structure[a]



[a]Reaction conditions: 1 equiv of *p*-tolylMgBr, 1.5 equiv of dinitrile, THF, 0 °C−rt. [b]HPLC assay yield.

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nitrile carbon but also at one of the cyclopropyl methylene carbons. The latter mode of reactivity would be favored by the release of ring strain. The related ring opening of a 1,1-dicyanocyclopropane with a methyl cuprate has been reported.[44] In contrast, the reaction with 1,1-dicyanocyclobutane (entry 2) resulted in a clean conversion to **6** (85% yield). The highest yield of **6** was obtained with the five membered ring derivative (entry 3, 95% yield), while the cyclohexane derivative also reacted efficiently (entry 4, 89% yield). The use of a tetrahydropyranyl dinitrile (entry 5) gave **6** in high yield (92%). Finally, the use of dibenzylmalononitrile (entry 6), a more sterically hindered variation of DMMN, resulted in a slightly reduced yield of 79%; by comparison, **6** was obtained in 89% isolated yield from *p*-tolylmagnesium bromide when DMMN was used (see Table 3).

Mechanistic Studies. The proposed mechanism of the transnitrilation reaction is shown in Figure 5. Addition of

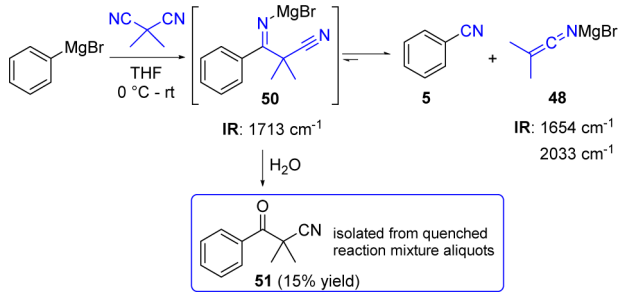

Figure 5. Proposed mechanism of the transnitrilation reaction.

DMMN to PhMgBr results in carbomagnesiation of one of the nitrile groups to give the imine intermediate **50**. The intermediacy of **50** was indirectly proven by quenching the reaction mixture with water and isolation of ketone **51** (15% yield). Attempts to isolate **50** as its N−H ketimine resulted in impure material contaminated with substantial amounts of ketone **51**, suggesting that the N−H ketimine is highly susceptible to hydrolysis.[45] The isolation of **51** provides strong evidence for the intermediacy of imine **50** in the reaction. Furthermore, IR monitoring of the reaction showed the formation of a species with a strong absorbance at 1713 cm^{-1}, a frequency expected for the C═N bond of a ketimine.[28] The fragmentation of imine adduct **50** by a retro-Thorpe reaction results in formation of benzonitrile **5** and the isobutyonitrile anion **48** (IR: 1654 and 2033 cm^{-1}). The identity of **48** was confirmed by a separate experiment in which this species was generated according to the procedure of Wilk by the reaction of *i*-PrMgBr and isobutyronitrile and the IR spectrum recorded, resulting in the same absorbances at 1654 and 2033 cm^{-1}.[42a] The retro-Thorpe fragmentation is likely a reversible process, as evidenced by the detection of small quantities of ketone **51** even after extended reaction times. However, the forward (i.e., fragmentation) direction is favored most likely due to the relief of steric strain imparted by the geminal methyl groups and also potentially due to increased entropy.

