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KF/Al_2O_3 Mediated organic synthesis

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Contents

1. Introduction

Over the past 25 years, there have been two major trends in the field of organic chemistry. The first is a push towards environmentally friendly processes using safer reagents, generating fewer side products and having decreased solvent requirements. The second is the development of combinatorial chemistry,[1] which has had a dramatic impact, especially in the pharmaceuticals industry, where libraries of thousands of new chemical entities have been prepared using both solution and solid phase organic synthesis. Both of these trends have lead to explosive growth in the fields of both solid phase organic synthesis and solid supported reagents such as potassium fluoride on alumina (KF/Al_2O_3). This versatile reagent was originally introduced in 1979 by Ando et al. as a useful agent for inducing alkylation reactions.[2] It possesses a number of the advantages of both solution and solid phase chemistry. Like solid phase synthesis, excess support bound reagent can be used and removed by filtration, avoiding cumbersome aqueous workups and decreasing solvent waste handling issues. In addition, since the compound of interest is never covalently bound to the solid support, monitoring of the reactions and analysis can be accomplished using standard methods (thin layer chromatography, solution ^1H NMR, etc.). In addition, the products are isolated by filtration and removal of the solvents, eliminating the need for a cleavage step that is required in solid phase preparations. Additional benefits have been achieved by taking advantage of the strongly basic nature of KF/Al_2O_3, which has allowed it to replace organic bases in a number of reactions including but not limited to selective *N*-alkylation of amides,[3] epoxidations,[4] diazetizations,[5] Sonogashira couplings,[6] Suzuki couplings,[7] Knoevenagel reactions,[8] and Horner–Emmons chemistry.[9] The source of this basicity has been the subject of some debate in the literature. Weinstock et al. have argued that KF/Al_2O_3 derives its basicity from the formation of KOH in

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Keywords: organic synthesis; potassium fluoride; alumina; solid supported reagent.

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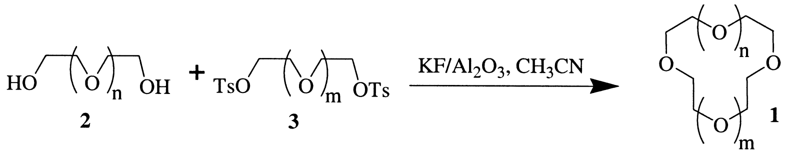
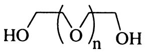
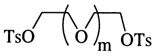
Table 1. KF/Al_2O_3 Mediate crown ether synthesis



Entry			Product	Yield (%)
1	n=2	m=1	15-Crown-5	25
2	n=2	m=2	18-Crown-6	78
3	n=2	m=3	21-Crown-7	54
4	n=3	m=3	24-Crown-8	27

the initial preparation of the solid supported material by reaction of KF with the alumina support.

$$12KF + Al_2O_3 + 3H_2O \rightarrow 2K_3AlF_6 + 6KOH$$

They cite as evidence their observation of the reaction of chloroform with *m*-nitrobenzaldehyde to produce α-trichloromethyl-(3-nitrophenyl)carbinol in 82% yield. They were able to demonstrate that when aqueous KOH is added to Al_2O_3 to produce a material with similar basicity (as measured by Hammett indicators to be pK_a=12–15 on the surface), the aforementioned reaction proceeds with similar rates and yields (81%).[10] However, Ando et al. have disputed this claim. They examined a number of samples of KF/Al_2O_3 by titrimetric analysis. Aqueous washing of the samples provided an alkaline solution which could be titrated to determine the amount of soluble base present. They also separately washed samples with a fixed excess of aqueous HCl, to determine the overall basicity of the samples. The total basicity was found to be significantly higher than could be accounted for by the formation of KOH during reagent preparation. The aqueous wash of 0.6 mmol/g loaded KF/Al_2O_3 resulted in a 0.18 M basic solution, whereas the solid material total basicity equated to 0.69 M solution, almost four times as basic. In addition, Ando et al. suggested that at loadings higher than 0.6 mmol/g KF (theoretical monolayer point) that the KOH formed would be mostly covered by further layers of KF and not available to promote basicity. Ando et al. concluded that there are three basic species or mechanisms of the appearance of the basicity of KF/Al_2O_3: (1) the presence of active fluoride, (2) the presence of $[Al-O^-]$ ion which generates OH^- when water is added, and (3) the cooperation of F^- and [Al–OH].[11]

2. Carbon–oxygen bond formation

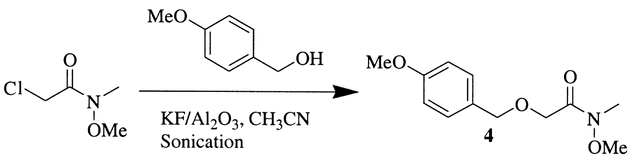
2.1. Ether synthesis

One of the first reported applications of KF/Al_2O_3 involved the nucleophilic displacement of tosylate leaving groups to form crown ethers (**1**) from polyethylene glycol (**2**) and polyethylene glycol ditosylates (**3**, Table 1). While the yields were moderate, they were consistently higher than the previously described methods, including the modified Williamson ether synthesis. This is in direct contrast to the findings of Reinhoudt et al. indicating that solid, unsupported metal fluorides were ineffective in the preparation of crown ethers and led to the corresponding difluoride. The presence of the Al_2O_3 support matrix alters the course of the reaction to favor the synthesis of crown ethers over halogen substitution.[12]

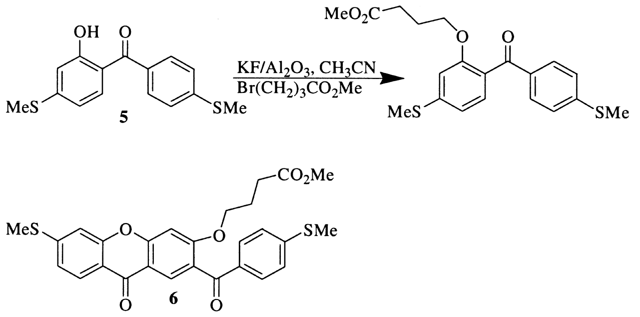
Tius et al. extended the utility of KF/Al_2O_3 for the synthesis of ethers by applying it to the synthesis of α-hetero-substituted Weinreb amides as part of their efforts to develop C-11 hydroxy cannabinoid analogs. They reported that while traditional sodium hydride mediated Williamson ether synthesis produced low yields (36%) of **4**, the application of KF/Al_2O_3 with sonication led to dramatically improved results (73%). More reactive alcohols, such as *p*-bromophenol, were found to produce the desired product in the absence of sonication (Scheme 1).[13]

This observation is similar to the results reported by Petal et al. in their investigations of the synthesis of safety catch linkers. They found that the intramolecularly hydrogen bonded phenol **5** could be activated to undergo ether synthesis with KF/Al_2O_3, rather than the more expensive tetraethylammonium fluoride used in the original work. They also found, however, that this new procedure produced the unusual xanthone by-product **6** in low yield (5–10%), presumably via a retro Friedel–Crafts reaction (Scheme 2).[14]

Diaryl ether synthesis using KF/Al_2O_3 as an alternative to the copper catalyzed Ullman ether synthesis has also been

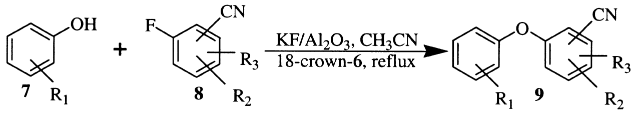


Scheme 1.



Scheme 2.

Table 2. KF/Al_2O_3 Mediated coupling of fluorobenzonitriles and phenols



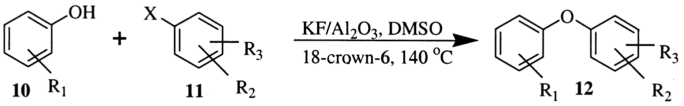
Entry	R_1	R_2	R_3	CN position	Time (h)	Yield (%)
1	H	H	H	2	48	98
2	H	H	H	4	72	91
3	3-OMe	H	H	2	72	99
4	3-OMe	H	H	4	72	99
5	3-OMe	3′-OMe	H	2	36	99
6	3-OMe	3′-(1-Pyrrolyl)	H	2	18	98
7	3-OMe	5′-NO_2	H	2	18	97
8	3-OMe	3′-(4-Methylthiophenoxy)	H	2	18	99
9	3-OMe	6′-Cl	H	2	18	98
10	3-OMe	3′-NMe_2	6′-CHO	2	96	91
11	2-*t*-Butyl	H	H	4	120	83
12	4-CO_2Me	H	H	2	168	83
13	4-NO_2	H	H	2	336	13

described. Sawyer et al. were able to demonstrate that a series of fluorobenzonitriles (**7**) could be condensed with phenols (**8**) to produce diaryl ethers (**9**) in the presence of KF/Al_2O_3 and 18-crown-6 in refluxing acetonitrile. 18-Crown-6 was not required for the reaction, but it was found that reaction rates were significantly improved when it was used as a co-catalyst. In addition, the reaction showed remarkable flexibility, as the desired products were formed in high yields with both electron rich and electron poor electrophiles. Limitations on the nucleophile were only observed with 4-nitrophenol, which produced only 13% of the desired product (Table 2).[15]

In subsequent papers, the scope of this method was expanded to include a broad range of halonitrobenzenes. It was also demonstrated that a wider range of halobenzene (**11**) derivatives and phenols (**10**) could be converted to diaryl ethers (**12**) if more forceful conditions were employed, such as conducting the reaction in DMSO at elevated temperatures (140°C). This minor modification of the reaction conditions allowed for a much greater range of substitution patterns and provided access to compounds that could not be formed using the typical Ullman coupling (Table 3). The electronically unfavorable 3-chlorobenzonitrile, for example, was condensed with 3-methoxyphenol to produce the corresponding diaryl ether in 66% yield.[16]

