Unsaturated Nitriles: Conjugate Additions of Carbon Nucleophiles to a Recalcitrant Class of Acceptors

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Qunzhao Wang completed his undergraduate B.S. degree at Beijing University, China, and then spent two years teaching at the Hunan Provincial Zijiang Chemical Industry College. He subsequently pursued an M.S. degree in polymer science at Zhongshan University, China, graduating in 1996 before moving to Gaoming Second Plastics Holding Shares Ltd., China. In 1997 he began graduate study with Fraser F. Fleming focusing on chelation-controlled conjugate additions to alkenenitriles, graduating with a Ph.D. degree in 2001. Currently he is a postdoctorate associate with Bruce Ganem at Cornell University, where his research is focused on multicomponent condensation reactions of isocyanides.

I. Introduction

Anionic conjugate additions are one of the most important carbon−carbon bond-forming reactions in organic synthesis.[1] The maturity of conjugate addition reactions is attested by the abundance of strategic carbon−carbon bond-forming reactions featured in complex syntheses, typically with excellent stereoselectivity.[1] The centrality of conjugate additions stems from installing a new bond two carbons

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removed from an electron-withdrawing group with the potential for an additional alkylation by intercepting the intermediate stabilized carbanion.[2]

Coaxing anionic additions of carbon nucleophiles to unsaturated nitriles represents the last frontier in conjugate addition reactions.[3] The paucity of conjugate additions to α,β-unsaturated nitriles stems from the reactivity being distinctly different from that of the more common α,β-unsaturated carbonyl counterparts. Many conventional nucleophiles are unreactive with α,β-unsaturated nitriles,[4] whereas more reactive nucleophiles divert the reactivity mode toward 1,2-addition. Acrylonitrile is an exception in being significantly more reactive than any other unsaturated nitrile,[5] analogous to the enhanced reactivity observed for related activated ethylenes.

Advances in conjugate additions to unsaturated nitriles parallel the development of increasingly reactive organometallic nucleophiles. In a few instances, difficulties encountered during total syntheses have spurred the development of new reagents and strategies for effecting conjugate addition reactions to unsaturated nitriles. In particular, temporary chelation with proximal alcohol groups is emerging as an alternative strategy for overcoming the challenging conjugate addition of carbon nucleophiles to these recalcitrant acceptors.

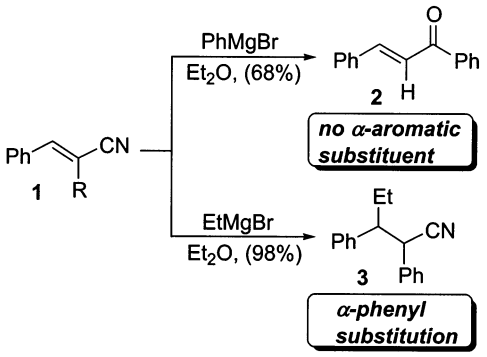
This review surveys conjugate additions of carbon nucleophiles to unsaturated nitriles, omitting alkenenitriles containing an additional electron-withdrawing group since these doubly activated olefins exhibit significantly different reactivity.[6] Radical chain additions to alkenenitriles are omitted, although several organometallic reagents with radical-like reactivity are included since there appears to be a continuum between radical and anionic conjugate addition processes, with the reactivity of the resulting species being more consistent with that of a metalated nitrile rather than a nitrile-stabilized radical. Emphasis is placed on the prerequisites for conjugate additions of carbon nucleophiles to alkenenitriles, partitioning the survey into six groups ordered by the nature of the nucleophile. Analogous reactions of alkynenitriles are surveyed collectively since there are relatively few conjugate additions to alkynenitriles. Identifying the key features for conjugate additions to unsaturated nitriles is anticipated to enhance their use as synthetic intermediates and facilitate the synthesis of nitrile-containing natural products.[7]

2. Conjugate Additions to Alkenenitriles

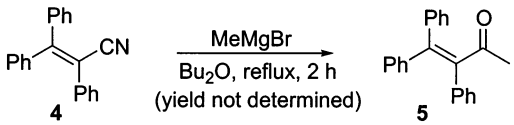
2.1. Conjugate Additions with Grignard Reagents

Historically, Grignard reagents were the first nonstabilized organometallics to undergo 1,4-conjugate additions to alkenenitriles.[8] In contrast to many carbonyl compounds,[9] 1,4-addition is favored in the absence of catalysts, provided that the alkenenitrile contains aromatic substituents on the α and β carbons (Table 1, entries 1−30). In the absence of an aromatic α−substituent, the addition is redirected exclusively to the nitrile group,[8,24] suggesting minimal conjugation between the nitrile and alkene[10] that is enhanced with aromatic α-substituents (Scheme 1).

Scheme 1



Solvent exerts a profound influence over the propensity for 1,2- and 1,4-addition. 1,2-Addition of Grignard reagents to alkenenitriles is favored with noncoordinating solvents such as hexane,[11] presumably promoting association between RMgX and the CN group, whereas ether and THF favor 1,4-addition, as attested by every entry in Table 1. Similarly, for comparative additions to triphenylacetonitrile (**4**), dibutyl ether favors 1,2-addition[12] (eq 1) whereas THF favors 1,4-addition (Table 1, entry 28−30).



The hybridization of the Grignard reagent influences the preference for 1,2- or 1,4-addition. Aryl Grignards tend to add more readily to the nitrile group[13] with the addition of PhMgBr to α-phenylcinnamonitrile (Table 1, entry 4) affording 30−40% of the 1,2-adduct as a minor component compared with minimal 1,2-addition with alkyl Grignards (Table 1, entries 1−3).

Conjugate additions to α,β-diaryl alkenenitriles necessarily generate diastereomers upon protonation (Table 1, entries 1−4, 9−26, and 39−42) and alkylation (Table 1, entries 5−8). Only modest stereoselectivity (∼1:3) is generally observed for protonation[24] and alkylation of the intermediate metallonitriles, limiting the conjugate addition−alkylation to the synthesis of symmetrically substituted nitriles (Table 1, entries 28−30).

Recently, conjugate additions of Grignard reagents to γ-hydroxyalkenenitriles has emerged as an efficient route to aliphatic β-substituted nitriles.[22,23] The key to harnessing this reaction lies in deprotonating the hydroxyalkenenitrile with *t*-BuMgCl, followed by transiently chelating a second Grignard reagent in a γ-alkoxide complex **7**[23] (Scheme 2 and Table 1 entries 31−42). Presumably the close proximity between the two centers favors the conjugate addition[25] since no conjugate addition occurs in the absence of hydroxyl group. Structurally diverse Grignard reagents add efficiently in what is one of the few conjugate additions to an alkenenitrile without aromatic substituents. The addition−alkylation of Grignard reagents to aliphatic alkenenitriles exhibits a surprising degree of selectivity, affording the benzyl nitriles **9** and **10** in a diastereoisomeric ratio of 6.6:1 (Scheme 2).[22]

Table 1. Conjugate Addition of Grignard Reagents to α,β-Alkenenitriles

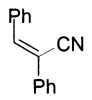
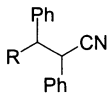
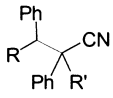
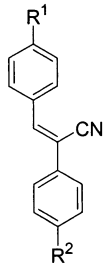
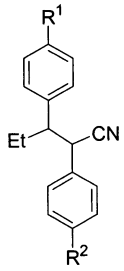
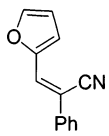
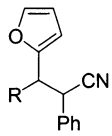
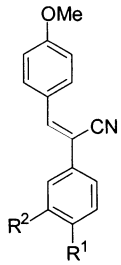
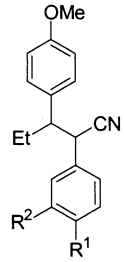
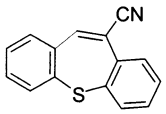
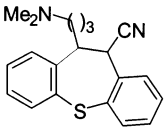
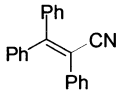
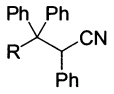
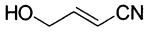
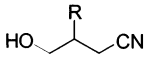
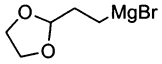
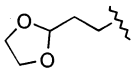
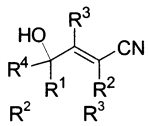
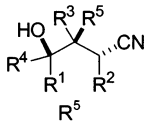
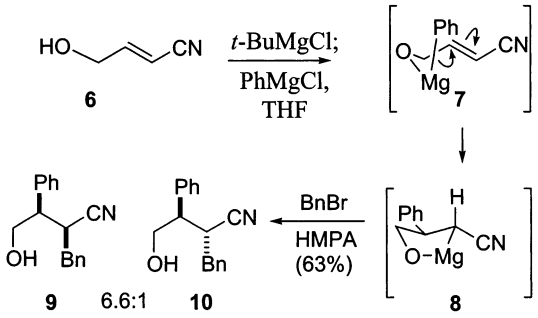
entry	alkenenitrile	Grignard	alkanenitrile	yield	ref(s)
		RMgBr			
		R			
1		Et		98%	8
2		*n*-Bu		98%	14
3		*i*-Bu		91%	14
4		Ph		60-70%	8
		R MgBr ; R'X			
		R R'X			
5		Me MeI		-	15
6		Et EtI		86%	8
7		Et BnBr		100%	8
8		Et PhCOCl		100%	16
		EtMgBr			
	R^1 R^2				
9	H H			93%	12
10	H OMe			91%	12
11	H Cl			94%	12
12	H Me			84%	12
13	Cl Me			86%	12
14	OMe H			81%	12
15	OMe H			79%	12
16	NMe_2 OMe			84%	12
17	Cl H			92%	12
18	Cl Cl			90%	12
19	OMe OMe			87%	12
		RMgX			
			R		
20		MeMgI	Me	85%	17
21		EtMgBr	Et	81%	17
22		PrMgBr	Pr	80%	17
23		$Me_2CHCH_2CH_2MgBr$	$Me_2CHCH_2CH_2$	33%	17
		EtMgBr			
	R^1 R^2				
24	OMe H			89%	18
25	H OMe			81%	19
26	H H			94%	18

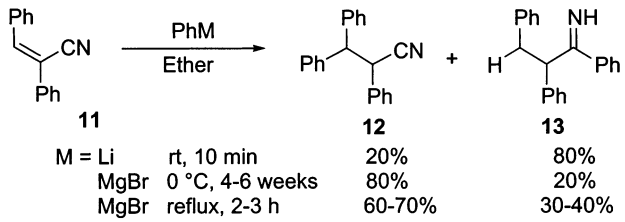
Table 1. (Continued)

entry	alkenenitrile	Grignard	alkanenitrile	yield	ref(s)
27		$Me_2N(CH_2)_3MgCl$		91%	20
		RMgBr			
		R			
28		Bu		48%	21
29		C_5H_{11}		41%	21
30		C_6H_{13}		44%	21
		*t*-BuMgCl; RMgX			
		RMgX	R		
31		MeMgCl	Me	74%	22
32		BuMgCl	Bu	80%	22
33		$Cl(CH_2)_4MgBr$	$Cl(CH_2)_4$	50%	22
34		*cyclo*-C_5H_9MgBr	*cyclo*-C_5H_9	78%	22
35				78%	22
36		PhMgCl	Ph	76%	22
37		$CH_2CHMgBr$	CH_2CH	63%	22
38		PhC≡CMgBr	PhC≡C	62%	22
		*t*-BuMgCl; R^5MgX			
	R^1 R^2 R^3 R^4	R^5MgX	R^5		
39	H H Me H	PhMgCl	Ph	63%	23
40	-$(CH_2)_3$- H H	MeMgCl	Me	60%	23
41	-$(CH_2)_3$- H H	PhMgCl	Ph	86%	23
42	H H -$(CH_2)_4$-	PhMgCl	Ph	57%	23

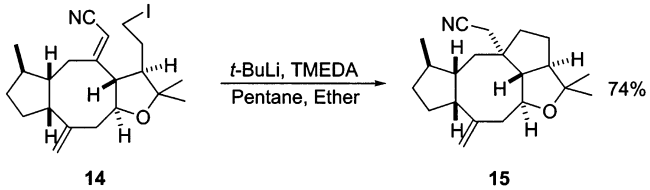
Scheme 2



The limited number of organolithium additions to alkenenitriles stems from an increased propensity toward 1,2-addition compared to Grignard reagents (eq 2).[8,12]



The cyclization of **14** implies that alkyllithium reagents are effective anionic nucleophile[26] in conjugate additions to alkenenitriles, provided that 1,2-addition is prevented (eq 3).[27] Presumably the reaction is facilitated by geometric constraints that position the alkyllithium in close proximity to the β-carbon while preventing 1,2-addition to the nitrile group. Installing the quaternary center is remarkably efficient, given that the β-carbon is doubly substituted and that the δ-proton is sufficiently acidic[28] to potentially protonate the alkyllithium intermediate.



2.2. Copper-Based Conjugate Additions to α,β-Alkenenitriles

Organocopper reagents mediate a plethora of conjugate additions to unsaturated carbonyl compounds.[29] Comparatively, organocopper reagents are generally unreactive toward alkenenitriles[4] with the few successful conjugate additions requiring particularly

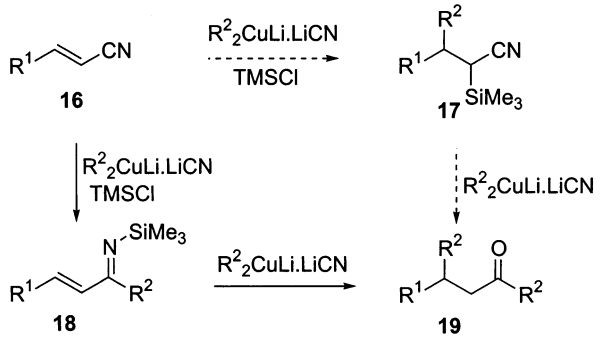
reactive cuprates, usually in combination with acrylonitrile or a similarly activated alkenenitrile. The disparate reactivity of alkenenitriles and unsaturated carbonyl compounds toward organocopper reactions may reflect the more negative reduction potential of alkenenitriles[4b] and the facile lithium complexation that activates carbonyl-derived acceptors[30] which is more difficult[31] for the less Lewis basic nitrile group.[32]

Particularly reactive cuprates, such as lithium diallylcuprate,[33] are generally required for efficient organocopper additions to alkenenitriles (Table 2, entries 1−5). Conjugate additions with lithium diallylcuprate typify the general trends; conjugate additions to aryl-substituted acrylonitriles are significantly more efficient than those with the corresponding alkyl-substituents, particularly when both α- and β-carbons are substituted. α-Substituents capable of additional π-delocalization significantly promote the conjugate additions (Table 2, entries 14−17), probably by simultaneous electronic activation and sterically retarding competitive 1,2-addition. Similar activation of the allenyl nitrile, by virtue of the more electropositive sp β-carbon, permits one of the few conjugate additions with a conventional Gilman reagent (Table 2, entries 18−19).

$R_2CuLi{\cdot}LiCN$ cuprates, and an unusual fluxional cuprate, are particularly prone to 1,2-addition with alkenenitriles (Table 2, entries 20−27). $Me_2CuLi{\cdot}LiCN$ causes 1,2-addition and reduction of cinnamonitrile (Table 2, entry 20), whereas addition of TMSCl redirects the reaction toward double 1,2- and 1,4-addition to afford β-substituted ketones (Table 2, entries 21−23). A similar activation by TMSCl occurs in copper-catalyzed organosamarium additions where conjugate adducts are only obtained in the presence of TMSCl (Table 2, entry 13).[4d,34]

Two pathways are possible for the double addition of organocopper reagents to alkenenitriles (Scheme 3). Sequential 1,4-addition−silylation followed by 1,2-

Scheme 3



addition (**16** → **17** → **19**) appears unlikely, given the stability of the putative α-silyl nitriles **17** to $R_2CuLi{\cdot}LiCN$[35] and the inability to detect α-silyl ketones that would result from 1,2-addition to **17**.[36] A more plausible scenario is 1,2-addition−*N*-silylation followed by conjugate addition to the unsaturated silyl imine (**16** → **18** → **19**) and hydrolysis to the ketone upon workup, analogous to the conjugate addition of Grignard reagents to unsaturated imines.[37] Further support for an initial 1,2-addition of $R_2CuLi{\cdot}LiCN$ to alkenenitrile **16** is the ability of copper (I) salts to catalyze the addition of Grignard reagents to the nitrile group,[38] possibly representing a major side reaction that accounts for the low yields observed with several organocopper reagents, particularly copper catalyzed additions of Grignard reagents (Table 2, entries 15−17).