The reaction was studied by computational analysis to probe the energetics of the retro-Thorpe fragmentation. All calculations were conducted with the Gaussian 09[46] suite at the DFT level of theory employing B3LYP[47] and LanL2DZ with the effective core potential of Hay and Wadt[48] as the basis set. The structures were optimized in THF using the SMD implicit solvation model of Truhlar, which has a mean unsigned error of ∼1 kcal/mol in computed solvation free energies of neutral molecules.[49] Frequency analyses on the adduct (**52**) and product complex (**53**) have verified their nature as potential energy minima while the transition state was verified as a potential energy maximum. The resulting transition state (**TS**), shown in Figure 6, was subject to an Intrinsic Reaction

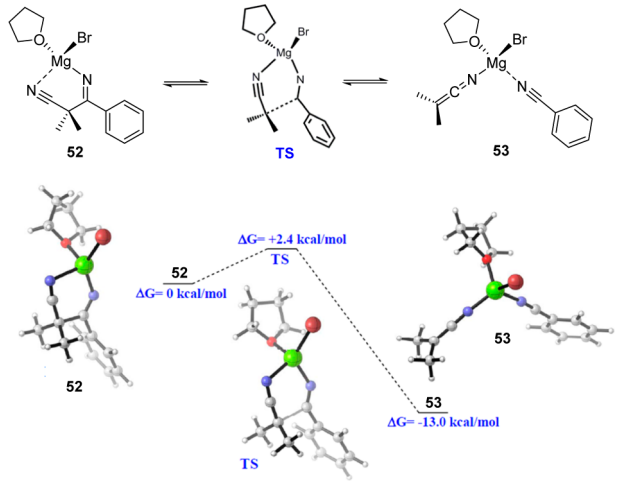

Figure 6. Calculated energetics for the fragmentation of adduct **52** to product complex **53** via transition state **TS** optimized at the B3LYP/LanL2DZ level of theory.

Coordinate[50,51] calculation (B3LYP/LanL2DZ) in which the path of steepest descent on the energy surface was followed to verify a viable reaction pathway that connected the starting adduct (**52**) and product (**53**) geometries. In order to exclude a radical mechanism, the stability of the SCF wave function was verified at each stationary point. The computed free energy barrier for this reaction was 2.4 kcal/mol, which provides compelling support for the favorability of the retro-Thorpe fragmentation of adduct **52**. The drop in free energy from adduct **52** to product complex **53** is presumably largely due to the relief of steric strain upon fragmentation.

CONCLUSIONS

In conclusion, dimethylmalononitrile has been shown to be an effective reagent for cyanation of aryl Grignard and aryllithium reagents by a transnitrilation process. The reaction is amenable to Grignard reagents either derived from commercial sources or prepared *in situ* from aryl iodides or bromides. Aryllithium reagents perform equally well in the transnitrilation process and can be generated *in situ* by either bromine/lithium exchange or directed *ortho*-lithiation. The latter method enables a net C−H cyanation. Importantly, the transnitrilation of highly sterically hindered aryl bromides occurred under mild conditions, in short reaction times, and in high yields, in contrast to the harsh reaction conditions required by transition metal catalyzed processes for these challenging substrates. The reaction of 4-fluorophenylmagnesium bromide with DMMN proceeded by a net 1,4-difunctionalization in which the initially formed aryl nitrile underwent an S_NAr reaction with the liberated isobutyronitrile anion. The effects of variation of the structure of the 2,2-disubstituted malononitrile on the efficiency of the transnitrilation reaction were explored, and 1,1-dicyanocycloalkanes with four- to six-membered rings were found to give comparable yields of transnitrilation product compared to

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DMMN. The intermediacy of a ketimine adduct in the transnitrilation reaction was supported by FTIR studies as well as the isolation from the quenched reaction mixture of the corresponding ketone. The retro-Thorpe fragmentation of the ketimine intermediate was examined by computational analysis and was shown to be energetically favorable compared with the reverse (Thorpe) reaction. Importantly, DMMN is a safe, stable, commercially available, and easily handled solid. The use of DMMN provides a safe and accessible avenue for aryl nitrile synthesis and avoids the toxicity and robustness issues of transition metal catalyzed cyanation. The potential utility of DMMN in other transnitrilations and related processes is under investigation.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analytical data (^{1}H and ^{13}C NMR), computational study details. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b06136.

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Notes

The authors declare no competing financial interest.

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