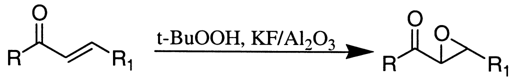
In contrast to the synthesis of aryl ethers, the application of KF/Al_2O_3 to the synthesis of dialkyl ether has been somewhat limited. Hattori et al. reported the cyanoethylation of methanol by a KF/Al_2O_3 mediated Michael addition of methanol to acrylonitrile (**13**) to produce **14** in good yield, but further exploration of this chemistry has not been reported (Scheme 3).[17]

Table 3. KF/Al_2O_3 Mediated diaryl ether synthesis in DMSO



Entry	R_1	R_2	R_3	X	Time (h)	Yield (%)
1	H	4-CHO	H	F	16	81
2	3-OMe	4-Ac	H	F	16	70
3	H	4-CO_2Et	H	F	124	82
4	3-OMe	4-CO_2Et	H	F	18	65
5	H	2-$CONH_2$	H	F	48	66
6	3-OMe	4-Br	H	F	48	36
7	4-OMe	3-CF_3	H	F	140	38
8	3-OMe	4-Ph	H	F	172	19
9	H	2-CN	3-Cl	F	20	90
10	3-OMe	3-CN	H	F	6	68
11	2-CN	4-CN	H	F	18	84
12	2-CN	2-CN	H	F	36	88
13	4-OMe	4-CN	H	Br	2	78
14	4-OMe	4-CN	H	Cl	3	84
15	3-OMe	3-CN	H	Cl	6	66
16	3-OMe	4-CN	H	Cl	18	82
17	H	2-CN	H	Cl	18	68
18	4-OMe	3-CN	4′-CF_3	Cl	3	69
19	4-OMe	2-Cl	4′-CN	Cl	16	72

Table 4. KF/Al_2O_3 Mediated epoxidation of enones with *t*-butyl hydroperoxide



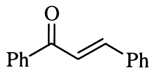
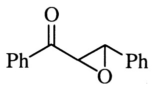
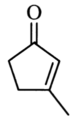
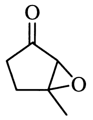
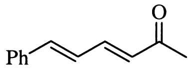
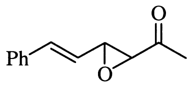
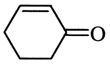
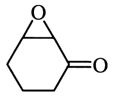
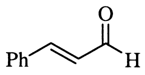
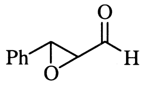
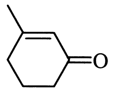
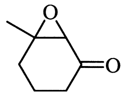
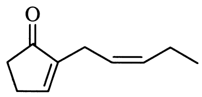
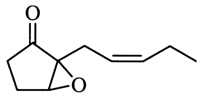
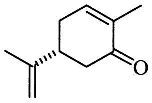
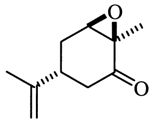
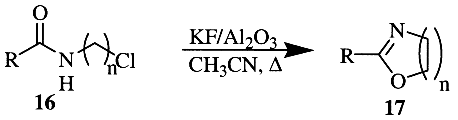
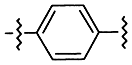
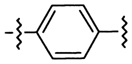
Entry	Substrate	Product	Yield (%)	Entry	Substrate	Product	Yield (%)
1			100	5			65
2	 **15**		45	6			85
3			75	7			40
4			100	8			85

Table 5. KF/Al_2O_3 Mediated cyclizations of haloamides

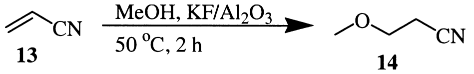


16 **17**

Entry	R	*n*	Time (h)	Yield (%)
1	Ph	3	24	93
2	Ph	2	24	83
3	$CH_3(CH_2)_8$	3	72	31
4	$CH_3(CH_2)_8$	2	6	93
5		3	24	78
6		2	24	86
7	CH_3	2	2	75

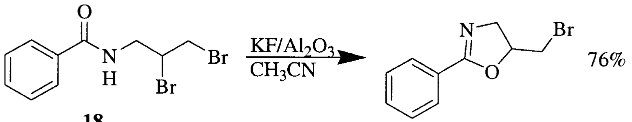
2.2. Epoxidation

The KF/Al_2O_3 mediated preparation of epoxides from alkenes has been the subject of a number of papers. Early reports of the successful formation of epoxides from electron deficient alkenes in the presence of *t*-butyl hydroperoxide and KF/Al_2O_3 showed that this method complemented the existing literature in a number of ways.[18] First, dienones such as **15** (entry 2, Table 4) were shown to produce only the α,β-product in the presence of KF/Al_2O_3, while *m*-CPBA oxidation produces significant quantities of the undesired γ,δ-epoxide. In addition, cyclopentenones, which are known to undergo base catalyzed aldol self-condensation, were shown to produce the desired epoxide in high yield. The initial reports of this chemistry suggested that sterically demanding cases such as isophorone and testosterone were reactive under the described conditions. However, a later report with different solvents successfully demonstrated the epoxidaton of both of these compounds.[19]



13 **14**

Scheme 3.



18 **19**

Scheme 4.

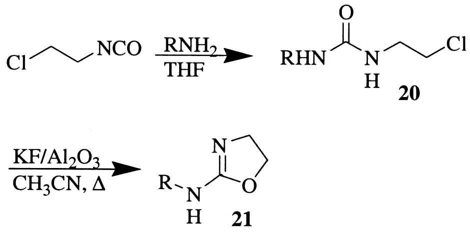
2.3. Ring closures

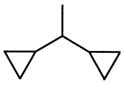
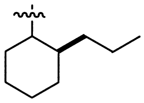
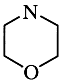
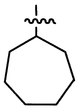
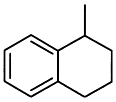
The application of KF/Al_2O_3 to the synthesis of ring systems by C–O bond formation has been limited to a handful of reports that focus primarily on the synthesis of oxazines and oxazolines. Mitchell and Benicewicz demonstrated that suitably substituted haloamides (**16**) could undergo cyclization via nucleophilic displacement of the halide by the carbonyl oxygen to form the desired ring system (**17**) in moderate to excellent yield (Table 5). This is in contrast to similar experiments preformed using more conventional, stronger bases (e.g. aqueous potassium hydroxide or ethanolic sodium hydroxide), which provide low yields of the cyclized products.

Excellent selectivity in this reaction was demonstrated in the preparation oxazoline **18** from dihaloamide **19**. The corresponding oxazine, a by-product often seen in other methods, was not observed under the conditions described (Scheme 4).[20]

Wong et al. further expanded the utility of this method by applying the chemistry to the cyclization of halourea

Table 6. KF/Al_2O_3 Mediated oxazoline synthesis



Entry	R	Yield (%)	Entry	R	Yield (%)
1		53	4		88
2		57	5		64
3		58			

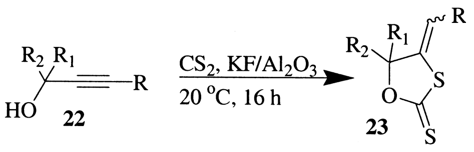
derivatives (**20**) in their efforts to develop novel adrenergic receptor antagonists related to Rilmenidine. Preparation of the necessary haloureа from 2-chloroethylisocyanate was followed by KF/Al_2O_3 mediated cyclization to yield the desired oxazoline products (**21**, Table 6).[21]

2.4. Thiocarbonyl chemistry

Carbon disulfide and various thiocarbamyl chlorides have been shown to be susceptible to nucleophilic attack under KF/Al_2O_3 mediated conditions. Villemin et al. demonstrated that propargylic alcohols (**22**) will condense with carbon disulfide under solvent free conditions to produce 1,3-oxathiolanes (**23**, Table 7) in moderate to high yields. Previously reported solution based methods produced complex mixtures with very little of the desired products.[22]

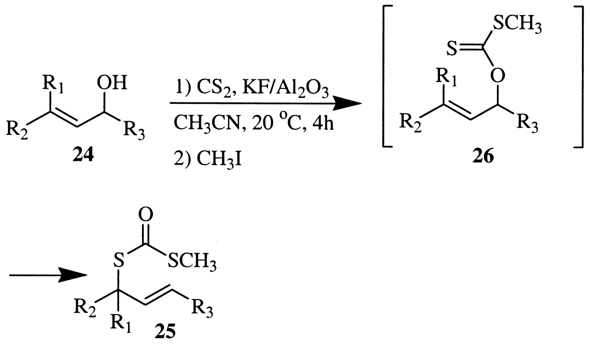
Allylic alcohols (**24**) were also shown to undergo similar chemistry. Condensation with carbon disulfide under solvent free conditions, followed by the addition of iodomethane led to *S*-allyl-*S*-methyldithiocarbonates (**25**). This is thought to occur by initial nucleophilic attack of the allylic alcohol on the carbon disulfide, followed by alkylation with iodomethane. The resulting xanthate (**26**) then undergoes a sigmatropic rearrangement to the observed product (Table 8).[23]

Table 7. KF/Al_2O_3 Mediated 1,3-oxathiolane synthesis



Entry	R_1	R_2	R	Yield (%)
1	CH_3	CH_2CH_3	H	70
2	H	$CH(CH_3)_2$	CH_3	57
3	CH_3	CH_3	H	94
4	CH_3	CH_3	$CHCCH_2$	64
5	Cylohexyl		H	60

Table 8. KF/Al_2O_3 Mediated synthesis of dithiocarbonates



Entry	Alcohol	Yield (%)	Entry	Alcohol	Yield (%)
1	2-Methyl-3-buten-1-ol	50	4	Geraniol	55
2	3-Methyl-2-buten-1-ol	90	5	Linalool	55
3	Cinnamyl alcohol	75	6	Farnesyl alcohol	40

The condensation of various phenols with dialkylthiocarbamyl chlorides (**27**) under KF/Al_2O_3 mediated conditions was also reported by Villemin et al. as part of their efforts to prepare *S*-aryl-*N*,*N*-dialkylthiocarbamates (**28**).[24] It is interesting to note that the corresponding KF/Al_2O_3 mediated condensation of phenols with chlorofomates and acid chlorides has not been reported, suggesting that their inherent susceptibility to hydrolysis prevents them from taking part in this type of chemistry (Table 9).