Boron-containing cuprate reagents are relatively effective for promoting conjugate additions to alkenenitriles. The reagent combination R_3BMeLi and Cu(I)Br shows a delicate dependence on the halide, suggesting radical or radicaloid intermediates (Table 2, entries 28−31) that may promote the addition since alkenenitriles are particularly effective radical acceptors.[53] However, boron halides are effective Lewis acids for complexing nitriles[54] and may facilitate the conjugate addition even with less nucleophilic organocopper reagents (Table 2, entries 32−33). Promotion by Lewis acid activation is consistent with the double 1,2−1,4-addition of cyclohexenecarbonitrile through a mechanism involving nitrile activation leading to a boron imine, followed by 1,4-addition (Table 2, entries 32−33, cf. Scheme 3).

Copper (I) salts effectively promote the conjugate addition of activated polyhalomethanes to alkenenitriles (Table 2, entries 34−53). Originally CuCl was proposed to initiate a radical chain mechanism,[55] although the product distribution differs from that obtained by free radical initiation, suggesting coordination of the radical with copper or an anionic conjugate addition through a Cu (III) intermediate.[51] Anionic conjugate addition of trichloromethane is possible in the absence of a copper catalyst[56] providing further support for a reaction-dependent crossover between anionic and radical mechanisms,[50] although the predominance of conjugate addition−chlorination products implies that a radical-type mechanism operates in most cases.

2.3. Radical-Type Organometallic Additions to Alkenenitriles

Alkenenitriles are excellent radical acceptors,[53] undergoing facile conjugate addition with organomercury and organotin reagents. Mechanistically distinct from these classical radical chain reactions are several radical-type conjugate additions mediated by zinc, nickel, cobalt, chromium, and manganese which generate metalated nitriles capable of reacting with conventional electrophiles. Partitioning the conjugate additions into radical or anionic reactions is particularly difficult since there appears to be an easily traversed continuum between the two different mechanisms, in some instances simply through the use of different solvents. Consequently only conjugate additions affording metalated nitriles are surveyed with an accompanying description of the most likely reaction mode, anionic addition or radical addition−reduction.

2.3.1. Metallic Zn and Organozinc Additions to Alkenenitriles

Metallic zinc mediates the conjugate addition of diverse alkyl halides to acrylonitrile and monosubstituted acrylonitriles. Although the precise mechanistic details remain uncertain,[57] several key features point to radical formation with metallic zinc.[58] For-

Table 2. Conjugate Additions of Organocopper Reagents to Alkenenitriles

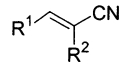
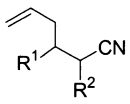
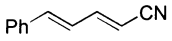
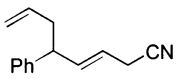
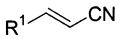
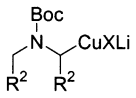
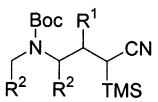
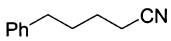
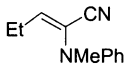
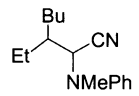
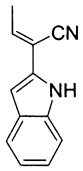
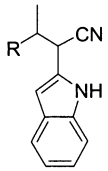
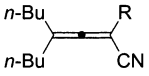
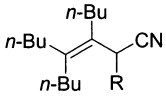
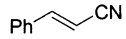
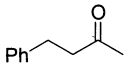
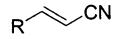
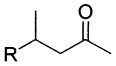
Entry	Alkenenitrile	organocopper reagent	alkanenitrile	yield	ref(s)
		$(Allyl)_2CuLi$			
	R^1 R^2				
1	Ph H			52%	39
2	2-furyl H			73%	39
3	*t*-Bu H			47%	39
4	$-(CH_2)_3-$			23%	39
5		$(Allyl)_2CuLi$		80%	39
					
	R^1	mRLi+CuCN·2LiCl R^2 m			
6	H	H 2		100%	35
7	Me	H 1		38%	35
8	H	$-(CH_2)_2-$ 2		78%	35
9	H	$-(CH_2)_2-$ 1		60%	35
10	Me	$-(CH_2)_2-$ 2		trace	35
11	Me	$-(CH_2)_2-$ 1		22%	35
12	H	$-(CH_2)_3-$ 1		54%	35
13		$PhCH_2CH_2SmI_2$, CuI, TMSCl, HMPA, THF; *n*-Bu_4NF		34%	34
14		Bu_2CuLi		52%	40
		RMgI/CuI			
		R			
15		Me		46%	11
16		CH_2=CH		7%	11
17		CH_2=$CHCH_2$		27%	11
		*n*-Bu_2CuLi			
	R				
18	Me			79%	41
19	Et			87%	41
20		$Me_2CuLi·LiCN$		nd	42
		$Me_2CuLi·LiCN$, Me_3SiCl			
	R				
21	H			69%	43
22	Me			72%	43

Table 2. (Continued)

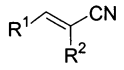
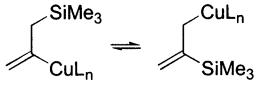
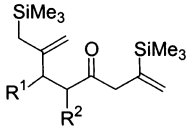
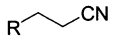
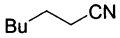
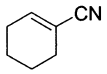
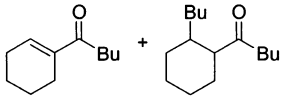
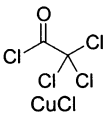
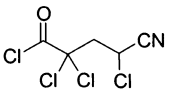
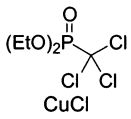
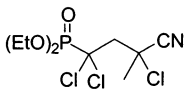
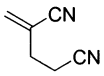
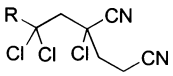
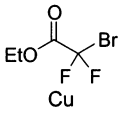
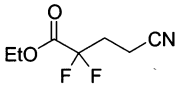
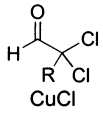
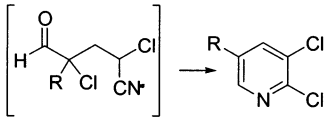
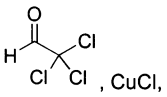
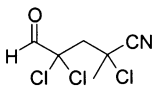
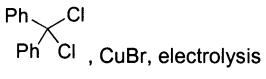
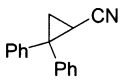
Entry	Alkenenitrile	organocopper reagent	alkanenitrile	yield	ref(s)
23	Ph			66%	43
					
	R^1 R^2				
24	H H			87%	44
25	Me H			83%	44
26	Ph H			81%	44
27	-$(CH_2)_3$-			79%	44
		R_3BMeLi, CuBr			
		R			
28		*n*-Pr		84%	45
29		*n*-Bu		88%	45
30		*n*-C_5H_{11}		89%	45
31		*n*-C_6H_{13}		93%	45
32		$BuCu{\cdot}BF_3$		40%	46
33		$BuCu{\cdot}BF_3$	 (4%) (36%)		46
34		 CuCl		91%[a]	47
35		 CuCl		31%	48
		 CuCl			
		R			
36		Cl		57%	49
37		CN		72%	49
38		COOEt		72%	49
39		COCl		41%	49
40		CHO		36%	49
41		 CuCl		42%	50
		 CuCl			
		R			
42		Cl		65%	51
43		CH_3		53%	51
44		CF_3		60%	51
45		CH_2CH_3		49%	51
46		CH_2CH_2Cl		57%	51

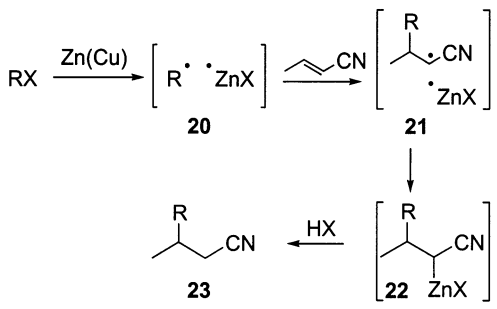
Table 2. (Continued)

Entry	Alkenenitrile	organocopper reagent	alkanenitrile	yield	ref(s)
47		CH_2CCl_3		46%	51
48		*n*-C_3H_7		35%	51
49		*i*-C_3H_7		33%	51
50		*n*-C_4H_9		52%	51
51		*n*-C_5H_{11}		51%	51
52		 , CuCl,		64%	51
53		 , CuBr, electrolysis		60%	52

[a] 50% conversion.

mation of alkyl radicals correlates with the greater reaction efficiency of tertiary alkyl halides compared with primary alkyl halides, and the lack of reactivity with phenyl iodide. Particularly compelling is the zinc-induced conjugate addition of bromomethylcyclopropane (Table 3, entry 13) that installs an allyl substituent, classic evidence for a radical mechanism, although the possibility exists for a radical intermediate during organozinc formation followed by anionic conjugate addition.[59] Mechanistically the most plausible scenario is radical formation during interaction of the alkyl halide with the metal surface, conjugate addition of a radical or radicaloid nucleophile, followed by a second one-electron reduction of the resulting radical to generate a zincated nitrile (Scheme 4). [60,61] Consistent with this radicaloid mechanism are

Scheme 4



the conjugate additions in the presence of carbon monoxide where CO insertion causes preferential formation of an acyl nucleophile leading to γ-ketonitriles (Table 3, entries 19−20).

In most instances the zincated nitrile is protonated since protic solvents or solvent mixtures are generally used, although sequential addition−alkylations are possible in dry acetonitrile (Table 3, entries 21−32). Alkylation is limited to TMSCl (Table 3, entries 33−34) and carbonyl electrophiles (Table 3, entries 21−32), perhaps reflecting the low nucleophilicity of zincated nitriles that generally require activated electrophiles and solvation with HMPA for efficient alkylations.[62]

Optimization experiments with a functionalized iodide identified the Zn−$FeCl_3$ couple with added NaI as a more efficient reagent than zinc alone.[63] Comparative conjugate additions of the functionalized "ethyl iodide" generated with metallic zinc (Table 3, entry 6, 35%) and ethyl iodide generated with Zn−$FeCl_3$ (Table 3, entry 7, 62%) demonstrate the value of $FeCl_3$, perhaps stabilizing the primary radicaloid intermediate.

Two lone examples describe the rather unusual conjugate addition of dialkylzincs to acrylonitrile (Table 3, entries 33−34).[64,65] Accumulating evidence suggests that dialkylzinc reagents do not react via the intermediacy of radicals[66] but rather are activated for the conjugate addition by complexation with *N*-methylpyrrolidinone solvent, thereby increasing the electron density on the metal.[64] TMSCl is required, and incorporated, within the conjugate addition product, suggesting that the conjugate addition proceeds through a TMSCl−zinc complex.[67]

2.3.2. Organonickel and Nickel Catalyzed Additions to Alkenenitriles

Organonickel reagents share a similarity with organozinc reagents in promoting conjugate addition through anionic-[73] and radical-type mechanisms.[74] Zerovalent nickel catalysts **24**, generated by electrolytic or metal-induced reduction of nickel (II) salts, undergo oxidative addition to sp^2 and sp^3-hybridized alkylhalides, generating reactive organonickel (II) intermediates **25** (Scheme 5). Pyridine is an essential additive, or solvent, in many cases, acting as a weak stabilizing ligand for the organonickel catalyst while

Scheme 5

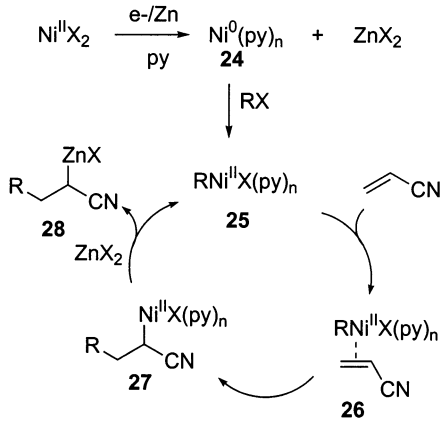


Table 3. Metallic Zn and Organozinc Additions to Alkenenitriles

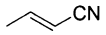
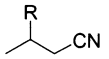
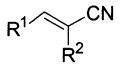
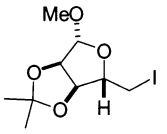
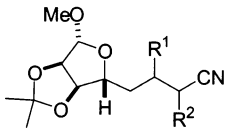
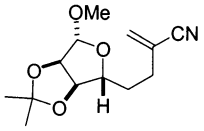
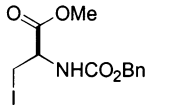
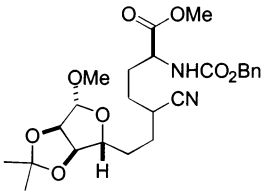
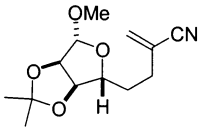
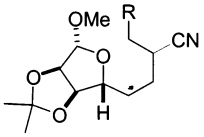
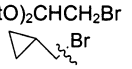
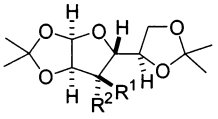
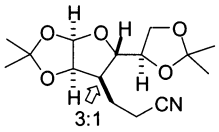
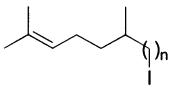
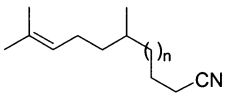
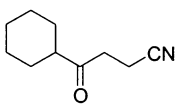
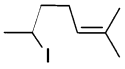
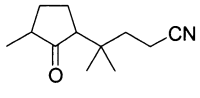
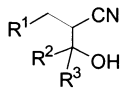
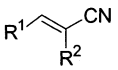
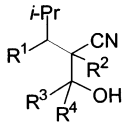
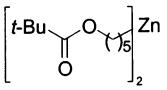
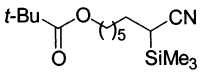
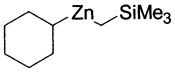
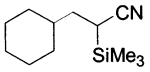
entry	alkenenitrile	organozinc	alkanenitrile	yield	ref(s)
		RBr, Zn(Cu), ultrasound, EtOH-H_2O			
		R			
1		*t*-Bu		75%	68
2		*cyclo*-pentyliodide		63%	68
		 Zn(Cu), Et_2O,THF, H_2O			
	R^1 R^2				
3	H H			78%	69
4	Me H			53%	69
5	H Me			55%	69
6		 Zn(Cu), Et_2O, THF, H_2O		35%	69
		RX, Zn, $FeCl_3$, NaI, pyridine, rt, 45 min			
		RX			
7		EtI		62%	63
8		*i*-PrI		72%	63
9		*i*-PrBr		62%	63
10		*t*-BuI		75%	63
11		*t*-BuBr		62%	63
12		$(EtO)_2CHCH_2Br$		36%	63
13			R' = 	29%	63
14		$F_3CONHCH_2CH_2I$		85%	63
		 Zn(Cu), EtOH, H_2O	 3:1		
	R^1 R^2				
15	H I			75%	70
16	I H			75%	70
		 Zn(Cu), Et_2O, THF, H_2O			
	n				
17	0			81%	71
18	2			76%	71
19		 CO, Zn, CuI, EtOH-H_2O (6:4)		42%	60
20		 CO, Zn, CuI, EtOH-H_2O (6:4)	 (37:63 *cis*:*trans*)	58%	60
		R^1X, Zn, CH_3CN R^2COR^3			
	R^1X	R^2 R^3			

Table 3. (Continued)

entry	alkenenitrile	organozinc			alkanenitrile	yield	ref(s)
21		*i*-PrI	Me	Me		98%	72
22		*i*-PrI	Ph	H		94%	72
23		*i*-PrI	-$(CH_2)_4$-			92%	72
24		*i*-PrI	Et	H		65%	72
25		*cyclo*-C_6H_{11}I	Ph	H		95%	72
26		*n*-PrI	Me	Me		63%	72
27		MeI	Me	Me		52%	72
28		*i*-PrI	Me	Me		31%	72
29		BnBr	Me	Me		46%	72
		*i*-PrI, Zn, CH_3CN R^3COR^4					
	R^1	R^2	R^3	R^4			
30	Me	H	Me	H		95%	63
31	H	Me	Me	H		73%	63
32	H	Me	Me	Me		72%	63
33		 TMSCl, THF, NMP,[a] -30°C				82%	64
34		 TMSCl, THF, NMP, -30°C				54%	65

[a] NMP: methylpyrrolidinone.

permitting complexation with the alkenenitrile.[75] Analogous reactions with better ligands, such as bipyridine,[80] are thwarted because oxidative addition is prevented. Oxidative addition of the zerovalent nickel may occur prior to, or after, complexation[76] with the alkenenitrile. Subsequent addition of the nitrile-complexed organonickel **26** across the activated π-system generates a nickellated nitrile that is protonated or transmetalated with zinc (II) salts.[75] Consistent with the mechanism is the direct carbonickellation of alkenenitriles with organonickels (Table 4, entries 4−6), the formation of trace alkenenitrile resulting from β-hydride elimination of the nickellated nitrile intermediate **27**,[73] and the protonation of nickellated nitriles by water.[77]

Mechanistically distinct from the anionic reactions are a series of nickel-mediated radical-type reactions (Table 4, entries 7−22). Nickel-stabilized radical-type intermediates are inferred from product stereochemistry[78] and comparison with known radical and anionic reactions,[79] although the resulting intermediates are metallonitriles that are subsequently protonated. Anhydrous conditions can be employed which are particularly advantageous for the conjugate addition of water-sensitive substrates, such as sensitive glycosyl bromides (Table 4, entries 10−11), that would not be amenable to radical-type additions with analogous zinc-water reagents.

2.3.3. Organo-Mn, Cr, and Co Additions to Alkenenitriles

Metallic manganese initiates the conjugate addition of alkyl iodides to alkenenitriles in a reaction that is directly analogous to that of metallic zinc (Table 5, entry 1). Strong mechanistic parallels between the zinc and manganese reactions support a common radical mechanism initiated by reduction from a Pb−Mn couple ($E^0 = -1.05$V for Pb−Mn and $E^0 = -1.10$V for Zn−Cu). Competition experiments indicate a fast reduction of the nitrile radical to the metalated nitrile followed by alkylation with carbonyl electrophiles (Table 5, entries 1−3) directly analogous to pioneering organozinc additions.[72]

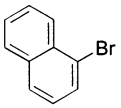
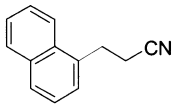
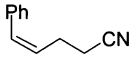
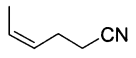
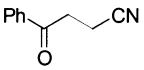
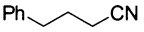
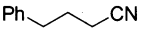
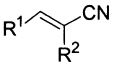
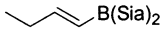
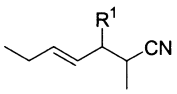
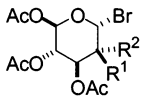
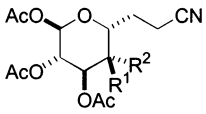
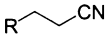
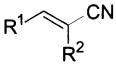
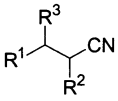
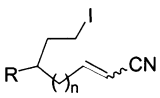
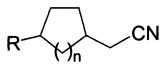
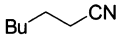
Radical mechanisms are not the only viable addition mechanism for manganese reagents since allylic manganese chlorides and aryl manganese complexes both mediate conjugate additions (Table 5, entries 4−11). Ligation of acrylonitrile with the aryl manganese complex occurs prior to aryl manganesation, analogous to nickel (Scheme 5), generating manganesated nitriles that are subsequently protonation to afford aryl-substituted propanenitriles (Table 5, entries 10−11)

Evidence for a radical-mediated conjugate addition of benzyl chromium was inconclusive,[86] but the reaction of alkylchromium and Fisher carbenes is consistent with a radical addition followed by reduction to a chromated nitrile (Table 5, entries 12−16).[87] The radical species may well maintain association with the chromium accounting for the stability of acylradicals (Table 5, entries 17−18) and facilitating conjugate addition by positioning the radical in close proximity to a coordinated alkenenitrile.[88]

2.4. Conjugate Additions of Stabilized Carbanions to Alkenenitriles

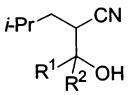
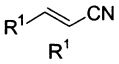
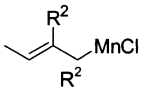
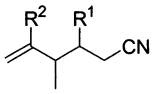
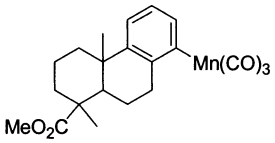
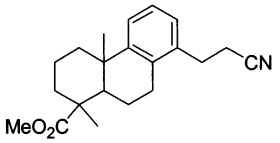
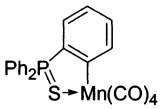
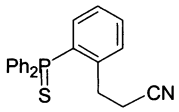
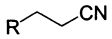
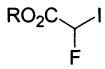
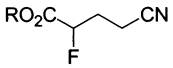
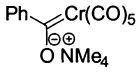
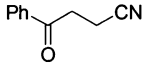
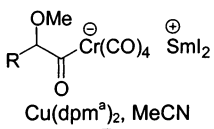
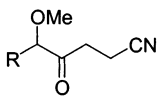
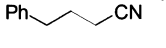
Numerous malonate-type anions add to alkenenitriles in a classic conjugate addition that was last

Table 4. Organonickel and Nickel Catalyzed Additions to Alkenenitriles

Entry	Alkenenitrile	Conditions	Product	Yields	ref(s)
1		 $NiBr_2 \cdot 3H_2O$, electrolysis DMF, Bu_4Br, NBu_4I, py,		61%	80
2		 $NiBr_2 \cdot 3H_2O$, electrolysis, DMF/MeCN: 1:1		68%	76, 81
3		 $NiBr_2 \cdot xH_2O$, Zn, THF, py		66%	75
4		PhCOCl, Rieke-Ni, glyme		18%	82
5		$PhCH_2Cl$, Rieke-Ni, glyme		14%	73
6		$PhCH_2Br$, $K_2Ni_2(CN)_6$, CO, H_2O		23%	77
		 $Ni(acac)_2$, DMF, 25°C, 24 h			
	R^1 R^2				
7	H H			96%	83
8	H Me			45%	83
9	Me H			39%	83
		 $Ni(tmc)_2(BF_4)_2$[a], Mn, Ph_2PH, THF			
	R^1 R^2				
10	H OAc			76%	78
11	OAc H			49%	78
		$Ni(Ph_3P)_2Cl_2$, RBr, Zn CH_3CN, C_5H_5N, 65°C R			
12		*n*-hex		17%	74
13		*cyclo*-hex		31%	74
14		*t*-Bu		50%	74
15		Me_3C		60%	74
16		Ph		0	74
		R^3I, BER-N.B.,[b] MeOH			
	R^1 R^2	R^3			
17	Me H	*c*-C_6H_{11}		93%	84
18	H Me	*c*-C_6H_{11}		90%	84
19	H H	*c*-C_6H_{11}		90%	84
		SmI_2, cat. NiI_2 *t*-BuOH			
	R n				
20	H 1			85%	79
21	Me 2			81%	79
22		Bu_3In, $Ni(COD)_2$, THF,		72%	85

[a] tmc: tetramethylcyclam. [b] BER-N.B.: nickel boride on borohydride exchange resin.

Table 5. Organo-Mn, Cr, and Co Additions to Alkenenitriles

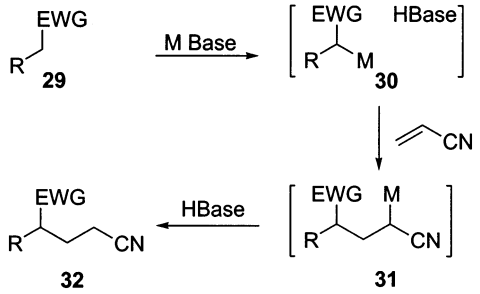
Entry	alkenenitrile	conditions	alkanenitrile	yield	ref(s)
		*i*-PrI, Mn, $PbCl_2$, R^1COR^2 Me_3SiCl, THF, DMF			
		R^1 R^2			
1		Et H		85%	61
2		Ph H		96%	61
3		$-(CH_2)_2-$		86%	61
					
	R^1	R^2			
4	*n*-Pr	Me		55%	89
5	Ph	Me		73%	89
6	MeCH=CH	Me		31%	89
7	Me	*n*-Bu		72%	89
8	Me	H		96%	89
9	Me	Bn		42%	89
10		 Me_3NO, MeCN		35%	90
11		 refluxing MeCN		44%	91
		$Cr(H_2NCH_2CH_2NH_2)_2]^{2+}Cl^-_2$, RX, DMF; H_2O			
		RX	R		
12		*c*-C_6H_{11}I	*c*-C_6H_{11}	68%	92
13		BnBr	Bn	70%	92
		 $CrCl_3 \cdot H_2O$, bipy, EtOH			
		R			
14		Me		74%	93
15		Et		78%	93
16		 $Cu(dpm^a)_2$, MeCN		58%	94
		 $Cu(dpm^a)_2$, MeCN			
		R			
17		*n*-Bu		69%	88
18		*s*-Bu		56%	88
19		$PhCH_2Br$, $Cr(ClO4)_2$, EtOH-H_2O		50%	86

[a] dpm: 2,2,6,6-tetramethyl-3,5-heptandionato.

surveyed almost 50 years ago.[5] More challenging, and of greater synthetic importance, are the conjugate additions of nucleophiles formed by deprotonating adjacent to a single electron-withdrawing group. Since carbonyl compounds are typically more acidic than nitriles ($\Delta pK_a \sim 5$),[95] many conjugate additions are performed in a buffered solution mode where the nitrile anion, generated by conjugate addition, is

protonated by either the conjugate acid HBase or the carbonyl compound **29** (Scheme 6).

Scheme 6



Nucleophilicity trends in the conjugate addition of stabilized anions to alkenenitriles parallel analogous reactions of highly stabilized malonate-type carbanions with π-electrophiles. The nucleophilicity parameters increase[96] for anions derived from diones < ketoesters < malononitrile < malonates < nitromethane, which is qualitatively the order of increasing ease for conjugate additions of metalated ketones, esters, nitriles, and nitroalkanes.

2.4.1. Conjugate Additions of Ketone Enolates to Alkenenitriles

Ketone enolates exhibit a surprisingly high degree of chemo- and regioselectivity in conjugate additions to alkenenitriles. Conjugate additions with α-aryl ketones typically employ protic solvents with hydroxide or Triton B ($BnNMe_3OH$) as a phase transfer catalyst (Table 6, entries 1−14). Weak bases selectively deprotonate unsymmetrical α-aryl-α′alkyl ketones adjacent to the more acidic α-aryl substituents, permitting chemoselective conjugate additions to acrylonitrile (Table 6, entries 1−5). α-Aryl ketones with two acidic protons trigger two sequential conjugate additions to acrylonitrile, as was advantageously employed with 2-tetralone in a concise route to the stemodin skeleton (Table 6, entry 5).

Conjugate additions of aliphatic ketones are considerably more difficult. Generally aliphatic ketones are more efficiently coaxed into conjugate addition by conversion to the corresponding enamine (section 2.5.) or by using an unsaturated carbonyl compound as the acceptor rather than an alkenenitrile.[97] Incomplete conversion is often a problem whereas forcing conditions favor two consecutive conjugate additions, although in some instances further conjugate addition of the initially formed cyanoethylated ketone is suppressed simply by lowering the reaction temperature (Table 6, entry 19). Conjugate additions with aliphatic ketones usually employ alkoxide or hydroxide bases, leading to preferential formation of thermodynamic enolates (Table 6, entries 16−27).

The efficacy of the conjugate addition depends critically on the nature of the anion. For example, for the same ketone, comparable conjugate additions with Triton B provided only 5% of the conjugate adduct, whereas the enolate derived by MeLi-induced cleavage of the corresponding enol silyl ether generates the conjugate adduct in 53% yield (Table 6, entry 26). Similarly, the CsF-promoted cleavage of enol silyl ethers formed in situ with $(MeO)_4Si$ triggers a relatively efficient conjugate addition even with substituted alkenenitriles (Table 6, entry 30−32).

Conjugate additions of enolates to substituted alkenenitriles are generally more difficult than the corresponding additions to acrylonitrile. A measure of the increased difficulty is gleaned from comparable conjugate additions of acetophenone to methacrylonitrile and acrylonitrile that proceed in 40% and 55% yields, respectively (Table 6, compare entries 33 and 34). The difficulty of enolate conjugate addition to a β-substituted alkenenitrile is overcome in an intramolecular reaction (Table 6, entry 35), demonstrating that ketone enolates do effectively add to substituted alkenenitriles when competitive ketone−enolate condensations are prevented. In fact, ketone enolates exhibit a much greater propensity for conjugate addition than malononitrile anion, at least in the case where both anions are generated through the use of excess base (Table 6, entry 29).

2.4.2. Conjugate Additions of Ester Enolates to Alkenenitriles

The conjugate addition of ester enolates to alkenenitriles usually requires esters activated toward deprotonation. The use of weak bases avoids deprotonation of the nitrile adduct and facilitates protonation of the nitrile anion resulting from the conjugate addition that otherwise react with acrylonitrile faster than the parent ester enolates.[121] Aryl acetates are therefore typical pronucleophiles that, in some additions to cinnamonitrile, generate predominantly one diastereoisomer, presumably through equilibration of the conjugate adduct (Table 7, entries 7−8).

Ester enolates generated from ethyl dibromophenylacetate and Bu_3Sb, or by deprotonating a chloroacetate, trigger Darzens-type conjugate addition−alkylations[120] to generate cyclopropanes (Table 7, entries 10−11). The Darzens-type reactions are favored by the irreversible cyclization, whereas the conjugate addition of LDA-derived ester enolates to α-amino acrylonitrile are likely favored by generating a more stable lithiated α-aminonitrile (Table 7, entries 13−14).

2.4.3. Conjugate Additions of Metalated Nitriles to Alkenenitriles

Metalated arylacetonitriles are excellent nucleophiles for conjugate additions to alkenenitriles. The high nucleophilicity parameter[96] correlates with the high charge density on the α-carbon of metalated arylacetonitriles,[129] reflecting the predominant inductive stabilization[130] and minimal resonance stabilization of nitrile anions.[95] Consistent with the inductive stabilization of nitrile anions are the low intrinsic barriers for malononitrile anion conjugate additions[131] when compared against those of most other carbanions.