2.5. Miscellaneous

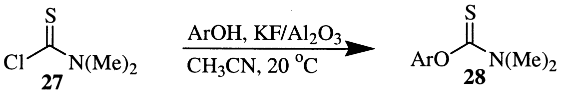
KF/Al_2O_3 mediated hydrolysis of nitriles has been described in the literature and both aliphatic and aromatic nitriles (**29**) were shown to produce the corresponding primary amides (**30**) when refluxed in *t*-butanol in the presence of KF/Al_2O_3 in good to excellent yields. Control reactions with only KF or Al_2O_3 did not produce the primary amide product (Table 10).[25]

3. Carbon–nitrogen bond formation

3.1. Amide chemistry

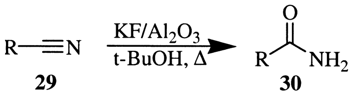
The chemistry of amides has been complicated by difficulties in the selective functionalization of amides with typical basic methods (e.g. NaOH, NaH, etc.) providing mixtures of *N*- and *O*-alkylated products, rather than selective formation of one over the other. An important early observation in the chemistry of KF/Al_2O_3 was its ability to promote selective *N*-alkylation of amides under the appropriate conditions. This was first reported by Ando et al. as they found that alkylation of amides could be accomplished with alkyl halides in either acetonitrile or 1,2-dimethoxyethane. Sensitive compounds such as β-lactams were found to produce high yields of the desired products (Table 11). In addition, both uracil and xanthine were

Table 9. KF/Al_2O_3 Mediated synthesis of *N*,*N*-dialkylthiocarbamates



Entry	Ar	Yield (%)	Entry	Ar	Yield (%)
1	Phenyl	80	6	3,4-Methylenedioxyphenyl	75
2	4-Methylphenyl	88	7	1-Naphthyl	58
3	Nitrophenyl	64	8	2-Naphthyl	70
4	4-Carboxymethylphenyl	98	9	3-(2-Carboxymethoxy)naphthyl	82
5	2-Carboxymethoxyphenyl	83			

Table 10. KF/Al_2O_3 Mediated nitrile hydrolysis



Entry	Substrate	Product	Yield (%)
1	*p*-Tolunitrile	*p*-Toluamide	95
2	Benzonitrile	Benzamide	98
3	Phenylacetonitrile	Phenylacetamide	74
4	Acetonitrile	Acetamide	71
5	Chloroacetonitrile	Chloroacetamide	65

selectively di-*N*-alkylated with dimethylsulfate, although monoalkylation could not be accomplished.[26]

Yamamoto et al. were able to take advantage of this chemistry in their efforts to develop novel Na/H exchange inhibitors, although the selectivity of the reactions were not as high as those reported by Ando et al. Akylations of compounds such as **31** with an alkyl halide in the presence of KF/Al_2O_3 produced the desired material as the predominant product of a mixture with the undesired *O*-alkylation product. A three step, one pot method of alkylation, acidic hydrolysis of the *O*-alkylated product, and subsequent repetition of the alkylation conditions, however, was found to produce high yields of the desired *N*-alkylated products (**32**, Table 12).[27]

Selective *N*-alkylation of benzodiazepin-2,5-diones (**33**) has also been demonstrated. The reaction was shown to be highly selective, as only one of the two possible monoalkylation products (**34**) was observed, and none of the dialkylated products (**35**) were detected when the reaction was performed in DMF (Table 13).

Further alkylation of the monoalkylated species (**35**) was also found to occur when the solvent was switched to either acetonitrile or dimethoxyethane, although a mixture of the *N*- and *O*-alkylated products (**36** and **37**) were observed (Scheme 5).[28]

The selective functionalization of carbamates has also been observed, as Gronowitz et al. reported the allylation of **38** in the presence of KF/Al_2O_3 as part of their efforts to prepare analogs on indole-3-acetic acids. Stronger bases, such as sodium hydride and potassium *t*-butoxide did not provide the desired products, and only starting materials were recovered (Scheme 6).[29]

Similar results were reported with the functionalization of oxazolidinones (**39**). As part of an effort to develop combinatorial libraries of 1-substituted oxazolidinones (**40**), it was recently reported that oxazolidinones could undergo alkylation, sulfonylation, and condensation with isocyanates to provide urea adducts in high yield and purity in the presence of KF/Al_2O_3 and the appropriate solvent (Table 14).[30]

3.2. Amine chemistry

The application of KF/Al_2O_3 to the chemistry of amines has been focused primarily on heteroaromatic ring systems. The only notable exception to this is Goldberg's description of a novel route to *N*-alkylated aziridine-2-carboxylic acids. Standard basic conditions for the alkyaltion of aziridines

Table 11. *N*-Alkylation of amides and lactams with KF/Al_2O_3

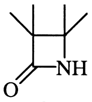
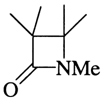
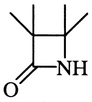
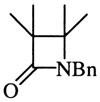
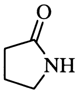
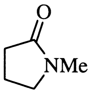
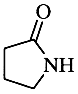
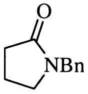
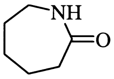
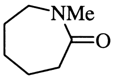
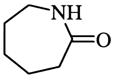
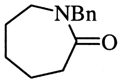
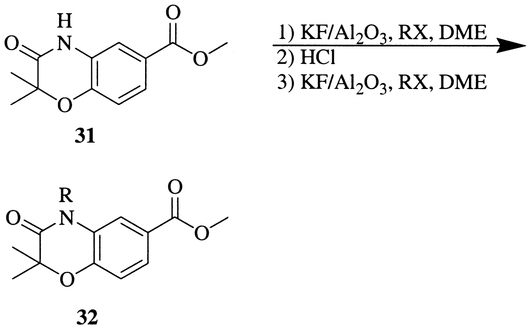
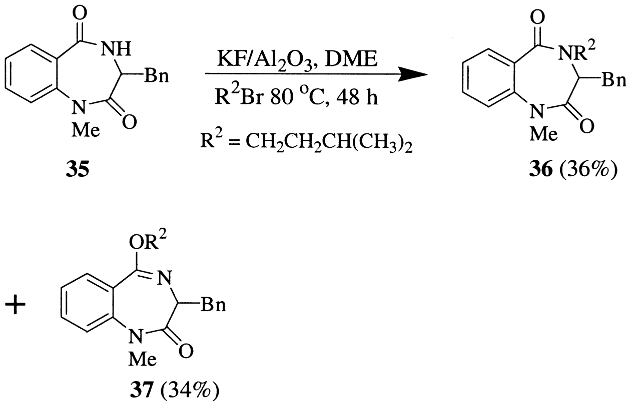
Substrate	Halide	Product	Yield (%)	Substrate	Halide	Product	Yield (%)
HCONHPh	MeI	HCON(Me)Ph	83	MeCONHBn	MeI	MeCON(Me)Bn	85
MeCONHPh	MeI	MeCON(Me)Ph	93	$PhCONH_2$	MeI	$PhCON(Me)_2$	75
MeCONHPh	BnCl	MeCON(Ph)Bn	82	PhCONHPh	MeI	PhCON(Me)Ph	90
	MeI		100		BnCl		83
	MeI		86		BnCl		81
	MeI		73		BnCl		61

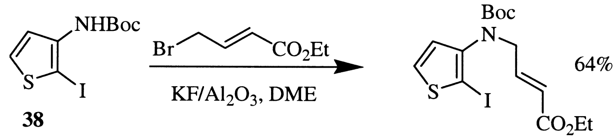
Table 12. *N*-Alkylation of amides by repeated KF/Al_2O_3 mediated alkylation



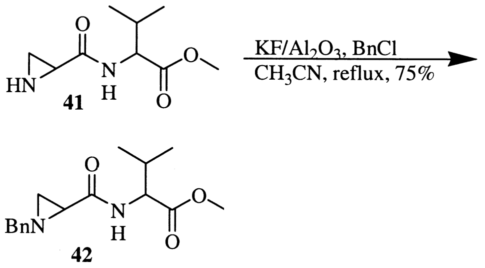
Entry	RX	Yield (%)	N/O first step	N/O second step	Yield (%)
1	*iso*-PrI	76	4.1	42	76
2	*sec*-BuI	73	5.6	62	73
3	CyclopentylBr	78	2.3	11	70



Scheme 5.



Scheme 6.

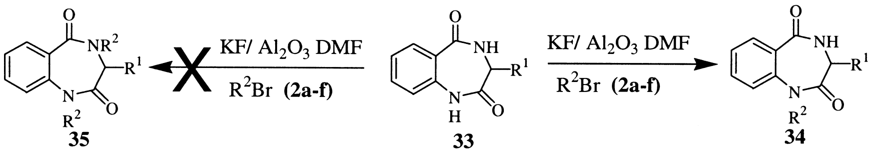


Scheme 7.