Numerous cyanohydrin-based conjugate additions have long exploited this nucleophilicity in a particularly effective acyl anion conjugate addition (Scheme 7). An excellent survey[132] of conjugate additions of metalated cyanohydrins and α-aminonitriles reveals the necessity for aromatic substituents on the meta-

Table 6. Conjugate Additions of Ketone Enolates to Alkenenitriles

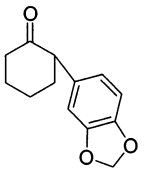
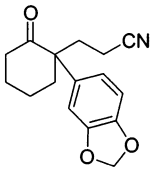
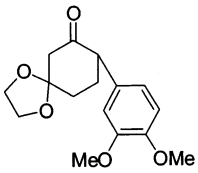
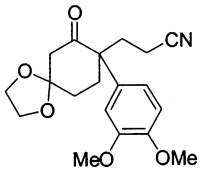
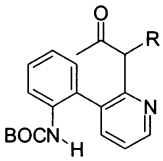
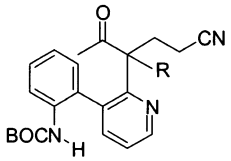
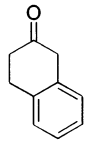
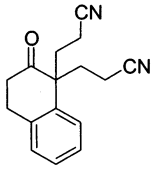
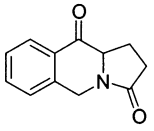
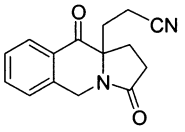
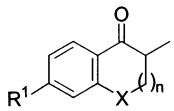
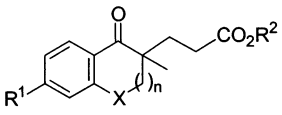
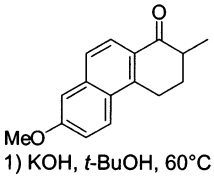
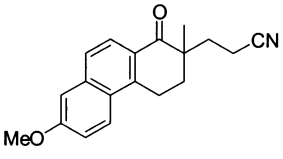
Entry	alkenenitrile	conditions	ketonitrile	yield	ref(s)
1		 50% NaOH, 18-C-6		40%	98
2		 50% NaOH, 18-C-6		23%	98
		 $BnMe_3NOH$ R			
3		Me		78%	99
4		Et		26%	99
5		 Cat. $BnNMe_3OH$, *t*-BuOH		80%	100
6		 $BnNEt_3OH$, MeOH		57%	101
		 1) KOH, *t*-BuOH, 60°C 2) KOH-H_2O; MeOH, H_2SO_4			
		R^1 X n			
7		H O 2		60%	102
8		O 2		81%	102
9		H S 2		79%	102
10		MeO CH_2 2		62%	102
11		MeO CH_2 1		79%	102
12		H S 1		73%	102
13		 1) KOH, *t*-BuOH, 60°C 2) KOH-H_2O, reflux		56%	103

Table 6. (Continued)

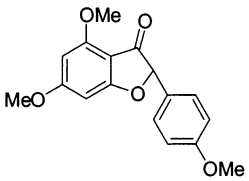
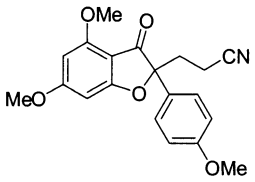
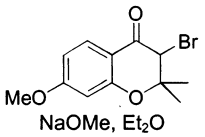
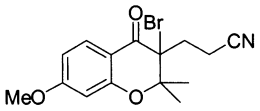
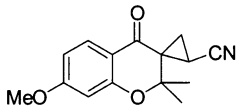
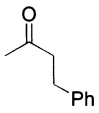
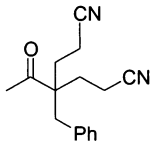
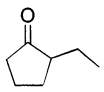
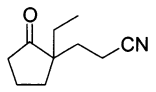
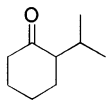
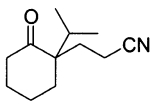
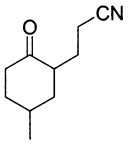
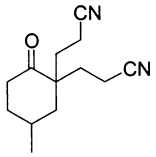
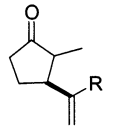
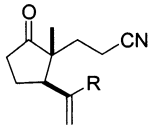
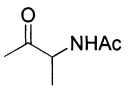
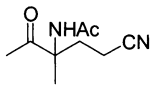
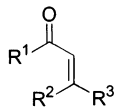
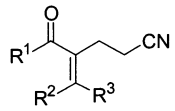
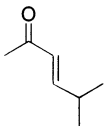
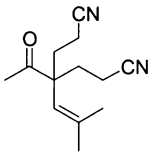
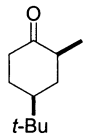
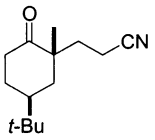
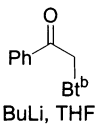
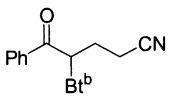
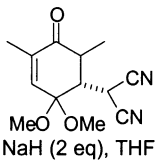
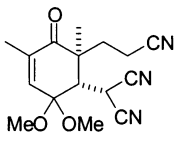
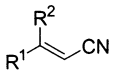
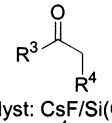
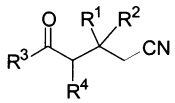
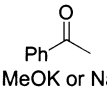
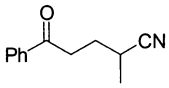
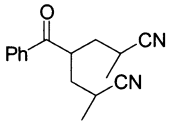
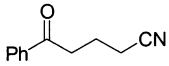
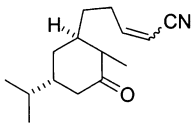
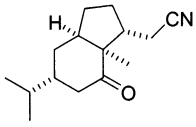
Entry	alkenenitrile	conditions	ketonitrile	yield	ref(s)
14		 BnNMe$_3$OH		91%	104
15		 NaOMe, Et$_2$O		14%[a]	97
				10%[a]	
16		 KOH, MeOH		60%	105
17		 NaOEt, THF		58%	106
18		 NaOEt, THF		90%	107
19		 *t*-BuOH, KOH-H$_2$O, 0°C		73%	108
		 NaOMe, Et$_2$O			
		R			
20		Me		66%	109
21		H		43%	109
22		 KOH, *t*-BuOH		60%	110
		 KOH, *t*-BuOH			
		R^1 R^2 R^3			
23		-(CH$_2$)$_3$- H		55%	111
24		Me H Me		60%	111

Table 6. (Continued)

Entry	alkenenitrile	conditions	ketonitrile	yield	ref(s)
25		 NaOH, $BuNEt_3Cl$		62%	112
					
26		LDA, TMSCl; MeLi		53%	113
27		$BnNMe_3OH$		5%	113
28		 BuLi, THF		-	114
29		 NaH (2 eq), THF		54%	115
		 catalyst: $CsF/Si(OR)_4$			
	R^1 R^2	R^3 R^4 $Si(OR)_4$			
30	Me Me	Ph H Me		55%	116
31	Ph H	Ph H Me		55%	116
32	Ph H	Bn Ph Et		65%	116
33	 **171**	 MeOK or Na		1%	117
				39%	
34		 MeOK		55%	118
35		*t*-BuOK *t*-BuOH-PhH		90%	119

[a] 72% of the starting material was recovered. [b] Bt = α-benzotriazolyl.

lated nitrile-bearing carbon, a requirement exhibited by the corresponding additions of metalated nitriles (Table 8). Cyanohydrin-derived conjugate additions continue to be used, particularly for assembling medicinal targets,[133] with extensions that allow for sequential β- and α-acylations by intramolecular acyl transfer (Scheme 7). [134]

Typically, weakly basic tetra-alkylammonium hydroxides are used to initiate conjugate additions of arylacetonitriles to alkenenitriles. Two rather unusual deprotonations are the use of NaCN at 225 °C (Table 8, entry 33) and CsF in $Si(OMe)_4$ (Table 8, entry 34), although in the latter case fluoride-induced cleavage of $Si(OMe)_4$ is proposed to generate methoxide as the base. Identification of methoxide as the base is consistent with the similar formation of a single diastereomer obtained with sodium methoxide in ether (Table 8, entry 35−47), suggesting that in

Table 7. Conjugate Additions of Ester Enolates to Alkenenitriles

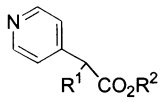
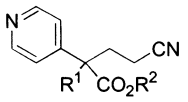
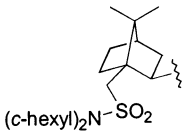
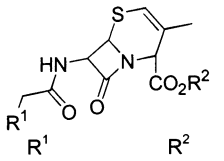
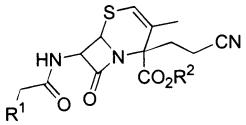
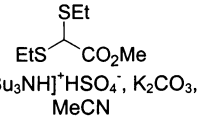
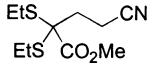
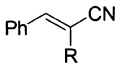
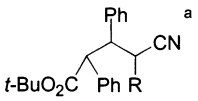
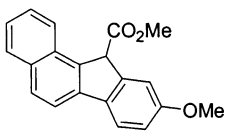
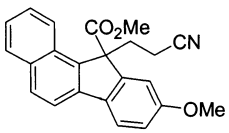
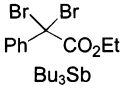
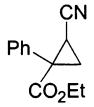
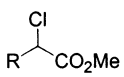
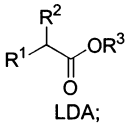
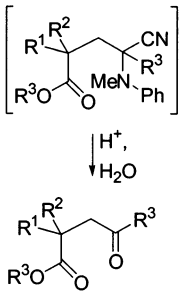
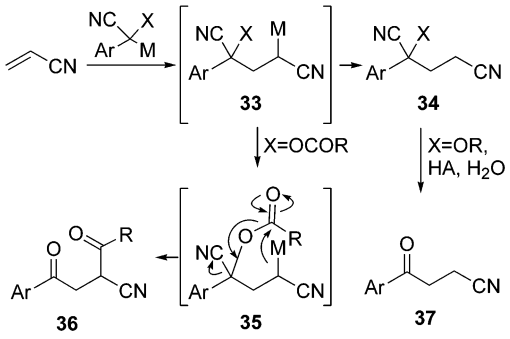
Entry	alkenenitrile	ester	ester nitrile	yield	Ref(s)
		 *t*-BuOK, *t*-BuOH or $BnNMe_3OH$			
		R^1 R^2			
1		H Et		25%	121
2		Et 		51%	121
		 R^1 R^2			
3		Ph CH_2CCl_3		75%	122
4		Ph $CHPh_2$		74%	122
5		 $CHPh_2$		87%	122
6		 $[n\text{-}Bu_3NH]^+HSO_4^-$, K_2CO_3, MeCN		94%	123
	 R	$PhCH_2COO$-*t*-Bu NaOH, $BnNEt_3Cl$, H_2O, MeCN	 [a]		
7	H			75%	124
8	Ph			70%	124
9		 NaOH		96%	125
10		 Bu_3Sb		60%	126
		 *t*-BuOK or NaH, THF 20°C , 12 h R			
11		Me		59%[b]	127

Table 7. (Continued)

Entry	alkenenitrile	ester	ester nitrile	yield	Ref(s)
12		 LDA; R^3CH_2X		64%	127
		R^1 R^2 R^3			
13		Me Me Me		79%	128
14		Et H Me		44%	128

[a] The diastereomeric ratio is unknown. [b] *cis*:trans 3:1. [c] cis:trans 4:1.

Scheme 7



each case there is an equilibration to the more stable diastereomer. Aryl-monosubstituted acetonitriles having two acidic protons react with excess acrylonitrile in two sequential conjugate additions (Table 8, entries 49−54). Less acidic α,*β*- or *β*,*γ*-alkenenitriles ($pK_a \sim 21$)[28] are deprotonated with nonionic superbases, triggering conjugate addition of the allylic anion with the α,*β*-alkenenitrile present by equilibration (Table 8, entry 55−59). The self-condensation is then followed by conjugation to the corresponding α-substituted alkenenitrile.[149]

Conjugate additions under aprotic conditions permit domino addition−alkylations.[135] Darzens-type reactions[120] (Table 8, entries 60−61) with α-chloroacetonitrile trigger conjugate addition−cyclization to cyclopropanes, whereas the attack of a pendant nitrogen on the nitrile leads to a six-membered heterocycle (Table 8, entry 62).

2.4.4. Conjugate Additions of Metalated Nitroalkanes to Alkenenitriles

Metalated nitroalkanes are particularly effective nucleophiles for conjugate additions,[152] with the conjugate additions to alkenenitriles being no exception. The high acidity of nitroalkanes permits selective deprotonation with weak bases while avoiding deprotonation of ketone, ester, and alcohol functionalities that can be incorporated within the nitroalkane without protection (Table 9, entries 6−9). In many instances the choice of base and solvent is critical; typically if the base is too weak, no reaction occurs whereas stronger bases and less polar solvents, such as THF rather than CH_3CN, favor a second conjugate addition of the first-formed cyanoethyl nitroalkane.[153]

Conjugate addition generates secondary nitroalkanes that are electronically and sterically deactivated toward further addition. Secondary nitroalkanes require activating substituents, ester, nitrile, vinyl, fluoro, and CF_3, for facile conjugate additions to acrylonitrile (Table 9, entries 9−13), although elevated temperatures or the use of acrylonitrile as a cosolvent[154] promotes the conjugate addition with unactivated secondary nitroalkanes (Table 9, entry 26). Particularly challenging are conjugate additions of secondary nitroalkanes to substituted acceptors such as crotononitrile (Table 9, entries 14−18 and 28) where DBU is a particularly effective base.[155]

2.4.5. Conjugate Additions of Metalated Sulfones and Sulfoxides to Alkenenitriles

Conjugate additions of metalated sulfones and sulfoxides typically require adjacent substituents that stabilize the nucleophilic carbanion. Deprotonating these activated sulfones is usually performed in a biphasic system with phase transfer catalysts and hydroxide, which prevents addition of the resulting nitrile anion to acrylonitrile by rapid protonation.[170] Alternatively, dilute aprotic solvents favor displacement of the sulfone[171] or sulfoxide[172] by the metalated nitrile to form cyclopropanes (Table 10, entries 11−12). Double conjugate addition occurs with allylphenyl[170] and chloromethyl sulfone[173] (Table 10, entries 5−6), although the reaction is solvent dependent on allylphenyl sulfone, with CH_2Cl_2−MeCN favoring a single conjugate addition and MeCN alone favoring two consecutive conjugate additions.

2.4.6. Conjugate Additions of Miscellaneous Stabilized Carbanions to Alkenenitriles

Conjugate additions to alkenenitriles typically require carbanions having one or more adjacent charge-stabilizing groups (Table 11). In one of the few

Table 8. Conjugate Additions of Metalated Nitriles to Alkenenitriles

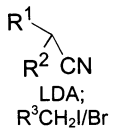
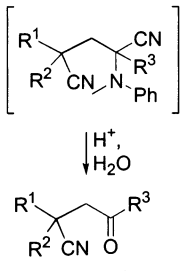
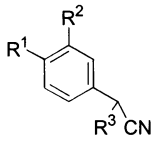
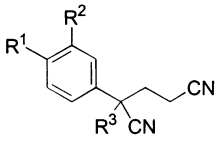
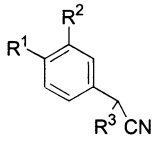
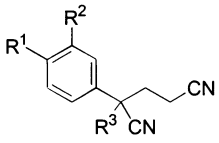
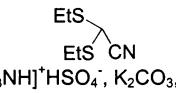
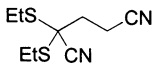
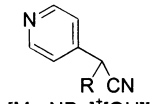
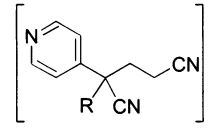
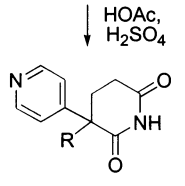
entry	alkenenitrile	alkanenitrile	dinitrile	yield	ref(s)
					
		R^1	R^2		
1		H	Me	40-92%	136
2		H	Bu	70-94%	136
3		Me	Me	69-76%	136
4		-$(CH_2)_5$-		70-88%	136
					
		cat.	R^1 R^2 R^3		
5		NaOH, cat. *n*-Bu_4NBr	H H SMe	67%	137
6		$RuH_2(PPh_3)_4$	H H Me	50%	138
					
		$BnNMe_3OH$			
		R^1 R^2 R^3			
7		H OMe H		58%	139
8		NO_2 H H		90%	140
9		H H $CH=CH_2$		32%	141
10		H H $CH_2CH_2CO_2Me$		79%	141
11		H H H		21%	142
12		H H Me		51%	142
13		H H Et		56%	142
14		H H *n*-Pr		30%	142
15		H H *i*-Pr		51%	142
16		H H *n*-Bu		39%	142
17		H H $CH_2CH(CH_3)_2$		32%	142
18		H H $CH(CH_3)CH_2CH_3$		37%	142
19		H H n-C_5H_{11}		39%	142
20		H H $(CH_2)_2CH(CH_3)_2$		33%	142
21		H H $CH_2CH(CH_3)CH_2CH_3$		37%	142
22		H H $CH(CH_3)(CH_2)_2CH_3$		46%	142
23		H H n-C_6H_{13}		47%	142
24				86%	123
		$[n\text{-}Bu_3NH]^+HSO_4^-$, K_2CO_3, MeCN			
					
		$[Me_3NBn]^+[OH]^-$			
					
		R			
25		Me		39%	143

Table 8. (Continued)