(**41**), such as $CHCl_3/NEt_3$, K_2CO_3 in acetone, and NaOH with phase transfer conditions, were not successful, as they lead largely to hydrolysis of the methyl esters. KF/Al_2O_3 in acetonitrile, however, provided the desired product (**42**) with an acceptable yield (Scheme 7).[31]

The functionalization of indoles and pyrazoles has also been examined. Sawyer et al. demonstrated that KF/Al_2O_3 could facilitate the arylation of indoles as part of their work to develop alternatives to the Ullmann coupling. It was demonstrated that a wide range of substituted aryl halides (**43**) could be condensed with indole to provide the arylated product (**44**), although the conditions required were more forceful than is usually required for KF/Al_2O_3 chemistry. The reactions typically required the use of 18-crown-6 in hot DMSO (120°C), but the reported yields were good to

Table 13. KF/Al_2O_3 Mediated monoalkylation of benzodiazepin-2,5-diones



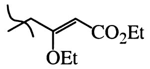
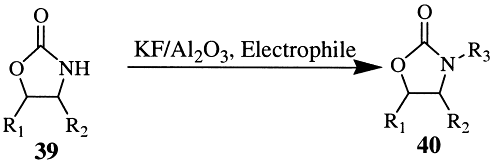
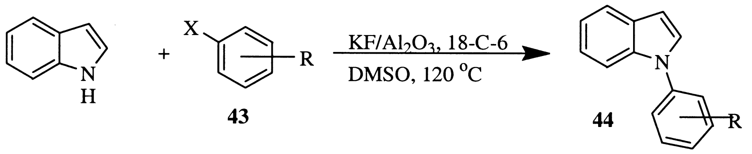
Entry	R_1	R_2	Yield (%)	Entry	R_1	R_2	Yield (%)
1	Bn	$(CH_2)_2CH(CH_3)_2$	81	4	Bn	Me	90
2	Me	$(CH_2)_2CH(CH_3)_2$	84	5	Bn	*p*-ClBn	87
3	$(CH_2)_2SCH_3$	$(CH_2)_2CH(CH_3)_2$	84	6	Bn		90

Table 14. KF/Al_2O_3 Mediated functionalization of 2-oxazolidinones with an electrophile



Entry	R^1	R^2	Electrophile	R^3	Yield (%)	Entry	R^1	R^2	Electrophile	R^3	Yield (%)
3	H	Ph	*n*-C_4H_9Br	*n*-C_4H_9	83	2	Ph	CH_3	TsCl	Ts	86
4	H	Bn	*n*-C_3H_7Br	*n*-C_3H_7	77	1	Ph	CH_3	PhNCO	CONHPh	81
6	H	Bn	$C_6H_5CH_2Br$	CH_2Ph	82	5	Ph	CH_3	$C_6H_{11}NCO$	$CONHC_6H_{11}$	90

Table 15. KF/Al_2O_3 Mediated condensation of indole with substituted aryl electrophiles

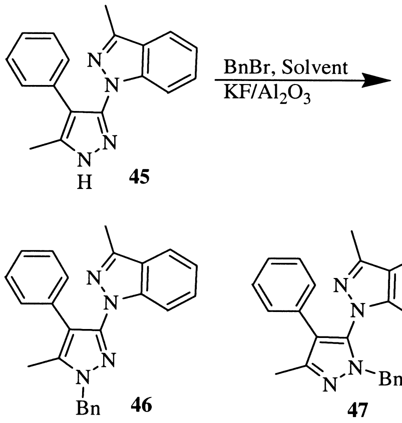


Entry	X	R	Yield (%)	Entry	X	R	Yield (%)	Entry	X	R	Yield (%)
1	Cl	4-CN	60	8	F	2-CN	93	15	F	4-Ph	62
2	Cl	4-CN	80	9	F	3-CN	78	16	F	4-Br	55
3	Br	4-CN	48	10	F	4-CN	94	17	F	4-H	33
4	I	4-CN	27	11	F	$4-SO_2Ph$	79	18	F	$4-NO_2$	98
5	NO_2	4-CN	63	12	F	4-COPh	70	19	F	$4-CF_3$	72
6	CN	4-CN	34	13	F	$4-CONH_2$	88	20	F	4-CHO	Trace
7	OMe	4-CN	8	14	F	$4-CO_2Et$	74				

excellent (Table 15). An S_NAr mechanistic pathway is supported by the reactivity pattern for the leaving groups ($F>Cl=NO_2>Br>I=CN>OMe$).[32]

Efforts in the area of pyrazole chemistry have been less extensive, but the results reported demonstrate the strong influence solvent effects can have on the reactivity observed in the presence of KF/Al_2O_3. Liu et al. reported a remarkable level of selectivity in the benzylation of pyrazole **45** as compared to benzylations performed in the absence of solid support. The ratios of the two benzylated products (**46** and **47**) formed was found to be highly dependent on the solvent chosen ranging from 2:1 with acetone to greater than 100:1 with 1,4-dioxane. The author argues that in this case, the specificity of the reaction is linked to the ability of the pyrazole ring to form hydrogen bonds to the surface of the alumina, blocking one of the two possible alkylation sites (Table 16).[33]

Table 16. KF/Al_2O_3 Mediated benzylation of pyrazole rings in selected solvents



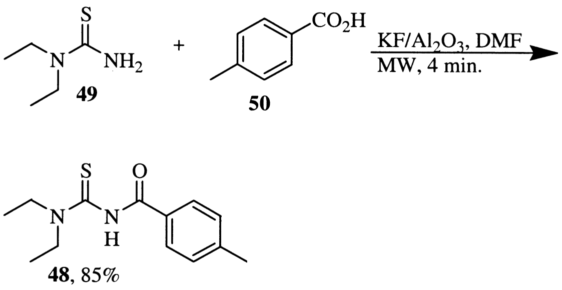
Entry	Solvent	Yield **46** (%)	Yield **47** (%)
1	Acetone	70	30
2	Ethyl acetate	90	10
3	THF	85	15
4	1,4-Dioxane	100	0
5	DMF	63	37

3.3. Miscellaneous

Transamidation and the synthesis of alkylthioureas in the presence of KF/Al_2O_3 have been reported, but in both reported cases the reactions required the application of microwave irradiation in addition to KF/Al_2O_3. Initial reports by Marquez et al. demonstrated that the substituted thiourea **48** could be prepared in high yield from the corresponding primary urea (**49**) and a free acid (**50**) with microwave irradiation and KF/Al_2O_3. Experiments performed with a standard heating mantle failed to provide the desired product (Scheme 8).[34]

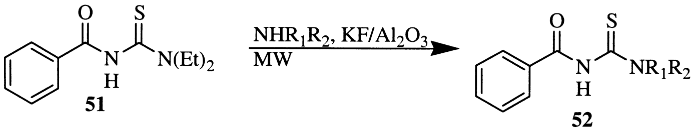
A subsequent report from the same research team showed that similar conditions could induce transamidation of thioureas under solvent free conditions. Thus, microwave irradiation of thiourea **51** in the presence of KF/Al_2O_3, an amine, and in the absence of solvent produced high yields of the transamidated products (**52**). Loss of the volatile diethyl amine prevented reversibility of the reaction. Comparable reactions using oil baths or heating mantles lead to recovery of the unchanged starting materials (Table 17).[35]

A simplified diazo transfer reaction has also been reported by Villemin et al. They observed that methylene acids (**53**) could be diazotized in the presence of tosyl azide and KF/Al_2O_3. The products (**54**) were isolated by simple filtration and removal of solvents, eliminating the need for more cumbersome workup procedures employed in previously reported methods. In addition, tosyl amide, a by-product typically seen in standard solution phase chemistry,



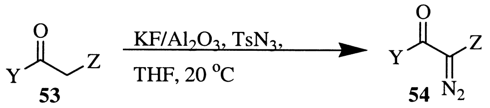
Scheme 8.

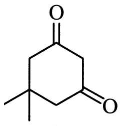
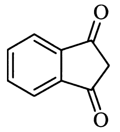
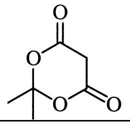
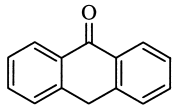
Table 17. KF/Al_2O_3 Mediated microwave assisted transamination of a 1-benzoyl-3-alkythiourea



Entry	R$_1$	R$_2$	Time (min)	Yield (%)	Entry	R$_1$	R$_2$	Time (min)	Yield (%)
1	H	Bn	2	81	4	H	CH_2CO_2H	4	86
2	Bn	Bn	4	83	5	H	$CH_2(CH_2)_4CO_2H$	3	90
3	Ph	Ph	4.5	69	6	H	$CH(Bn)CO_2H$	3.5	78

Table 18. KF/Al_2O_3 Mediated preparation of diazocarbonyl compounds



Entry	Y	Z	Yield (%)	Entry	Y	Z	Yield (%)
1	CO_2Et	OEt	63	6	$COCH_3$	OEt	94
2	CN	OEt	60	7	$COCH_3$	$COCH_3$	46
3	$PO(OEt)_2$	OEt	96	8	COPh	COPh	93
4		N/A	85	9		N/A	88
5		N/A	90	10		N/A	78

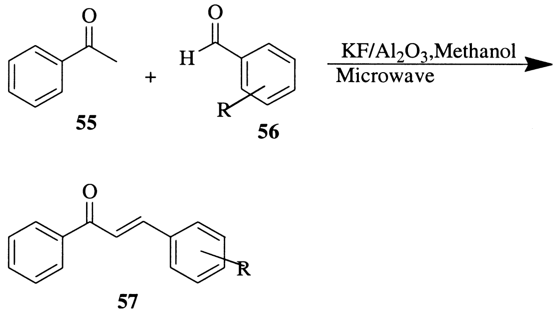
was trapped by the KF/Al_2O_3, allowing simple purification of the desired diazo product for future use (Table 18).[36]

4. Carbon–carbon bond formation

4.1. Aldol condensations and related chemistry

The aldol condensation is a well known method for the preparation of carbon–carbon bonds. It has been reported that in a number of cases, KF/Al_2O_3 can be used to facilitate the formation of the desired products. The condensation of acetophenone (**55**) with substituted benzaldehyes (**56**) has been shown to occur under solvent free conditions in the presence of KF/Al_2O_3 and microwave. The expected α,β-unsaturated ketone (**57**) is formed in moderate to high yield. In addition, it was demonstrated that the rate of reaction was greatly accelerated when compared to more conventional methods (up to 700 times faster), allowing the reactions to be completed in a matter of minutes rather than hours (Table 19).[37]

Table 19. KF/Al_2O_3 Mediated aldol condensation of acetophenone

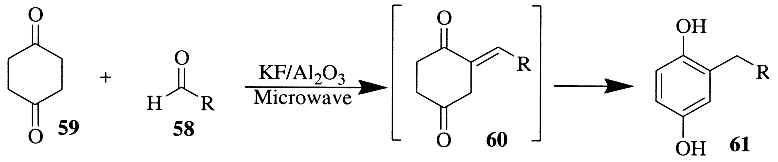


Entry	R	Yield (%)	Entry	R	Yield (%)
1	p-Me_2N	69	4	p-Cl	96
2	p-MeO	97	5	p-NO_2	96
3	H	97	6	m-NO_2	97

Similar conditions have been employed to prepare alkylated hydroquinones from benzaldehyde derivatives (**58**) and 1,4-cyclohexadione (**59**). Microwave irradiation under solvent free conditions in the presence of KF/Al_2O_3 produces the initial aldol condensation product (**60**), which tautomerizes and aromatizes to the 2-alkylated hydroquinone (**61**). Unlike the conventional thermal methods (150–160°C), the reactions are complete with a matter of minutes, and reaction conditions are much milder (Table 20).[38]

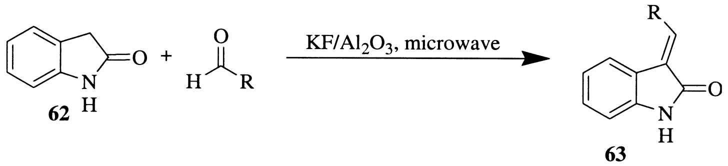
The aldol condensation and related reactions have also been employed to derivatize various heterocyclic scaffolds. It has been demonstrated that 1,3-dihydroindol-2-one (**62**) may be condensed with aldehydes in the presence of KF/Al_2O_3 and microwave irradiation under solvent free conditions to produce the arylidene product (**63**). Attempts to apply similar conditions to ketones produced the desired products, but in lower yields (Table 21).[39]

Table 20. KF/Al_2O_3 Mediated preparation of 2-alkylated hydroquinones



Entry	R	Time (min)	Yield (%)	Entry	R	Time (min)	Yield (%)
1	Ph	3	85	8	1-Anthracenyl	5	78
2	*p*-$MeOC_6H_4$	3	90	9	3,4-$CH_2O_2C_6H_3$	3	87
3	*p*-MeC_6H_4	3	95	10	1-Thienyl	2	90
4	*p*-BrC_6H_4	4	85	11	1-Furyl	2	88
5	*p*-$NO_2C_6H_4$	5	75	12	*n*-C_5H_{11}	2	75
6	*p*-ClC_6H_4	4	82	13	*n*-C_7H_{15}	2	77
7	2-Napthyl	4	80	14	*n*-C_9H_{19}	2	80

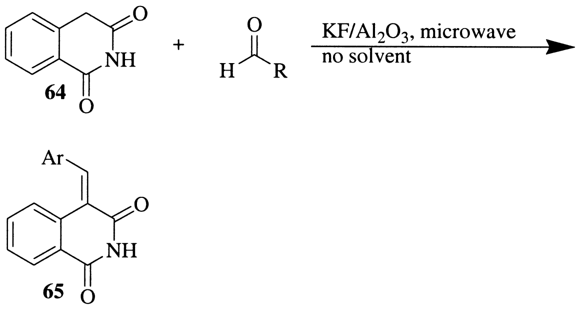
Table 21. KF/Al_2O_3 Mediated condensation of aldehydes and 1,3-dihydroindole-2-ones



Entry	Aldehyde	Yield (%)	Entry	Aldehyde	Yield (%)
1	Benzaldehyde	94	6	2-Thiophenecarbozaldehyde	85
2	3,4-(Methylenedioxy)benzaldehyde	92	7	Cinnamaldehyde	88
3	2-Cl-Benzaldehyde	81	8	Furylidenecarboxaldehyde	81
4	2,6-Di-Cl-benzaldehyde	69	9	Cyclohexanone	76
5	2-Furancarboxaldehyde	83	10	Benzophenone	35

Functionalization of isoquinolinediones (**64**) has also been accomplished in a similar manner, although only with aromatic aldehydes. Aliphatic aldehydes failed to provide the desired products (**65**) and condensation with ketones was not reported. The more sterically demanding aldehyde 2,6-dichlorobenzaldehyde provided the desired product, but in lower yield than other, less hindered reagents (Table 22).[40]

Table 22. KF/Al_2O_3 Mediated condensation of aldehydes and isoquinolinediones



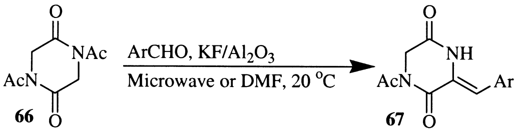
Entry	Aldehyde	Yield (%)
1	Benzaldehyde	82
2	2-Cl-Benzaldehyde	72
3	2,6-Di-Cl-benzaldehyde	64
4	2-Furancarboxaldehyde	93
5	2-Thiophenecarbozaldehyde	88

Condensation of aldehydes with 1,4-diketopiperazines (**66**) under KF/Al_2O_3 mediated conditions was reported by Villemin et al. The reaction was found to occur both with and without microwave irradiation, providing the desired products (**67**) in high yields. As seen in previous cases, the application of microwave irradiation in addition to KF/Al_2O_3 provides substantial benefit, as the rate of reaction is substantially accelerated. Reaction performed in DMF at room temperature required 16 h. The use of both KF/Al_2O_3 and microwave irradiation provided the same products in 15 min in comparable yields (Table 23).

Disubstituted 1,4-diketopiperazines were also prepared using similar chemistry. The initial monoalkylated adduct **67** was used without purification. After initial condensation with benzaldehyde to form **67**, a second aldehyde is added and the disubstituted product **68** is formed in high yield. The preparation of albunoursin was accomplished using this method.[41] Also, Piperafizine analogs have been prepared using this chemistry to examine their potential use as multidrug resistance reversal agents (Table 24).[42]

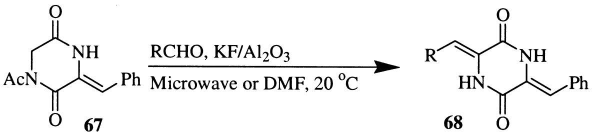
Derivatization of isoxazolones (**69**) and thiazolidinones (**70**) has also been accomplished using KF/Al_2O_3 mediated aldol condensation chemistry. In both cases, only aromatic aldehydes were successful. The reactions occur under solvent free conditions with microwave irradiation. While isomeric mixtures are possible, only the *E*-isomer of the isoxazolones was observed. The regiochemistry of the

Table 23. KF/Al_2O_3 Mediated monocondensation of aldehydes with 1,4-diketopiperazines



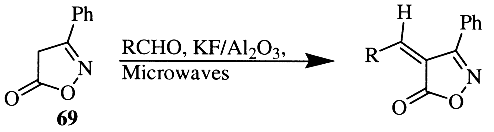
Entry	Ar	Yield DMF (%)	Yield microwave (%)	Entry	Ar	Yield DMF (%)	Yield microwave (%)
1	Ph	90	94	4	*p*-CH_3OPh	86	86
2	*p*-CH_3Ph	84	89	5	4-C_5H_4N	96	100
3	*p*-$(CH_3)_2NPh$	70	83	6	*p*-NO_2Ph	98	100

Table 24. KF/Al_2O_3 Mediated condensation of aldehydes with functionalized 1,4-diketopiperazines



Entry	R	Yield DMF 20°C (%)	Yield microwave (%)
1	Ph	82	91
2	*p*-CH_3OPh	76	78
3	*i*-C_3H_7	58	70 (Albunoursin)

Table 25. KF/Al_2O_3 Mediated condensation of oxazolones and aldehydes



Entry	R	Yield (%)	Entry	R	Yield (%)
1	4-$MeOC_6H_4$	79	5	3-Thienyl	92
2	3,4-$(CH_3O)_2C_6H_3$	85	6	2-Thienyl	77
3	4-ClC_6H_4	76	7	2-Furyl	71
4	2,6-Di-Cl-C_6H_3	72	8	$CH_2O_2C_6H_3$	84

exocyclic alkene in the thiazolidinones product was not determined, however, only one product was formed in all cases (Tables 25 and 26).[43]

The synthesis of benzofurans (**71**) from α-tosyloxyketones (**72**) and salicylaldehyde derivatives (**73**) has also been facilitated with KF/Al_2O_3 in conjunction with microwave irradiation. Under solvent free conditions, the initial enolate of an α-tosyloxyketone undergoes an aldol reaction with the salicylaldehyde. The resulting intermediate then cyclizes via nucleophilic displacement of the tosylate, and dehydration of the resulting material produces the benzofuran product (Table 27).[44]

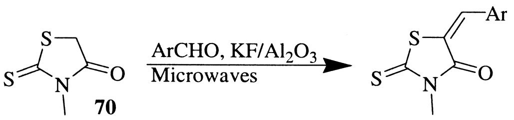
Although they are not usually considered to be substantially acidic, it has also been shown that both indene and fluorene can be used as nucleophiles for aldol condensations with various benzaldehyde derivatives in the presence of KF/Al_2O_3. In the case of fluorene (**74**), the best results were obtained using dry DMF at 150°C, which produced the dibenzofulvene (**75**) products in excellent to moderate yield (Table 28).[45]

Aldol condensations with indene were found to be somewhat more complex, as the product of the reaction was found to be dependent on the electronic nature of the benzaldehdye analog. Electron rich benzaldehydes produced the monoaddition product **76**, while electron poor benzaldehydes tended to favor the double addition product **77** (Table 29).[46]

In a more complex example of aldol condensation chemistry, Shi et al. have reported the preparation of cyclohexenones **78** using a KF/Al_2O_3-mediated, four-component condensation. Initial Knoevenagel condensation of an aldehdye with Meldrum's acid is followed by Michael addition of the 1,3-cyclohexanedione. The resulting intermediate is then trans-esterified and undergoes a spontaneous decarboxylation to provide the products in excellent yield. The chemistry is, however, limited to aromatic aldehydes (Table 30).[47]

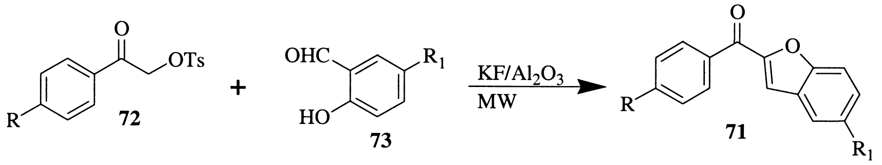
The Knoevenagel reaction is also the basis for the KF/Al_2O_3 mediated synthesis of complex pyridines such as **79**.