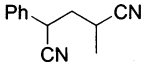
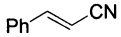
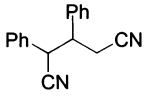
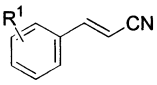
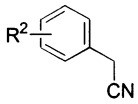
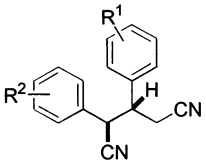
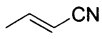
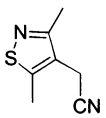
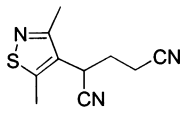
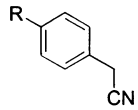
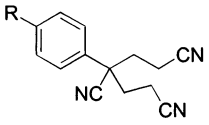
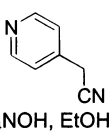
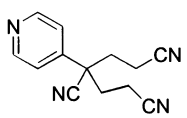
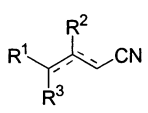
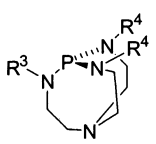
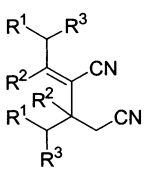
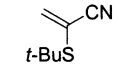
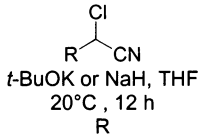
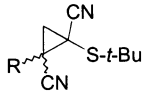
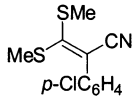
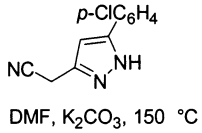
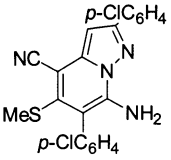
entry	alkenenitrile	alkanenitrile	dinitrile	yield	ref(s)
26		n-C_3H_7		66%	143
27		n-C_4H_9		65%	143
28		n-C_5H_{11}		51%	143
29		n-C_6H_{13}		53%	143
30		n-C_7H_{15}		47%	143
31		n-C_8H_{17}		67%	143
32		n-C_9H_{19}		60%	143
33		 NaCN, 225°C		84%	144
34		 $CsF/Si(OMe)_4$, rt		85%	123
		 NaOMe, ether			
	R^1	R^2			
35	H	3,4-dichloro		70%	145
36	H	2,4-dichloro		74%	145
37	H	4-chloro		85%	145
38	H	4-bromo		72%	145
39	H	3-chloro		81%	145
40	H	2-fluoro		72%	145
41	H	2,6-dichloro		70%	145
42	H	2-methyl		73%	145
43	H	2-chloro		65%	145
44	4-chloro	2,6-dichloro		80%	145
45	4-methoxy	2,6-dichloro		80%	145
46	2,3-dimethoxy	4-chloro		74%	145
47	2,3-dimethoxy	2,6-dichloro		82%	145
48		 $Li^+[cyclo\text{-}C_6H_{11}N\text{-}i\text{-}Pr]^-$, THF		76%	146
		 MeOH, KOH, reflux			
	R				
49	CO_2Me			60%	147
50	i-Pr			65%	147
51	F			85%	147
52	Br			70%	147
53	Me			75%	147
54		 Et_4NOH, EtOH, rt		60%	148
		 cat. Benzene			
	R^1 R^2 R^3				

Table 8. (Continued)

entry	alkenenitrile	alkanenitrile	dinitrile	yield	ref(s)
55	Me H H			98% (β, γ)	149
56	H H H			94% (β, γ)	149
57	Me H Me			96% (α, β)	149
58	Me H H			96% (β, γ)	149
59	-$(CH_2)_4$- H			90% (β, γ)	149
					
60		PhS		85%[a]	150
61		Ph		88%[b]	150
62				84%	151

[a] cis:trans, 63:57. [b] cis:trans, 55:45.

chiral conjugate additions, metalated oxazolidinones add stereoselectively to acrylonitrile (Table 11, entries 10−12), as do resin-bound oxazolidinones,[177] but are not sufficiently nucleophilic to add to the poorer acceptor crotononitrile.[178] γ-Deprotonation of unsaturated lactam and lactones (Table 11, entries 14−18) directs conjugate addition δ to the carbonyl, and curiously in the case of the lactone,[179] the resulting lithiated nitrile undergoes further conjugate addition unless the nitrile is pretreated with $[Et_3O]^+[BF_4]^-$. Comparative conjugate additions of metalated imines and an electrochemically generated anion typify the correlation between the efficiency and increased delocalization of the nucleophile (Table 11, compare entries 19−21 with 23, where the carbanion does not have a π-stabilizing group and proceeds in modest yield).

Allylic nucleophiles are particularly effective in performing conjugate additions,[33] with alkenenitriles being no exception. Allylsilane, in the presence of n-Bu_4NF, triggers conjugate addition to several alkyl- and aryl substituted-nitriles, as does allyllithium (Table 11, entries 24−29). Despite the modest yield, the allyllithium addition is particularly unusual since alkyllithium reagents generally show a propensity for 1,2-addition unless prevented by geometric constraints (see eq 3, section 2.1). Several metalated diarylmethanes, formally allyllithium analogues, add efficiently to acrylonitile and the modestly more difficult acceptor cinnamonitrile, with the conjugate addition of the phenanthrene triggering a double conjugate addition−Thorpe-Ziegler cyclization (Table 11, entry 34).

Dithiane anions illustrate general features required for conjugate additions to alkenenitriles (Table 11, entries 35−42). Aromatic α-substitution on the nitrile considerably facilitates the conjugate addition with the lithiodithiane addition to aryl-substituted nitriles occurring at low temperatures, whereas an aliphatic nitrile requires room temperature, is 14 times as long, and proceeds much less efficiently (50% yield, Table 11, entries 35−39 and 40, respectively). Promoting the reaction through an intramolecular conjugate addition with aliphatic β-amino alkenenitriles restores the reaction efficiency in a route to indolizidine and quinolizidines (Table 11, entries 41−42). These cyclizations demonstrate that the nitrile group is not particularly reactive toward butyllithium since deprotonation of the dithiane occurs in preference to addition to the nitrile group. Related sulfur-stabilized carbanions are effective nucleophiles, particularly when further stabilized by an adjacent olefin, with lithiated allylphenyl sulfide being sufficiently nucleophilic to overcome the difficulty usually associated with challenging β,β-disubstituted alkenenitriles (Table 11, entry 43).

2.5. Conjugate Additions of Enamines to Alkenenitriles

A diverse range of enamines participate in conjugate additions to alkenenitriles. The combination of enamine conjugate addition and hydrolysis is usually significantly more efficient than direct ketone enolate additions (section 2.4.1) and, in some instances, can be performed directly from the ketone with catalytic amine. Most enamine conjugate additions employ the more nucleophilic pyrrolidine derivatives[199] rather than the corresponding piperidine analogues, reflecting the higher p-character of the nitrogen lone pair in a five-membered ring. The less reactive oxygen-containing amines[199] afford conjugate adducts in significantly diminished yields (Table 12, compare entries 1 and 7).

Enamine conjugate additions to acrylonitrile are complementary to direct enolate additions. Enolates often cause a second conjugate addition from the more substituted carbon of the cyanoethylated ketone, whereas enamines derived from cyclic amines favor mono conjugate addition at the less substituted carbon (compare Table 6 entries 16−22 with Table

Table 9. Conjugate Additions of Metalated Nitroalkanes to Alkenenitriles

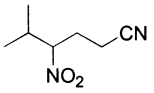
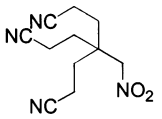
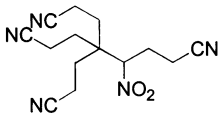
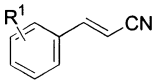
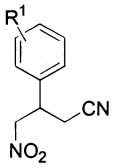
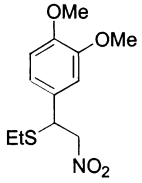
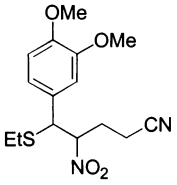
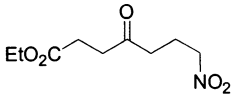
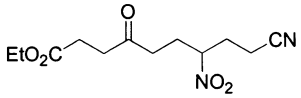
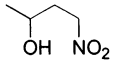
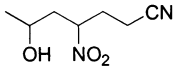
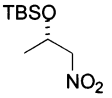
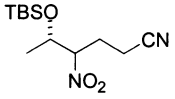
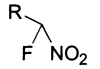
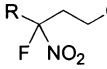
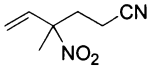
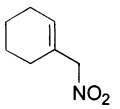
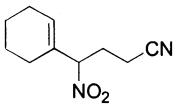
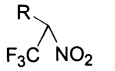
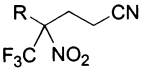
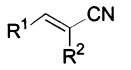
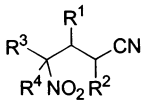
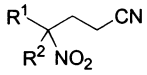
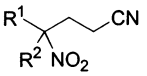
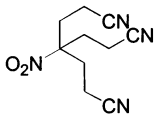
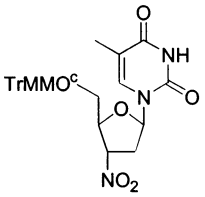
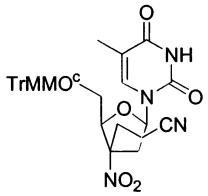
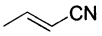
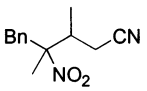
Entry	alkenenitrile	nitroalkane	nitro nitrile	yield	ref(s)
1		 KF/EtOH, reflux		60%	156
2		 $BnNMe_3OH$ or DBU, DME, rt		40%	157
		CH_3NO_2, $BnNMe_3OH$, reflux			
	R^1				
3	2,3-MeO			96%	158
4	3,4-MeO			90%	158
5		 *i-Pr*$_2$NH, neat, 0 °C		80%	159
6		 $BnNMe_3OH$, THF		40%	160
7		 TMG[a], MeCN, rt		50%	161
8		 TMG[a], MeCN, rt		67%	153
9		 KF, MeCN or sulfolane, rt	 R=Bn, CH_2CH_2COOEt, CH_2CH_2COOMe, CH_2CH_2CN, $CH(Ph)CH_2COOMe$	43-82%[b]	162
10		 TMG[a] (cat.), MeCN, rt		72%	163
11		 33% KOH, EtOAc		No yield given	164
		 KF, MeCN, rt			
	R				
12	H			43%	165

Table 9. (Continued)

Entry	alkenenitrile	nitroalkane	nitro nitrile	yield	ref(s)
13		Me		84%	165
		 DBU[c] or TMG[a], THF, rt			
	R^1 R^2	R^3 R^4			
14	Ph H	Me H		75%	166
15	Me *n*-hex	H H		82%	166
16	-$(CH_2)_4$-	H H		84%	166
17	Bn Me	Me H		74%	166
18	Bn Me	H Me		95%	166
		 NaOH (0.025-0.1 M), $Me_3N(CH_2)_{15}CH_3Cl$,			
		R^1 R^2			
19		H Me		50%	167
20		H Et		57%	167
21		Me Me		74%	167
22		H *n*-Bu		61%	167
23		-$(CH_2)_5$-		78%	167
		 Amberlyst A-27, no solvent			
		R^1 R^2			
24		Et Me		75%	168
25		H *n*-Bu		60%	168
26		CH_3NO_2, $Bu_4N^+HSO_4^-$, KOH, H_2O, dioxane, 80-85°C		51%	154
27		 *n*-Bu_4NF, THF, rt		83%	169
28		 DBU[b], MeCN, rt		74%	155

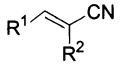
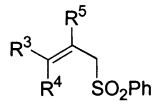
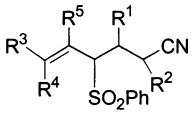
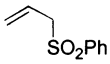
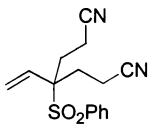
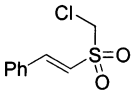
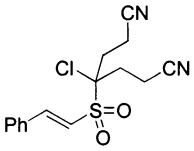
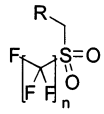
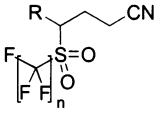
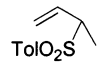
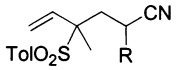
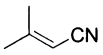
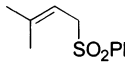
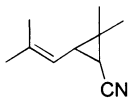
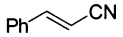
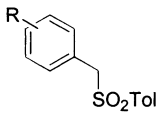
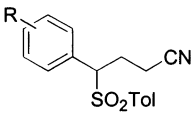
[a] TMG: tetramethylguanidine. [b] Individual yields were not specified. [c] DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene. [c] MMTr: monomethoxytrityl.

12 entries 3−4).[200c] Consecutive conjugate additions of acrylonitrile are favored with pyrrolidine enamines in ethanol, generating α,α′-cyanoethylated ketones[200c] (Table 12, entries 14−15) in contrast to α,α-cyanoethylated ketones obtained with enolates.

Mechanistically, enamine-initiated conjugate additions generate zwitterions capable of deprotonation or cyclization to a cyclobutanecarbonitrile (Scheme 8). Intramolecular proton transfer from **39** leads directly to the cyanoethylated enamine,[200c] whereas attack of the nitrile anion on the Schiff base causes cyclization to a cyclobutane (Table 12, entries 34−43). Several of the cyclobutanecarbonitriles are unstable, reverting to acrylonitrile and enamine or generating the "normal" cyanoethylated enamine upon heating, implying that the cyclobutane may be an intermediate in all reactions.[201] *N*-Alkylating the cyclobutanecarbonitrile in situ, with alkyl halides and tosylates, irreversibly displaces the equilibrium toward the cyclic nitrile which, upon addition of base, causes elimination to cyclobutenecarbonitriles.[201,202]

Asymmetric conjugate additions with chiral enamines achieve the highest enantiomeric ratios with enamines derived from chiral amines (Table 12, entries 44−54). Minimal asymmetric induction is observed with the enamine derived from chiral pule-

Table 10. Conjugate Additions of Metalated Sulfones and Sulfoxides to Alkenenitriles

entry	alkenenitrile	alkylsulphonyl	sulfonyl nitrile	yield	ref(s)
		 aq. NaOH, *n*-Bu_4NBr, CH_2Cl_2			
	R^1 R^2	R^3 R^4 R^5			
1	H H	Me Me H		73%	170
2	H Me	Me Me H		75%	170
3	Me H	Me Me H		40%	170
4	H H	H H Me		40%	170
5		 aq. NaOH, *n*-Bu_4NBr, CH_2Cl_2		60%	170
6		 aq. NaOH, $BnNEt_3Cl$		38%	173
		 $BnNMe_3OH$			
	R n				
7	H 6			71%	174
8	Ph 8			78%	174
		 *t*-BuOK, *t*-BuOH-THF			
	R				
9	H			83%	175
10	Me			66%	175
11		 *t*-BuOK, *t*-BuOH-THF, NaOMe		27%	171
12		Me_3SOI, NaH, DMSO		47%	172
		 $BnNMe_3OH$			
	R				
13	2-MeO			92%	176
14	4-MeO			57%	176
15	3,4-CH_2O-			78%	176
16	4-NO_2			83%	176
17	H			94%	176

gone (Table 12 entry 44), whereas modest enantiomeric ratios are obtained with chiral proline-derived enamines (Table 12, entry 45−48). Screening the alkyl substituents of proline esters identified *tert*-butyl esters in nonpolar solvents as optimal although the TMS-prolinol derived enamine and magnesium chloride provides the highest asymmetric induction (Table 12, entry 49). Conjugate additions with phenethylamine-derived enamines are highly enantio- and diastereoselective with acrylonitrile and α-acetoxyacrylonitriles (Table 12, entries 50−54), suggesting that this powerful enamine chemistry may be general for conjugate additions to alkenenitriles. Exploratory conjugate additions with metalated enamines indicate modest chemical yields with asymmetric induction lower than with proline or phenethylamine-derived enamines (Table 12, entries 55−60).