Table 26. KF/Al_2O_3 Mediated condensation of thiazolidinones and aldehydes



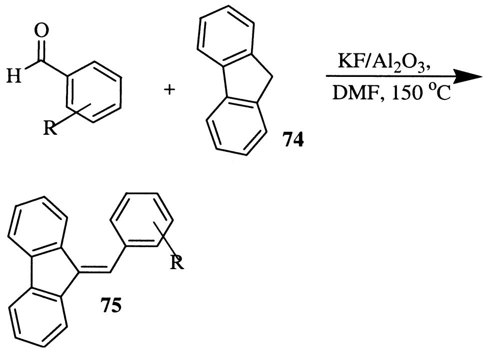
Entry	Ar	Yield (%)	Entry	Ar	Yield (%)	Entry	Ar	Yield (%)
1	C_6H_5	82	6	*o*-$MeOC_6H_4$	92	11	*p*-MeC_6H_4	78
2	*o*-ClC_6H_4	80	7	*p*-$MeOC_6H_4$	78	12	Styryl	73
3	*p*-ClC_6H_4	94	8	3,4$(MeO)_2C_6H_3$	93	13	2-thienyl	84
4	*m*-$NO_2C_6H_4$	91	9	3,4$(CH_2O_2)_2C_6H_3$	90	14	2-furanyl	86
5	*p*-$NO_2C_6H_4$	98	10	3,4, 5$(MeO)_3C_6H_2$	91	15	2-furanylCHCH	70

Table 27. KF/Al_2O_3 Mediated synthesis of benzofurans



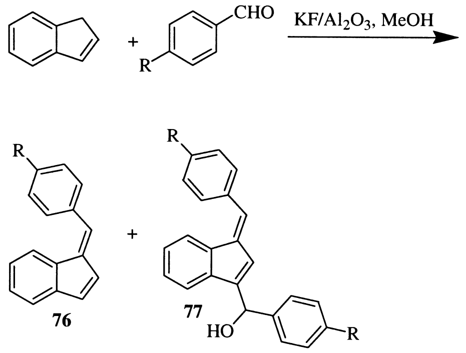
Entry	R	R_1	Time (min)	Yield (%)	Entry	R	R_1	Time (min)	Yield (%)
1	H	H	3.0	94	5	H	Cl	2.5	95
2	Cl	H	3.0	94	6	Cl	Cl	2.5	92
3	Me	H	2.5	91	7	Me	Cl	2.5	96
4	OMe	H	3.5	89	8	OMe	Cl	3.5	89

Table 28. KF/Al_2O_3 Mediated aldol condensation of fluorine



Entry	R	Yield (%)	Entry	R	Yield (%)
1	*p*-F	65	5	*p*-OMe	85
2	*p*-Cl	90	6	*p*-$N(CH_3)_2$	67
3	H	44	7	*m*-Cl	78
4	*p*-Me	73			

Table 29. KF/Al_2O_3 Mediated aldol condensation of indene



Entry	R	Yield **76** (%)	Yield **77** (%)	Entry	R	Yield **76** (%)	Yield **77** (%)
1	*p*-Me	66	0	4	H	3	67
2	*p*-MeO	58	0	5	*p*-Cl	5	80
3	*p*-Me_2N	45	0	6	*p*-F	11	81

Nakano et al. demonstrated that unhindered, primary alkyl methyl ketones (**80**) react with malononitrile in the presence of KF/Al_2O_3 in acetonitrile to produce a bridged bicycle (**81**) through a series of Knoevenagel hydrolysis reactions. Subsequent pyrolysis of the bridged intermediate via a retro Diels–Alder reaction produces the pyridine derivatives (Table 31).[48]

A variation on the Reformatsky reaction has also been reported. In their examination of the use of metal halides as catalysts to the silyl Reformatsky reaction, Latouche et al. report a single example of a KF/Al_2O_3 mediated reaction which provided the silyl ether (**82**), the corresponding alcohol (**83**), or the elimination product (**84**) depending on the conditions used. A wider examination of the application of this reaction has not been reported (Table 32).[49]

4.2. Michael additions

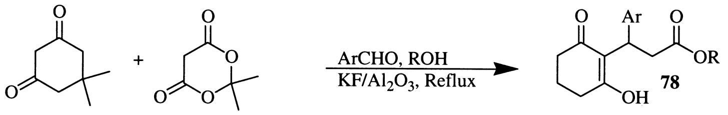
The application of KF/Al_2O_3 to Michael addition chemistry has been reported by a number of authors, but the nucleophilic agent of the reaction has been limited to nitroalkanes and malonate derivatives. Clark et al. initially reported on the KF/Al_2O_3 mediated Michael addition of nitroethane to methyl vinyl ketone as part of an examination of various fluoride ion bases. They were able to demonstrate that KF/Al_2O_3 is a superior source of basic fluoride ion as compared to various inorganic salts and crown ethers (Scheme 9).[50]

Hu et al. has taken advantage of this chemistry in their preparation of **85**. The use of standard organic bases such as DBU and triethyl amine lead to complex mixture with very little detectable product. Solvent free KF/Al_2O_3, however, produced an exceptionally high yield (Scheme 10).[51]

A broader range of potential Michael acceptors useful in KF/Al_2O_3 mediated chemistry were examined by Hattori et al., as part of their overall study of the use of solid bases for Michael additions with nitromethane. With the exception of methyl crotonate, the desired product (**86**) was obtained in high yield. While the reported yield for the KF/Al_2O_3 mediated condensation of methyl crotonate with nitromethane was low, it was the highest yield reported of all of the solid bases that were examined (Table 33).[52]

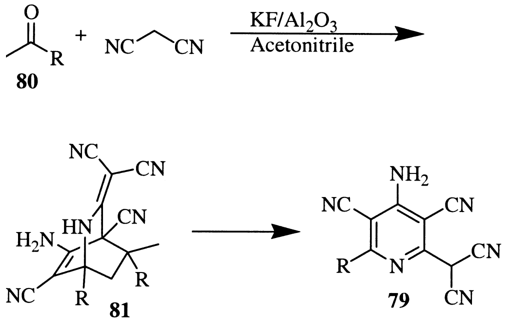
Ring formation via the KF/Al_2O_3 mediated Michael addition has also been demonstrated, as cyclopropanes, dihyrdrofuans, and isoxazoline *N*-oxides have been prepared from nitroalkanes and a suitable electrophile. Cyclopropanation of electron deficient alkenes was reported by Foucaud et al., and occurs by initial Michael addition of a

Table 30. KF/Al_2O_3 Mediated four component condensation



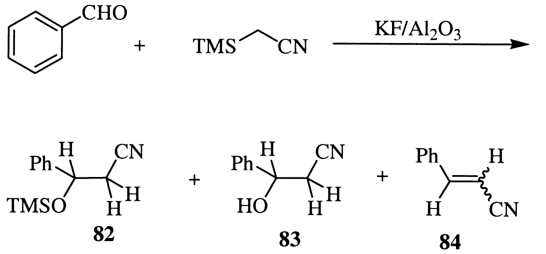
Entry	Ar	R	Yield (%)	Entry	Ar	R	Yield (%)
1	2-ClC_6H_4	CH_3	95	7	3,4-$OCH_2OC_6H_3$	$CH_3CH_2CH_2CH_2$	62
2	2-ClC_6H_4	CH_3CH_2	74	8	2-$NO_2C_6H_4$	CH_3	70
3	2-ClC_6H_4	$CH_3CH_2CH_2$	66	9	2-$NO_2C_6H_4$	CH_3CH_2	85
4	2-ClC_6H_4	$(CH_3)_2CH$	66	10	2-$NO_2C_6H_4$	$CH_3CH_2CH_2$	64
5	3,4-$OCH_2OC_6H_3$	CH_3CH_2	68	11	2-$NO_2C_6H_4$	$(CH_3)_2CH$	75
6	3,4-$OCH_2OC_6H_3$	$CH_3CH_2CH_2$	73	12	4-$NO_2C_6H_4$	CH_3CH_2	54

Table 31. KF/Al_2O_3 Mediated preparation of substituted pyridines

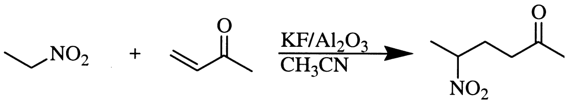


Entry	R	Yield **81** (%)	Yield **79** (%)
1	Ethyl	51	82
2	Propyl	12	71
3	CH_2CH_2Ph	45	61

Table 32. KF/Al_2O_3 Mediated silyl Reformatsky reaction



Temperature	Yield **82** (%)	Yield **83** (%)	Yield **84** (%)
20	22	78	0
100	0	0	100



Scheme 9.

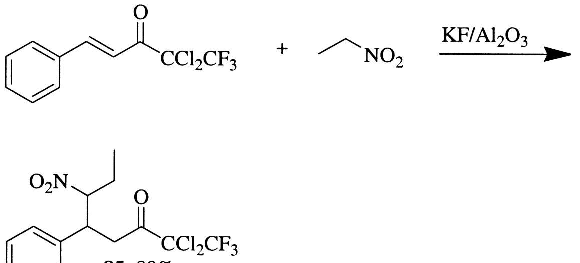
nitroalkane to the olefin. This is followed by displacement of the nitro group by the intermediate anion (**87**) to produce the desired cyclopropane (**88**) in good to excellent yields (Table 34).[53]

The synthesis of dihydrofurans (**89**) and isoxazoline *N*-oxides (**90**) from nitroalkanes occurs in a similar fashion, with an initial Michael addition occurring, followed by the nucleophilic displacement of a nitro group by the intermediate anion to close the desired ring system (Tables 35 and 36).[54]

To date, there has been one report of KF/Al_2O_3 mediated Michael additions with active methylene compounds other than nitroalkanes, detailing the addition of malononitrile to a series of chalcones (**91**, Table 37). While the same reaction can be accomplished with catalytic sodium methoxide, higher yields were obtained using KF/Al_2O_3 and the workup was greatly simplified.[55]

4.3. Palladium mediated chemistry

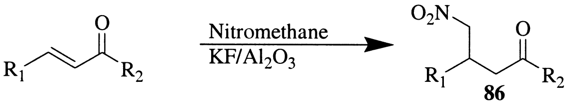
Palladium catalyzed methods for the formation of carbon–carbon bonds has become a mainstay of organic synthesis, and KF/Al_2O_3 has been examined for its potential use as an additive in these reactions. Kabalka et al. was able to demonstrate KF/Al_2O_3 is an effective base for the



85, 80%

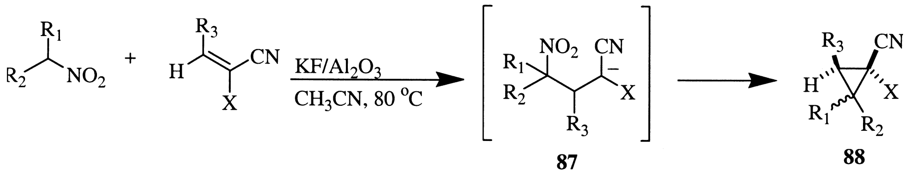
Scheme 10.

Table 33. KF/Al_2O_3 Mediated Michael additions of nitromethane



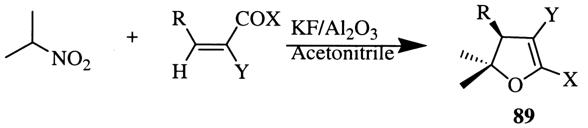
Entry	Michael acceptor	Temperature (°C)	Yield (%)
1	Methyl crotonate	50	22.8
2	Butene-2-one	0	93
3	2-Cyclohexene-1-one	50	99.8
4	Crotonaldehyde	50	95.5

Table 34. KF/Al$_2$O$_3$ Mediated cyclopropanation of electron deficient olefins via Michael addition



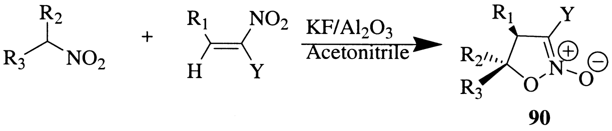
Entry	R$_1$	R$_2$	R$_3$	X	Yield (%)	Entry	R$_1$	R$_2$	R$_3$	X	Yield (%)
1	H	H	i-C$_3$H$_7$	CO$_2$CH$_3$	60	7	CH$_3$	CH$_3$	n-C$_5$H$_{11}$	CO$_2$CH$_3$	69
2	CH$_3$	CH$_3$	C$_6$H$_5$	CO$_2$CH$_3$	86	8	C$_6$H$_5$	H	C$_2$H$_5$	CO$_2$CH$_3$	66
3	C$_2$H$_5$	H	p-ClC$_6$H$_4$	CO$_2$CH$_3$	82	9	CH$_3$	CH$_3$	C$_6$H$_5$	CN	46
4	CH$_3$	CH$_3$	i-C$_3$H$_7$	CO$_2$CH$_3$	86	10	CH$_3$	CH$_3$	i-C$_3$H$_7$	CN	46
5	CH$_3$	H	i-C$_3$H$_7$	CO$_2$CH$_3$	86	11	CH$_3$	CH$_3$	C$_6$H$_5$	P(O)(OC$_2$H$_5$)$_2$	61
6	C$_2$H$_5$	H	n-C$_4$H$_9$	CO$_2$CH$_3$	86						

Table 35. KF/Al$_2$O$_3$ Mediated preparation of dihydrofurans



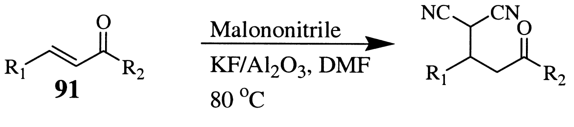
Entry	R	X	Y	Yield (%)	Entry	R	X	Y	Yield (%)
1	Ph	Me	COMe	88	6	Ph	Ph	CO$_2$Et	95
2	Ph	Me	CO$_2$Me	91	7	4-Cl-C$_6$H$_4$	Me	CO$_2$Et	93
3	*I*-Pr	Me	COMe	45	8	2-Furyl	Me	COMe	92
4	Ph	Me	COPh	98	9	Ph	Ph	SO$_2$Ph	91
5	Ph	Ph	COPh	80					

Table 36. KF/Al$_2$O$_3$ Mediated preparation of isoxazoline *N*-oxides



Entry	R	Y	Yield (%)	Entry	R	Y	Yield (%)
1	Ph	CO$_2$Me	63	4	4-Me$_2$N-C$_6$H$_4$	CO$_2$Me	60
2	4-MeO-C$_6$H$_4$	CO$_2$Me	74	5	2-Furyl	CO$_2$Me	42
3	3,4-(CH$_2$O$_2$)-C$_6$H$_3$	CO$_2$Me	66	6	Ph	COPh	61

Table 37. KF/Al$_2$O$_3$ Mediated Michael addition of malononitrile to chalcones



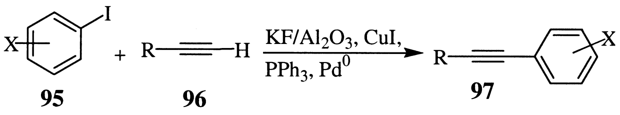
Entry	R$_1$	R$_2$	Time (h)	Yield (%)	Entry	R$_1$	R$_2$	Time	Yield (%)
1	4-ClC$_6$H$_4$	C$_6$H$_5$	2	88	5	3,4-OCH$_2$OC$_6$H$_3$	C$_6$H$_5$	6	57
2	4-ClC$_6$H$_4$	4-CH$_3$C$_6$H$_4$	2	81	6	2-ClC$_6$H$_4$	C$_6$H$_5$	2	88
3	C$_6$H$_5$	C$_6$H$_5$	5	85	7	2-NO$_2$C$_6$H$_4$	C$_6$H$_5$	1	94
4	C6H$_5$	4-CH$_3$C$_6$H$_4$	5	81					

Table 38. KF/Al$_2$O$_3$ Mediated Suzuki couplings

$$\underset{\mathbf{92}}{\mathrm{R{-}X}} \quad + \quad \underset{\mathbf{93}}{\mathrm{R_1{-}B(OH)_2}} \xrightarrow[100\,^{\circ}\mathrm{C},\ 4\mathrm{h}]{\mathrm{KF/Al_2O_3},\ 5\%\ \mathrm{Pd}} \underset{\mathbf{94}}{\mathrm{R_1{-}R}}$$

Entry	**92**	R$_1$	Yield (%)	Entry	**92**	R$_1$	Yield (%)
1	Iodobenzene	Ph	99	4	1-Bromobut-2-ene	Ph	66
2	Bromobenzene	Ph	60	5	Iodobezene	4-CH$_3$Ph$_2$	98
3	Allyl iodide	Ph	39	6	Iodobenzene	CH$_3$(CH$_2$)$_2$CHCH	79

Table 39. KF/Al_2O_3 Mediated Sonogashira couplings



Entry	R	X	Yield (%)	Entry	R	X	Yield (%)
1	n-C_7H_{17}	H	94	6	n-C_7H_{15}	3-F	96
2	n-C_5H_{11}	H	84	7	Ph	4-C(O)CH_3	82
3	Ph	H	91	8	Ph	4-NO_2	67
4	n-C_7H_{15}	4-Me	97	9	Ph	2-Iodothiophene	82
5	n-C_7H_{15}	4-MeO	93	10	Ph	2-NMe_2	82

Table 40. KF/Al_2O_3 Mediated β-elimination

Substrate	Solvent	Temperature (°C)	Time (h)	Product	Yield (%)
$PhCH_2CH_2Br$	Acetonitrile	25	24	$PhCHCH_2$	86
$PhCH_2CH_2Br$	None	25	20	$PhCHCH_2$	75
$PhOCH_2CH_2Br$	Tetraglyme	45	45	$PhOCHCH_2$	73
$CH_3(CH_2)_6CH_2Br$	Diglyme	100	24	$C_6H_{13}CHCH_2$	14
Cylcohexyl Bromide	Diglyme	100	15	Cyclohexene	88
$PhCHBrCH_2Br$	CH_3CN	25	27	$PhCBrCH_2$	80
$PhCHBrCH_2Br$	Penta ether	100	6	PhCCH	70
trans-PhCHCHBr	Diglyme	100	24	PhCCH	70
PhCHBrCHBrPh	Diglyme	100	3	PhCCPh	74

promotion of Suzuki couplings under solvent free conditions. Aryl bromides and iodides (**92**) were shown to undergo the desired coupling with a series boronic acids (**93**) to produce the cross coupled product (**94**) at elevated temperatures (Table 38). Vinyl halides, which readily undergo Suzuki cross coupling reactions under traditional condition, did not, however, produce the desired products under KF/Al_2O_3 mediated conditions.[56]