Table 11. Conjugate Additions of Miscellaneous Stabilized Carbanions to Alkenenitriles

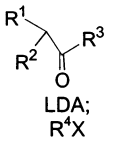
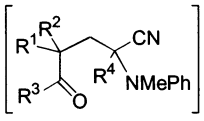
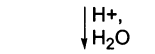
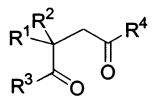
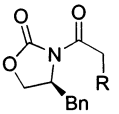
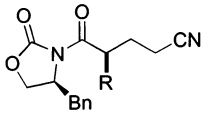
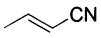
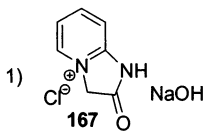
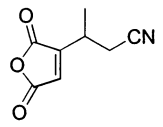
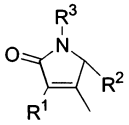
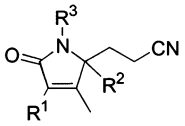
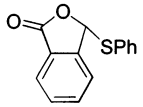
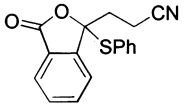
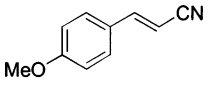
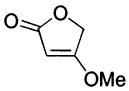
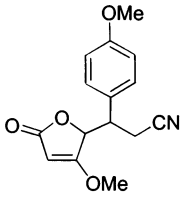
entry	alkenenitrile	stabilized carbanion	nitrile	yield	ref(s)
					
					
					
		R^1 R^2 R^3 R^4X			
1		H Me  MeI		76%	128
2		Me Me NEt_2 MeI		65%	128
3		H -$CH_2CH_2CH_2$NMe- MeI		65%	128
4		H -$CH_2CH_2CH_2CH_2$NMe- MeI		56%	128
5		H Et OH MeI		52%	128
6		Me Me OH *n*-BuBr		60%	128
7		Me Me OH *n*-C_8H_{17}I		47%	128
8		Et Et OH MeI		65%	128
9		Me H_2C=C OH MeI		59%	128
					
		i-Pr_2NEt, *i*-PrOTiCl_3, 0°C, CH_2Cl_2			
		R			
10		Me		93%	178
11		CH_2CH_2COOMe		70%	178
12		$CHMe_2$		84%	178
13				41%	180
		1) NaOH			
		167			
		2) Maleic anhydride, AcOH			
		3) H^+/H_2O			
					
		NaH, THF			
		R^1 R^2 R^3			
14		Me EtS Bn		90%	181
15		Me EtS DDB[a]		66%	181
16		H EtO Bn		80%	181
17				66%	182
		LDA, THF, -78 - 0°C			
18				55%	179
		LDA or BuLi			

Table 11. (Continued)

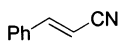
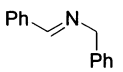
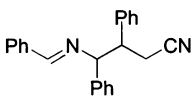
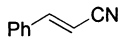
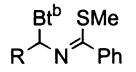
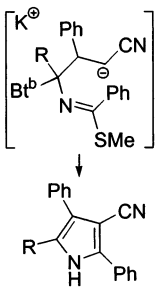
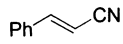
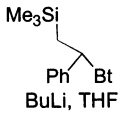
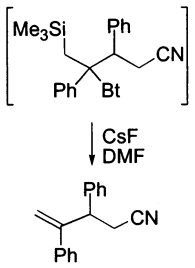
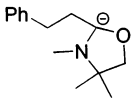
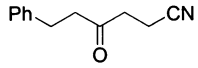
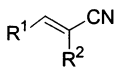
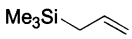
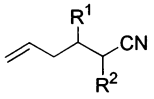
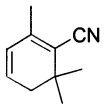
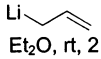
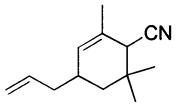
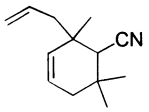
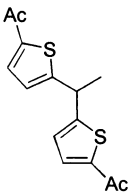
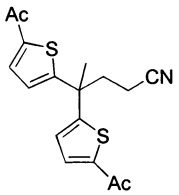
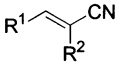
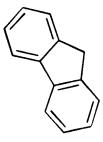
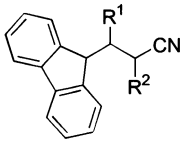
entry	alkenenitrile	stabilized carbanion	nitrile	yield	ref(s)
19		 NaOH, Et_3NBnCl, CH_3CN, rt		32%	183
		 *t*-BuOK, THF			
		R			
20		H		99%	184
21		2,4-$Cl_2C_6H_3$		63%	185
22		 BuLi, THF	 CsF, DMF	66% (two steps)	186
23		 Electrochemically generated; H^+, H_2O		44%	187
		 *n*-Bu_4NF			
	R^1 R^2				
24	Ph H			68%	39
25	2-furyl H			91%	39
26	*t*-Bu H			65%	39
27	PhCH=CH H			37%	39
28	-$(CH_2)_3$-			44%	39
29		 Et_2O, rt, 2 h	 	20% 13%	188
30		 NaH, THF		15%	189
					
	R^1 R^2	base			

Table 11. (Continued)

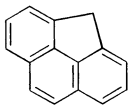
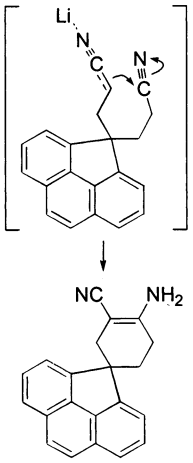
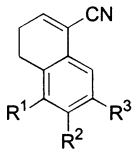
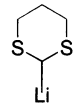
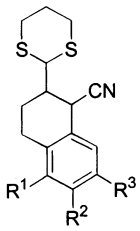
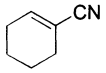
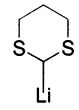
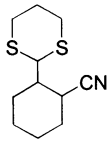
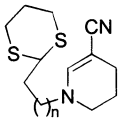
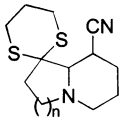
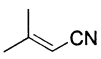
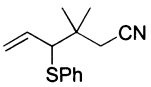
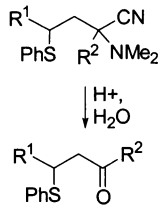
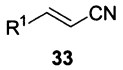
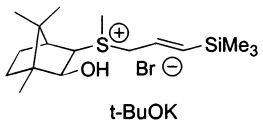
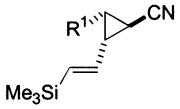
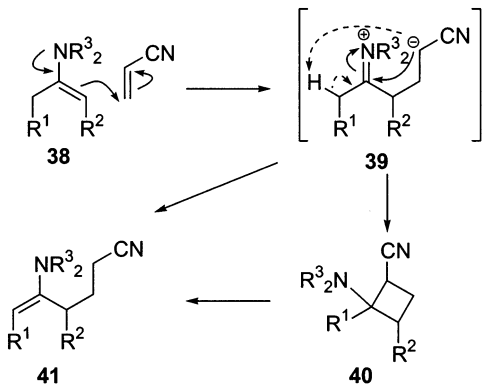
entry	alkenenitrile	stabilized carbanion	nitrile	yield	ref(s)
31	Ph Ph	KOH, Et_3NBnCl		56%	190
32	Ph H	*n*-Bu_4NF		88%	191
33	H Me	$BnNMe_3OH$		75%	192
34		 BuLi		Not determined	193
		 rt, 14 h, THF			
	R^1 R^2 R^3				
35	MeO MeO H			90%[c]	194
36	H H H			90%[c]	194
37	MeO H H			90%[c]	194
38	H MeO H			85%[c]	194
39	H MeO Me O			70%[c]	194
40		 rt, 14 h, THF		50%	194
	 n	BuLi, 12-C-4 THF			
41	1			90%	195
42	2			81%	195
43		 THF, HMPA, -78 – -20°C		76%	196
		 HMPA, THF; R^2X		65-92%	
	R^1 R^2X				
44	H MeI			75%	197
45	H EtI			77%	197
46	H *n*-C_3H_7Br			75%	197
47	H *n*-C_4H_9Br			84%	197

Table 11. (Continued)

entry	alkenenitrile	stabilized carbanion	nitrile	yield	ref(s)
48		H n-$C_5H_{11}Br$		78%	197
49		H n-$C_6H_{13}Br$		79%	197
50		H n-$C_8H_{17}I$		70%	197
51		H 2-cyclopentenone		64%	197
52		H 2-cyclohexenone		80%	197
53		H BnBr		82%	197
54		H H_2C=$CHCH_2Br$		66%	197
55		Me n-C_3H_7Br		80%	197
56		n-C_4H_9 MeI		90%	197
57		n-C_4H_9 EtI		90%	197
58		n-C_4H_9 n-C_3H_7Br		85%	197
59		H_2C=CH MeI		83%	197
60		H_2C=CH EtI		86%	197
61		H_2C=CH n-C_4H_9Br		80%	197
62		H_2C=CH n-$C_8H_{17}I$		75%	197
63		H_2C=CH 2-cyclohexenone		75%	197
	 33	 t-BuOK			
	R^1				
64	Ph			61%	198
65	p-BrC_6H_4			79%	198

[a] DDB: α,α-dimethyl-3, 5-dichlorobenzyl. [b] Bt: Benzotriazoyl. [c] 2−3:1, cis:trans.

Scheme 8



2.6. Miscellaneous Nucleophilic Conjugate Additions to Alkenenitriles

Organometallic reagents provide access to a rich array of unique reactions—conjugate additions to alkenenitriles being no exception. An unusual high-valent iron complex activates acrylonitrile for conjugate addition with cuprate, Grignard, and enolate nucleophiles (Table 13, entries 1−3). The iron complex is stable in the solid state but rearranges in solution to an *N*-bonded complex, obscuring whether activation toward conjugate addition occurs through a π-bonded, or an *N*-bonded, complex. Iron complexes not only permit the addition of external nucleophiles but allow conjugate addition of alkyl groups from organoiron complexes formed in situ by alkylation (Table 13, entries 4−7). Organoiron intermediates undergo migratory CO insertion, generating acyliron complexes that react 1,4 with precoordinated alkenenitriles. A changeover to radical addition occurs on photolysis of alkyliron complexes with alkyl addition from benzyl or phenylallyl organoirons whereas hindered *t*-Bu and Me_3Si substituents cause prior CO insertion and conjugate addition of an acyl radical (Table 13, entries 8−12). The resulting nitrile-stabilized radical recombines with the iron complex generating an organoiron species for subsequent protonation, deuteration, or β-hydride elimination. Related acyl conjugate additions occur with a chromium complex and with magnesium metal in the presence of anhydrides or acid chlorides, possibly by radical-type mechanisms (Table 13, entries 13−15).

Comparative conjugate additions of organocerium, organoytterbium, and organolithiums reveal distinct differences for the three metals (Table 13, entries 16−28). The reactivity differences may stem from minimal deprotonation of the indole with the less basic[230] organocerium and organoytterbium reagents, whereas the more basic organolithium reagents exhibit a greater propensity for deprotonation and addition to the nitrile group, particularly in hexane.

Several highly substituted silylketeneacetals undergo 1,4-conjugate addition to acrylonitrile (Table 13, entries 29−45). The Lewis acid exhibits a pronounced effect on the reaction with $ZnBr_2$ in CCl_4 favoring ring closure to cyclobutanecarbonitriles and ZnI_2 in CH_2Cl_2 favoring α-silylation (Scheme 9).

Scheme 9

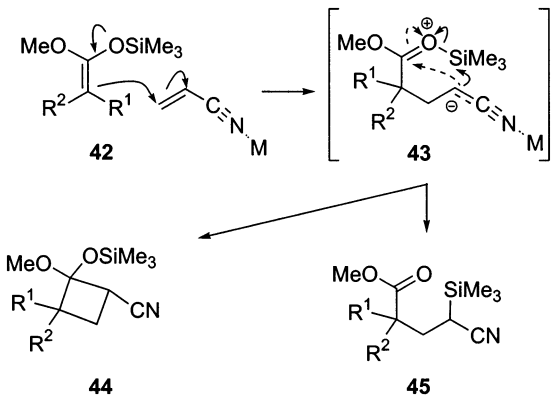


Table 12. Conjugate Additions of Enamines to Alkenenitriles

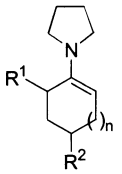
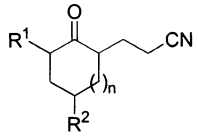
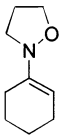
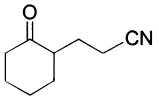
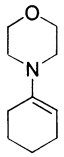
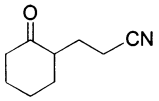
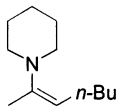
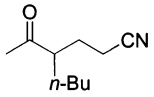
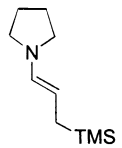
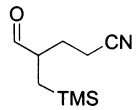
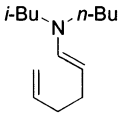
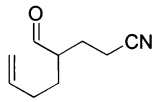
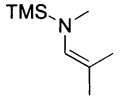
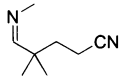
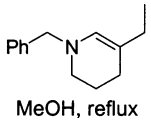
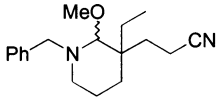
entry	alkenenitrile	enamine	alkanenitrile	Yield	Ref(s)
		 dioxane, reflux; H_2O, reflux			
		R^1 R^2 n			
1		H H 1		80%	200
2		H H 0		67%	200
3		Me H 1		55%	200
4		CH_2CN H 1		38%	200
5		H H 2		60%	200
6		H Me 1		65%	200
7		 neat, rt; H_2O		50%	203
8		 reflux; 20% HOAc		68%	204
9		 dioxane, reflux; H_2O, reflux		50%	108
10		 MeCN, reflux; $HOAc/H_2O$, reflux		30%	205
11		 MeCN, heat; $NaOAc/HOAc/H_2O$, heat		53%	206
12				17%[a]	207
13		 MeOH, reflux		-	106

Table 12. (Continued)

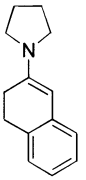
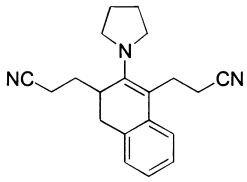
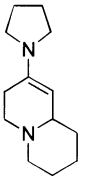
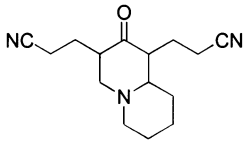
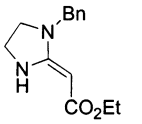
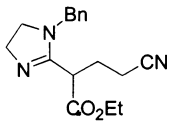
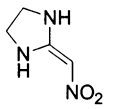
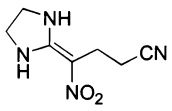
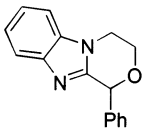
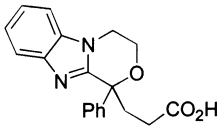
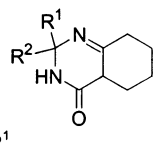
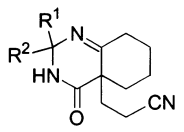
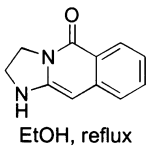
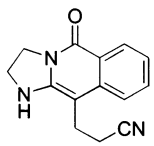
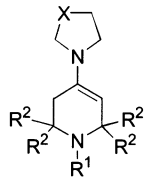
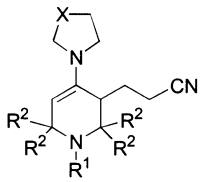
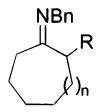
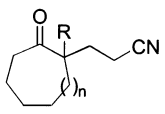
entry	alkenenitrile	enamine	alkanenitrile	Yield	Ref(s)
14		 EtOH, reflux		85%	208
15		 EtOH, DMF, reflux		-	209
16		 MeCN or dioxane, reflux		88%	210
17		 MeCN, reflux		87%	211
18		 $BnNMe_3OH$; H^+		59%	212
					
		R^1 R^2			
19		$-CH_2)_5-$		58%	213
20		H Ph		40%	213
21		 EtOH, reflux		25%	214
		 dioxane, reflux			
		R^1 R^2 X			
22		Me H CH_2		32%	215
23		H Me CH_2O		50%	216
		 MeOH, reflux; 10% HOAc, reflux			
		R n			

Table 12. (Continued)

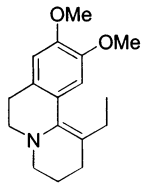
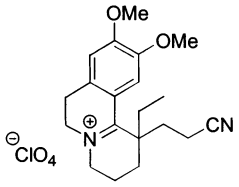
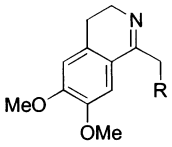
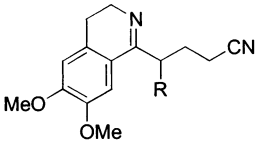
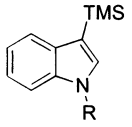
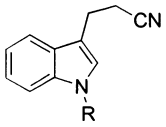
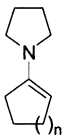
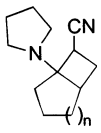
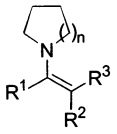
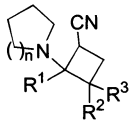
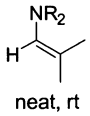
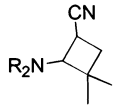
entry	alkenenitrile	enamine	alkanenitrile	Yield	Ref(s)
24		H 1		57%	217
25		Me 1		97%	217
26		H 5		66%	217
27		Me 5		54%	217
28		 MeOH, CH_2Cl_2; 10% HOAc, reflux		17%[b]	218
		 R			
29		$(CH_2)_2CO_2Me$		90%	219
30		$(CH_2)_2CO_2Et$		94%	219
31		H		95%	219
		 $AlCl_3$, $CHCl_3$, 0-65 °C or $AlCl_3$, CH_2Cl_2 R			
32		H		50%	220
33		Me		75%	220
		 neat, rt; MeI, ether n			
34		1		96%	201
35		2		52%	201
36		3		29%	201
		 neat			
		R^1 R^2 R^3 n			
37		H Et H 1		53%	201,202
38		H Me Me 1		62%	201,202
39		H pent H 1		53%	201,202
40		H $(CH_2)_2CONH_2$ Et 1		93%	201,202
41		H Et H 2		84%	201,202
		 neat, rt			
		R			
42		Me		64%	202
43		$(CH_2)_2O(CH_2)_2$		72%	202

Table 12. (Continued)

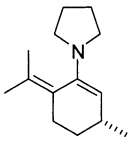
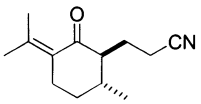
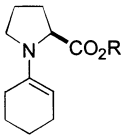
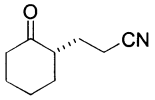
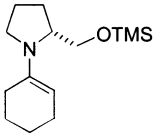
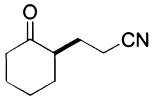
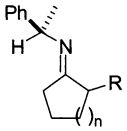
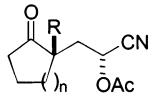
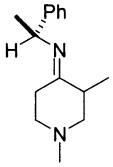
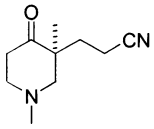
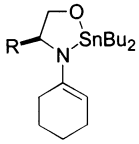
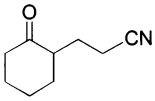
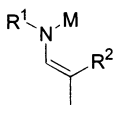
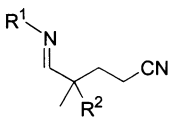
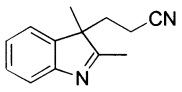
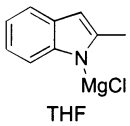
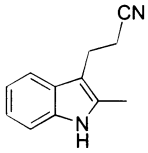
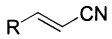
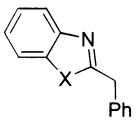
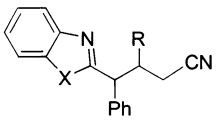
entry	alkenenitrile	enamine	alkanenitrile	Yield	Ref(s)
44		 EtOH, reflux; HOAc, NaOAc, H_2O, dioxane,		61%, 60:40 er	221
		 EtOH or MeOH reflux, 3h			
45		R			222
46		Me		34%[c]	222
47		Et		36%[c]	222
48		*t*-Bu		61%[c]	222
49		 $MgCl_2$, Benzene, reflux		48%, 95:5 er	223
		 $MgCl_2$, Benzene, reflux			
		R n			
50		OBn 1		55%[d]	224
51		Me 1		60%[d]	224
52		OBn 2		72%[d]	224
53		Me 1		74%[d]	224
54		 $MgCl_2$, Benzene, reflux		55%, 65:35 er	225
		 H_2O; KH_2PO_4,H_2O			
		R n			
55		H 2		33%, 55:45 er	226
56		Et 1		16%, 55:45 er	226
57		Et 2		68%, 60:40 er	226
58		Bn 1		23% , 68:32 er	226
59		*i*-Pr 1		50%, 72:28 er	226
60		*i*-Pr 2		52%, 57:43 er	226
					
		R^1 R^2 M			
61		*i*-Pr Me MgCl		65%	227
62		Me Me MgCl		41%	227
63		Et Me MgCl		30%	227
64		Et Me $SnBu_3$		37%	227
65		Me Me $SnBu_3$		40%	227

Table 12. (Continued)

entry	alkenenitrile	enamine	alkanenitrile	Yield	Ref(s)
66		*i*-Pr Me $SnBu_3$		27%	227
67		Et H $SnBu_3$		30%	227
68		*i*-Bu H $SnBu_3$		30%	227
69		*i*-Pr H $SnBu_3$		44%	227
70		 THF		64%	228
71		 THF		54%	228
		 NaOH, DMSO			
	R	X			
72	Ph	O		89%	229
73	Ph	S		79%	229
74	H	O		20%	229
75	Me	O		47%	229

[a] Yield based on a mixture of *N*- and *C*-silylated imines. [b] Contains an additional 59% of conjugate adducts that react further via a [4+2] cycloaddition. [c] The exact enantiomeric ratio is unspecified. [d] The enantiomeric and diastereomeric ratios are in excess of 97:3.

Analogous additions of tin enolates may generate stannylnitriles (**45**, $SiMe_3$ = $SnBu_3$) by the same mechanism followed by protonolysis of the weak tin bond.[251] $TiCl_4$ promotes conjugate addition−anion coupling possibly via a titanated nitrile (**45**, $SiMe_3$ = $TiCl_3$) followed by radical formation and dimerization, although the possibility of forming enoxy radicals followed by conjugate addition is also conceivable.[252]

Conjugate addition of cyanide to alkenenitriles provides a facile route to dinitriles (Table 13, entries 49−52). Two facile conjugate additions of phosphoranes provide a unique route to β-cyanoethylenones (Table 13, entries 53−56).

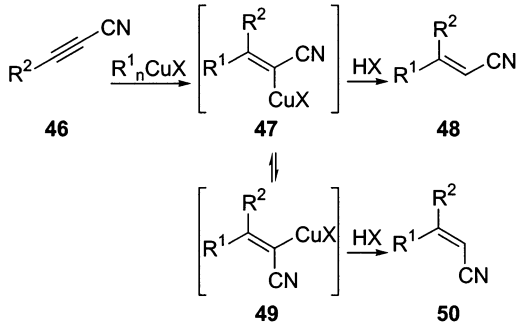
Although not usually considered as conjugate additions, several palladium and rhodium catalysts mediate efficient additions to acrylonitrile (Table 13, entries 57−84). Heck reactions generally require extended reaction times, on the order of days, and often proceed less efficiently than with ethyl acrylate.[247] Initial reports of the rhodium-catalyzed organosiloxane conjugate addition with crotononitrile are particularly exciting, as crotononitrile is a difficult substrate in many conjugate additions, suggesting that the cationic catalyst may be particularly well suited for conjugate additions of alkenenitriles.

3. Conjugate Additions to Alkynenitriles

Alkynenitriles undergo conjugate additions with organosilver and organocopper reagents, dialkyl cuprates, and Grignard reagents in the presence of a copper catalyst (Table 14). Compared with alkenenitriles, organocopper-mediated conjugate addition reactions are much easier (compare with section 2.2.2), signaling a mechanistic changeover from conjugate addition to carbocupration.[30]

Organocopper and dialkyl cuprates stereoselectively add *cis* to alkynenitriles generating a putative vinyl copper intermediate **47** (Scheme 10) that protonates with retention of configuration (Table 14, entries 1−26). The configurational stability of the vinyl copper intermediate **47** is modestly dependent on the structure of the organocopper reagent but strongly temperature dependent, with facile *E*−*Z* isomerization occurring at 30 °C (Scheme 10).

Scheme 10



Enynenitriles react with organocopper reagents exclusively by 1,4-addition, whereas most dienenitriles react with cuprates by 1,6-addition (compare Table 14, entries 21−27 with Table 2, entry 5). The

Table 13. Miscellaneous Nucleophiles Conjugate Additions to Alkenenitriles

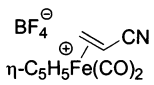
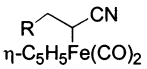
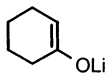
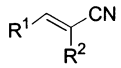
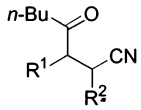
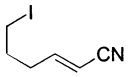
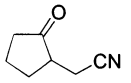
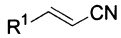
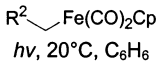
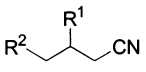
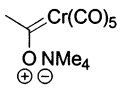
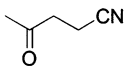
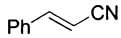
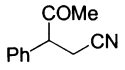
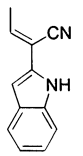
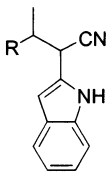
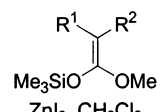
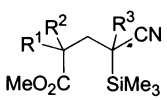
Entry	alkenenitrile	nucleophile	alkanenitrile	yield	Ref(s)
					
			R		
1		Me_2CuLi	Me	71%	231
2		PhMgBr	Ph	45%	231
3				68%	231
		*n*-BuI/$Na_2Fe(CO)_4$			
	R^1 R^2				
4	H H			95%	232
5	Me H			87%	232
6	H Me			92%	232
7		$Na_2Fe(CO)_4$		82%	232
					
	R^1	R^2			
8	H	Ph		45%[a]	233
9	Me	Ph		60%	233
10	H	PhCH=CH		67%	233
11	H	*t*-Bu		56%	233
12	H	Me_3Si		65%	233
13				38%	234
					
14		CH_3COCl, Mg, DMF, TMSCl		44%	235
15		$(CH_3CO)_2O$, Mg, DMF, TMSCl		76%	235
		RLi, MCl_3			
		R MCl_3			
16		Me $CeCl_3$		84%	11
17		Me $YbCl_3$		92%	11
18		Me -		36%	11
19		CH_2=CH $CeCl_3$		68%	11
20		CH_2=CH $YbCl_3$		59%	11
21		CH_2=CH -		10%	11
22		CH_2=CH CH_2 $CeCl_3$		74%	11
23		CH_2=CH CH_2 $YbCl_3$		91%	11
24		CH_2=CH CH_2 -		27%	11
25		 $CeCl_3$		72%	11
26		 $YbCl_3$		69%	11
27		 -		35%	11
28		 -		86%	11
					
	R^3	R^1 R^2			

Table 13. (Continued)

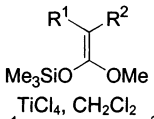
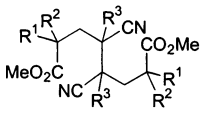
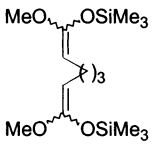
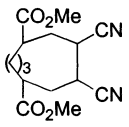
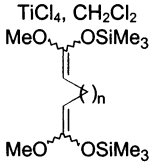
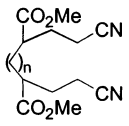
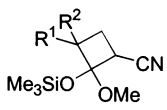
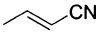
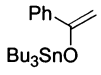
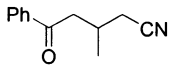
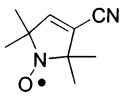
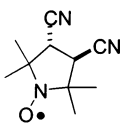
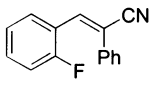
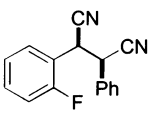
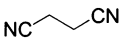
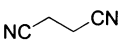
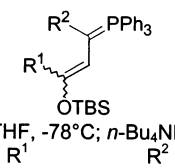
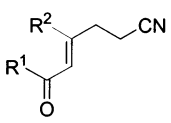
Entry	alkenenitrile	nucleophile	alkanenitrile	yield	Ref(s)
29	H	H C_5H_{11}		80%	36
30	H	H *c*-C_6H_{11}		80%	36
31	H	Me Me		90%	36
32	H	-$(CH_2)_2$-		87%	36
33	Me	Me Me		58%	36
		 $TiCl_4$, CH_2Cl_2			
	R^3	R^1 R^2			
34	H	H C_5H_{11}		62%	36
35	Me	H C_5H_{11}		37%	36
36	H	Me Me		63%	36
37	H	-$(CH_2)_5$-		66%	36
38	Me	Me Me		27%	36
39		 $TiCl_4$, CH_2Cl_2		53%	252
		 $TiCl_4$, CH_2Cl_2			
		n			
40		4		60%	252
41		9		40%	252
		 $ZnBr_2$, CCl_4			
		R^1 R^2			
42		H C_5H_{11}		80%	36
43		H *c*-C_6H_{11}		65%	36
44		Me Me		80%	36
45		-$(CH_2)_2$-		85%	36
		 cat., THF cat.			
46		none		0	236
47		Bu_4NBr		27%	236
48		Bu_4NCl		44%	236
49		KCN, NH_4Cl EtOH, H_2O		52%	237
50		KCN, AcOH EtOH, H2O		28%	238
51		HCN KOH/silica gel		85%	239
52		$Me_2C(OH)CN$, $PhCH_3$ $Cp_2Sm(THF)_2$		89%	240
		 THF, -78°C; *n*-Bu_4NF			
		R^1 R^2			

Table 13. (Continued)

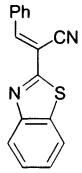
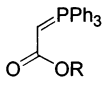
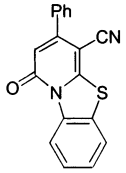
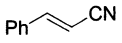
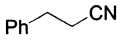
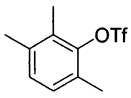
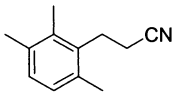
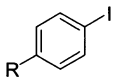
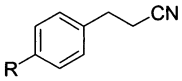
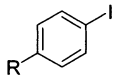
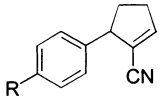
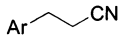
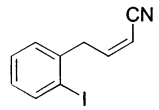
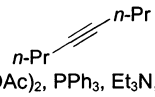
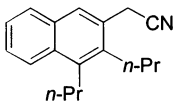
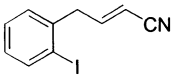
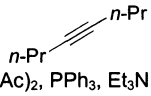
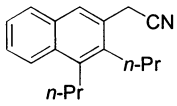
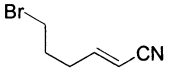
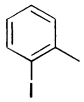
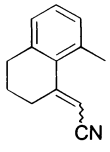
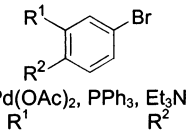
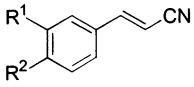
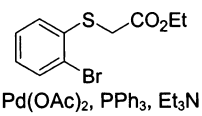
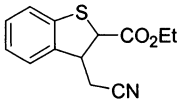
Entry	alkenenitrile	nucleophile	alkanenitrile	yield	Ref(s)
53		-$(CH_2)_3$-		58%	241
54		Et Me		77%	241
					
		R			
55		Me		54%	242
56		Et		68%	242
57		$PhSi(OMe)_3$, $[Rh(cod)(MeCN)_2]BF_4$, dioxane/H_2O		82%	243
58				69%	244
		$PdCl_2(PPh_3)_2$, Et_3N, dppp, DMF, 150°C			
					
		$Pd(OAc)_2$, KOAc, *n*-Bu_4NBr			
		R			
59		NH_2		78%	245
60		MeO		84%	245
61		AcNH		86%	245
62		Me		80%	245
63		H		74%	245
64		Cl		73%	245
65		MeCO		28%	245
66		CF_3		28%	245
					
		$Pd(OAc)_2$, *n*-Bu_4NCl, DMF			
		R			
67		H		78%	246
68		MeO		79%	246
69		R=CO_2Et		51%	246
		ArN_2BF_4 $Pd(OAc)_2$, imidazolium carbene			
		Ar			
70		Ph		47%	247
71		*o*-Me-C_6H_4		42%	247
72		*m*-Me-C_6H_4		41%	247
73		*p*-Me-C_6H_4		48%	247
74		*o*-MeO-C_6H_4		51%	247
75		*p*-MeO-C_6H_4		58%	247
76		*p*-Br-C_6H_4		61%	247
77		2-naphthyl		39%	247
78		1-naphthyl		37%	247
79				74%	248
		$Pd(OAc)_2$, PPh_3, Et_3N, DMF			
80				72%	248
		$Pd(OAc)_2$, PPh_3, Et_3N, DMF			
81				63%[a]	249
		$Pd(OAc)_2$, tri-2-furylphosphine, norbornene, Cs_2CO_3			

Table 13. (Continued)

Entry	alkenenitrile	nucleophile	alkanenitrile	yield	Ref(s)
					
		$Pd(OAc)_2$, PPh_3, Et_3N			
		R^1 R^2			
82		EtO_2CCH_2S H		60%	250
83		H EtO_2CCH_2S		78%	250
84				38%	250

[a] 2:1 *E:Z* mixture.

high stereoselectivity in additions to enynenitriles provides an excellent route to retinoids by reduction of the nitrile to the corresponding aldehydes (Table 14, entry 27).[257]

Alkylargintate reagents react with alkynenitrile in a trans addition, providing *E*-dienylnitriles. *E*-Stereoselectivity is maintained in additions to enynenitriles with primary alkylargintates (Table 14, entries 30−37) although secondary and tertiary alkylargintates afford mixtures resulting from 1,4- and 1,6-addition (Table 14, entries 38−39). Related silver (I) reagents add exclusively 1,6, generating allenyl nitriles (Table 14, entries 40−43). The beauty of alkylargintates and silver (I) reagents lies in the complementary reactivity with copper reagents, providing control over *E*, *Z* geometry and 1,4−1,6- regioselectivity.

Conjugate addition of the alkylidene diiron complex to propynenitrile is unique (Table 14, entries 44−46). Mechanistic experiments were inconclusive but point to the conjugate addition being initiated by the nucleophilic alkylidene carbon followed by an intramolecular proton transfer. Unfortunately alkylidene substitution reduces the reaction efficiency in what is otherwise an extremely unusual organometallic conjugate addition.

Grignard reagents exhibit a propensity for conjugate addition to alkynenitriles that is moderated by competitive 1,2-addition and deprotonation (Table 14, entry 47−49).[241] Increased efficiency ensues in chelation controlled conjugate additions where the nucleophile is temporarily chelated in close proximity to the alkynenitrile (Table 14, entries 50−57). Conjugate addition generates a cyclic magnesium chelate that can be activated for alkylation with benzaldehyde by prior addition of *t*-BuLi which presumably generates a more reactive magnesium ate complex (Table 14, entry 57).

4. Reactivity Trends in Conjugate Additions to Alkenenitriles

Anionic and organometallic conjugate additions to alkenenitriles are vastly different from related reactions of unsaturated carbonyl compounds. Disparate reactivities between alkenenitriles and unsaturated carbonyl compounds stem from polarization differences of the π-electrons that are not immediately apparent from comparative resonance structures (Figure 1). Insight into the polarization of alkenenitriles by NMR[261] indicates that the powerful inductive electron withdrawing effect of the CN group[262] polarizes alkenenitriles more by induction than resonance delocalization.[130] After correcting for anisotropy differences, the α-carbon of acrylonitrile is more deshielded than the β-carbon (Figure 1, **52a** vs **52c** ↔ **52d**). Analogous trends with nitrile anions demonstrate stabilization primarily from the inductive effect of the CN group[130] and a minimal delocalization,[95b] which suggests **52a** contributing the most to the polarization in alkenenitriles.

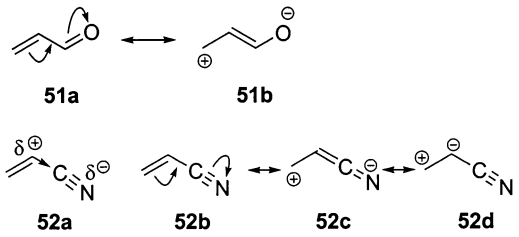


Figure 1.

The unusual polarization of alkenenitriles is evident from a comparison of the frontier molecular orbital coefficients of acrylonitrile and acrolein (Figure 2).[263] The coefficient of the nitrile carbon of acrylonitrile is small, consistent with the difficulty often encountered in organolithium and magnesium additions to the nitrile group[38] and the ability to incorporate nitriles within organolithium[264] and magnesium[265] reagents. The similar coefficients of the β-carbons suggest that alkenenitriles should be as reactive in anionic and organometallic conjugate additions as unsaturated carbonyl compounds, although a critical difference may be the much weaker Lewis basicity of alkenenitriles that prevents activation by Lewis acids which promote analogous conjugate additions to the corresponding unsaturated carbonyl compounds.[30]

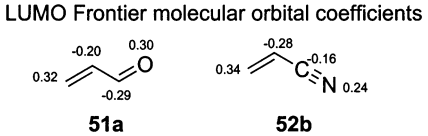


Figure 2.

Table 14. Conjugate Additions to Alkynenitriles

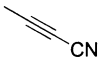
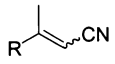
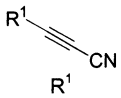
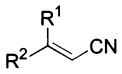
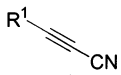
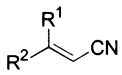
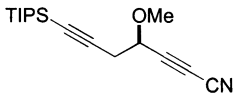
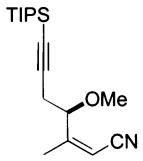
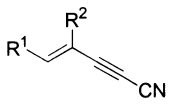
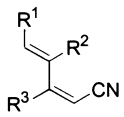
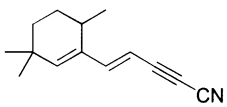
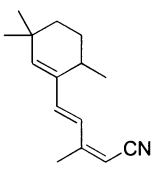
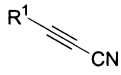
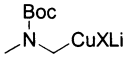
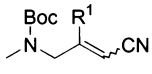
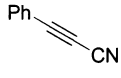
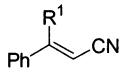
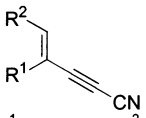
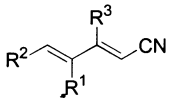
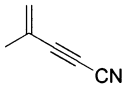
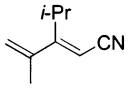
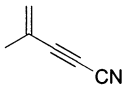
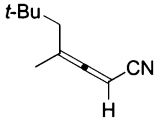
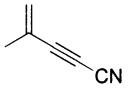
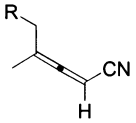
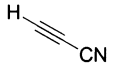
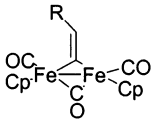
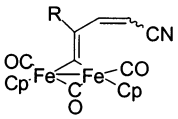
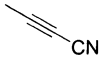
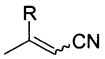
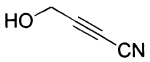
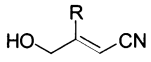
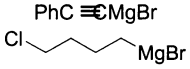
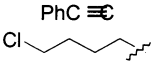
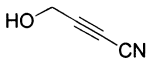
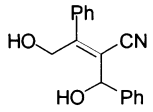
entry	alkynenitrile	organometallic	alkenenitrile	yield	ref(s)
		RMgCl/Br, CuCl (cat.) -5 – 5°C			
		R			
1		Me		58%	253
2		Et		74%	253
3		Ph		80%	253
4		*t*-Bu		0	253
		R^2M, CuX, THF-Et_2O -60 – 10°C, M=MgCl, MgBr or Li			
	R^1	R^2 M X			
5	Ph	Me MgCl Br		95%	254
6	Me	Ph MgBr Br		94%	254
7	Ph	Et MgBr Br		92%	254
8	Et	Ph MgBr Br		91%	254
9	Ph	*n*-Bu MgCl Br		96%	254
10	*n*-Bu	Ph MgBr Br		96%	254
11	(*E*)-Ph(Et)C=CH	Et MgBr Br		98%	254
12	Et	(*E*)-Ph(Et)C=CH MgBr Br		88%	254
13	Ph	Me Li I		90%	254
14	Ph	*n*-Bu Li I		92%	254
15	Ph	Ph Li I		75%	254
		R^2_2CuM, THF -50 – -85°C			
	R^1	R^2			
16	Ph	Me		98%	254
17	Et	Ph		93%	254
18	Ph	*n*-Bu		93%[a]	254
19	*n*-Bu	Ph		92%	254
20		Me_2CuLi, THF -78°C		86%	255
		R^3[CuBr]MgCl, THF/Et_2O			
	R^2 R^2	R^3			
21	-$(CH_2)_4$-	Me		90%[b]	254
22	-$(CH_2)_4$-	Et		70%	256
23	-$(CH_2)_4$-	*n*-Bu		80%	256
24	H Me	Et		90%	256
25	H Me	*n*-Bu		86%	256
26	H Me	*i*-Pr		76%	256
27		MeLi, CuI, THF/Et_2O -78°C		92%	257
		 2RLi+CuCN·2LiCl, THF			
	R^1				
28	Bu			85%[c]	35
29	Ph			74%[d]	35
		R^1_2AgMgCl·2LiBr, THF -35~-50°C			

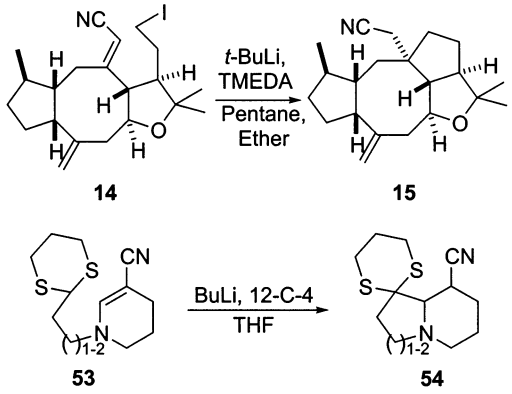
Table 14. (Continued)

entry	alkynenitrile	organometallic	alkenenitrile	yield	ref(s)
30		R^1			
31		Me		>98%	258
32		Et		>98%	258
33		Bu		>98%	258
		$R^3{}_2AgMgCl{\cdot}2LiBr$, THF -35 – -50°C			
	R^1 R^2	R^3			
34	-$(CH_2)_4$-	Et		80%	256
35	-$(CH_2)_4$-	*i*-Pr		70%	256
36	Me H	Et		85%	256
37	Me H	*n*-Bu		90%	256
38		*i*-$Pr_2AgMgCl{\cdot}2LiBr$, THF -50 – -60°C		nd[d]	256
39		*t*-$Bu_2AgMgCl{\cdot}2LiBr$, THF -50 – -60°C		90%	256
		RAg -50~-60°C			
		R^1			
40		Et		90%	256
41		*n*-Bu		85%	256
42		*i*-Pr		85%	256
43		*t*-Bu		90%	256
		 toluene, 77 °C, dark			
		R			
44		H		65%	259
45		*i*-Pr		30%	259
46		Me		21%	259
		RMgX			
		R			
47		Me		20%	253
48		Et		36%	253
49		Ph		50%	253
		*t*- BuMgCl; RMgX			
		RMgX	R		
50		MeMgCl	Me	92%	260
51		*i*-PrMgBr	*i*-Pr	87%	260
52		*n*-$Bu_3SnMgCl$	*n*-Bu_3Sn	70%	260
53		*t*-BuMgCl	*t*-Bu	60%	260
54		CH_2=CHMgBr	CH_2=CH	87%	260
55		PhC ≡CMgBr	PhC ≡C	85%	260
56				78%	260
57		*t*-BuMgCl; PhMgCl; PhCHO		60%	260

[a] *E*:*Z* 1:9. [b] Performed at 0 °C. [c] *E*:*Z* 7:3. [d] *E*:*Z* 43:57. [d] A 4:1 ratio of 1,4- and 1,6-addition in unspecified yield.

The key requirement for anionic conjugate additions to alkenenitriles lies in employing highly nucleophilic reagents that are not prone to 1,2-addition. The two intramolecular conjugate additions of **14** and **53** (Scheme 11) typify the requirement for highly

Scheme 11



reactive nucleophiles that are geometrically prevented from 1,2-addition. In the case of **53** the reaction efficiency directly correlates with the carbanion nucleophilicity.[195] Less nucleophilic organometallics, cuprates in particular, react poorly with alkenenitriles whereas stabilized carbanions undergo conjugate additions more readily, particularly when the carbanion nucleophilicity is enhanced with noncoordinating cations. Organometallics with radical character engage in particularly efficient conjugate additions, implying a beneficial changeover in mechanism that is presumably promoted by the excellent radical-acceptor properties of alkenenitriles.[53]

Conjugate additions tolerate diverse substitution in the nucleophile but are sensitive toward substitution of the unsaturated nitrile. β-Substituents dramatically retard the conjugate additions to alkenenitriles, whereas alkynenitriles, which necessarily contain only one β-substituent, exhibit a greater propensity toward conjugate addition. The combination of the greater electrophilicity of alkynenitriles and the mechanistic changeover to carbometalation, rather than conjugate addition, permits efficient reactions with relatively weak nucleophiles such as cuprates and alkylargintates.

Analyzing the tabulated conjugate additions establishes a general reactivity order for substituted acrylonitriles (Figure 3). In general, the substitution pattern parallels that of carbonyl compounds where increasing substitution progressively retards conjugate addition.[266] Presumably, β-substituents retard conjugate addition through an increased steric demand and by diminishing the modest electropositive character of the β-carbon. α-Substituents similarly exert a deleterious inductive effect although α-phenyl substituents activate some reactions, possibly through a combination of delocalization and sterically retarding 1,2-addition. Conjugate addition to the fully substituted acrylonitrile **60** is particularly difficult as attested with only five known examples (Table 1, entries 28−30; Table 8, entry 62; and Table 11, entry 29). The reactivity trends provide a guide for the ease

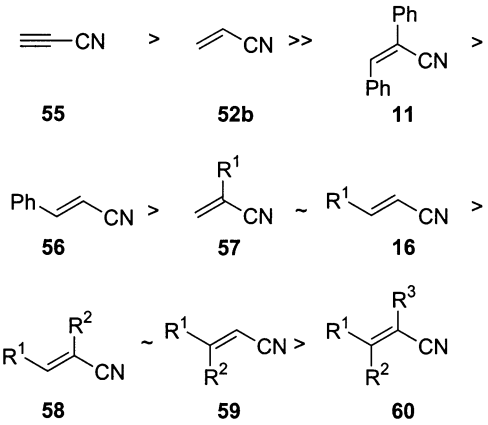


Figure 3.

of conjugate addition with some variability, particularly since the exact mechanism, anionic or radicaloid, depends on the solvent and the nature of the organometallic reagent.

5. New Directions

Unsaturated nitriles are generally recalcitrant electrophiles in conjugate addition reactions. Coaxing conjugate additions to unsaturated nitriles currently requires a judicious choice of reagent and reaction conditions, but the viability of the transformation is well established and bodes well for future profitable refinements. Developing conjugate additions to unsaturated nitriles has the potential advantage of exploiting the chemo- and regioselectivity differences between unsaturated nitriles and the corresponding carbonyl compounds. For example, preferential conjugate addition to an unsaturated carbonyl compound in the presence of an alkenenitrile is conceptually possible with an organocopper reagent, whereas the rapid chelation-controlled conjugate addition of Grignard reagents with hydroxy alkenenitriles may allow a preferential conjugate addition in the presence of an enone.

Two significant challenges remain for conjugate additions to alkenenitriles: enantio- and diastereoselective conjugate additions, and domino conjugate addition−alkylation sequences. Several precedents establish the viability of stereoselective conjugate additions and domino addition−alkylations, suggesting future profitable developments in these areas. Developing these conjugate additions to alkenenitriles provides potential routes to substituted nitriles that are ideal synthetic intermediates, particularly en route to nitrile-containing natural products. Dramatic advances in catalytic conjugate additions, combined with the complementary reactivity of unsaturated nitriles and carbonyl compounds, suggests an increased emphasis on unsaturated nitriles as valuable electrophiles in conjugate addition reactions.

6. Acknowledgment

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