Solvent free conditions for the KF/Al_2O_3 mediated Sonogashira coupling have also been reported. Aryl iodides (**95**) were found to undergo Sonogashira couplings with various terminal alkynes (**96**) in the presence of KF/Al_2O_3, copper(I) iodide, powdered palladium, and triphenylphosphine under solvent free conditions with microwave irradiation. The reaction times were very short (2.5 min) and yields were high in most cases. Unlike more traditional Sonogashira couplings, however, aryl bromides and chlorides did not produce the desired alkyne (**97**) and were recovered unchanged (Table 39).[57]

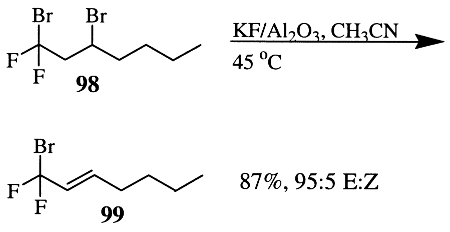
4.4. Alkene synthesis

The application of KF/Al_2O_3 to the preparation of alkenes has been focused on two areas, β-elimination and phosphorous ylide chemistry. Early efforts in this area by Ando et al. demonstrated that various styrene analogs could be prepared from the corresponding primary alkyl bromide via KF/Al_2O_3 mediated β-elimination (Table 40). Vicinal dibromides were also shown to provide the corresponding acetylenes under mild reaction conditions.[58]

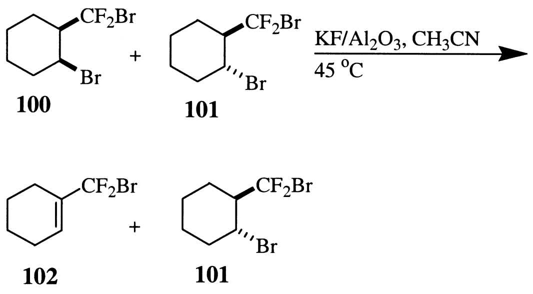
Dehydrobromination of alkyl bromides was also reported by Hu et al., but their efforts were not limited to the preparation of styrene analogs. In their efforts, 1,3-dibromides (**98**) were converted to the corresponding ally bromides (**99**) in good yields and under mild conditions. Reported *E*/*Z* ratios were also very high (Scheme 11).

The utility of this reaction was further demonstrated by its application to the separation of the *cis* and *trans* dibromocyclohexanes **100** and **101**. Dehydrobromination of the *cis* compound produces the expected allyl bromide (**102**), while the *trans* analog is stable to the reaction conditions, as it is unable to adopt the configuration necessary for elimination to occur (Scheme 12).

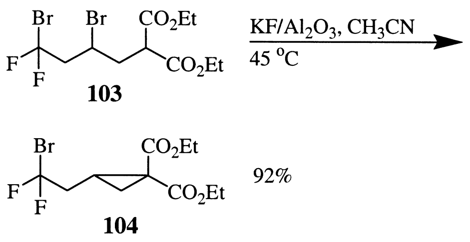
An interesting exception to this chemistry was observed when it was applied to the malonate analog **103**. Rather than



Scheme 11.

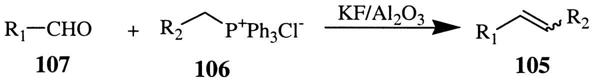


Scheme 12.



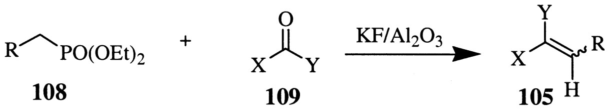
Scheme 13.

Table 41. KF/Al_2O_3 Mediated Wittig chemistry

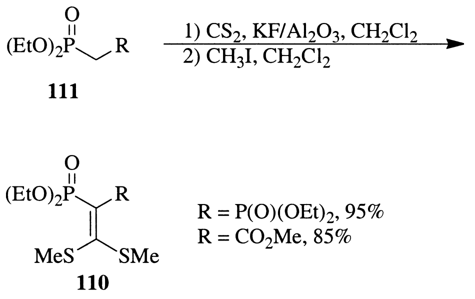


Entry	R_1	R_2	Time (h)	Temperature (°C)	E/Z	Yield (%)
1	Ph	Ph	24	20	1/1	71
2	Ph	Ph	24	70	1/1	72
3	Ph	Me	18	120	2/3	8
4	PhCHCH	Ph	18	20		70
5	p-$Me_2NC_6H_4$	Ph	18	20	31/69	76
6	Ph	2-$CH_2C_5H_5N$	24	20	28/74	68

Table 42. KF/Al_2O_3 Mediated Horner–Emmons chemistry



Entry	109	R	Time (h)	E/Z ratio	Yield (%)
1	PhCHO	Ph	18	100/0	85
2	PhCHO	$CH_3(CH_2)_6$	18	–	0
3	PhCHO	CO_2Et	18	95/5	76
4	$PhCOCH_3$	CO_2Et	18	85/15	36
5	$CH_3(CH_2)_8CHO$	CO_2Et	18	60/40	80
6	Cyclohexanone	CO_2Et	18	–	79
7	$PhCOCH_3$	CN	18	83/17	78
8	$CH_3(CH_2)_8CHO$	CN	18	74/26	78
9	Cyclohexanone	CN	18	–	41



Scheme 14.

producing the expected allyl bromide, cyclopropanation to **104** via nucleophilic displacement of the bromide by the relatively acidic malonate functionality was observed (Scheme 13).[59]

The application of KF/Al_2O_3 to phosphorous ylide chemistry for the synthesis of alkenes has been moderately successful, as Boullet et al. have reported that alkenes (**105**) may be prepared from semi-stabilized ylides (**106**) in the presence of KF/Al_2O_3 and a suitable aldehyde (**107**). Reported yields were moderate and selectivity of the reaction (*E*/*Z*) was poor (Table 41).

Better results were obtained from alkyphosphonates (**108**) using Horner–Emmons chemistry. Reported yields were moderately improved, as was the selectivity of the reaction. It is also interesting to note that while KF/Al_2O_3 Wittig reactions were limited to aldehydes, the KF/Al_2O_3 mediated Horner–Emmons reactions were successful with both aldehydes and ketones (**109**, Table 42).[60]

In an unusual adaptation of Horner–Emmons chemistry, Villemin et al. have disclosed the KF/Al_2O_3 mediated preparation of ketene dithioacetals (**110**). Initial KF/Al_2O_3 mediated condensation of an active methylene compound (**111**) is followed by alkylation with iodomethane to yield the desired dithioacetal. Under the appropriate conditions, dithioacetals will react with both electrophiles and nucleophiles, making them very versatile compounds (Scheme 14).[61]

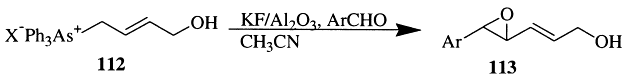
4.5. Miscellaneous

While they are not commonplace in the application of organic chemistry, arsonium ylides have been used in conjunction with KF/Al_2O_3 to prepare epoxides from aromatic aldehydes. The reaction is similar to the Wittig olefination. The arsonium salt (**112**) is displaced by the aldehyde oxygen to produce the desired epoxide (**113**) with concomitant chain extension. The reaction has also been reported to occur in the presence of KOH with similar yields, but without the added advantages of a solid phase reagent (Table 43).[62]

5. Cycloaddition and rearrangement chemistry

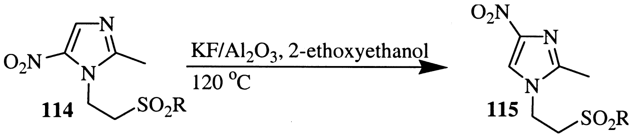
The application of KF/Al_2O_3 to cycloaddition reactions and rearrangement chemistry has been limited to only a few examples. Rao et al. examined the utility of this reagent for the interconversion of 4- and 5-substituted imidazoles as part of their examination of Tinidazole. They were able to demonstrate that 5-nitroimidazole (**114**) can be converted to

Table 43. KF/Al_2O_3 Mediated condensation of aldehydes and arsenic ylides



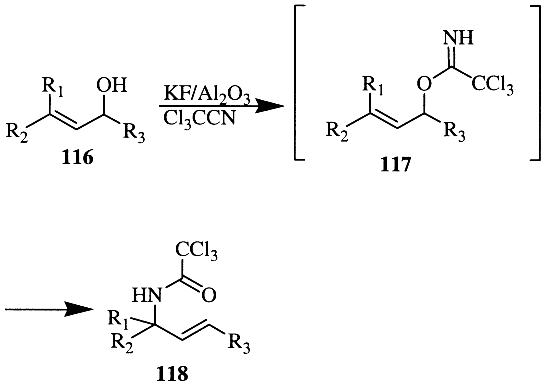
Entry	Aldehyde	Time (h)	Yield (%)	Entry	Aldehyde	Time (h)	Yield (%)
1	PhCHO	28	78	4	p-MeC_6H_4CHO	30	68
2	p-ClC_6H_4CHO	20	66	5	m-$NO_2C_6H_4CHO$	12	53
3	p-FC_6H_4CHO	35	64	6	PhCHCHCHO	30	70

Table 44. KF/Al_2O_3 Mediated imidazole rearrangements



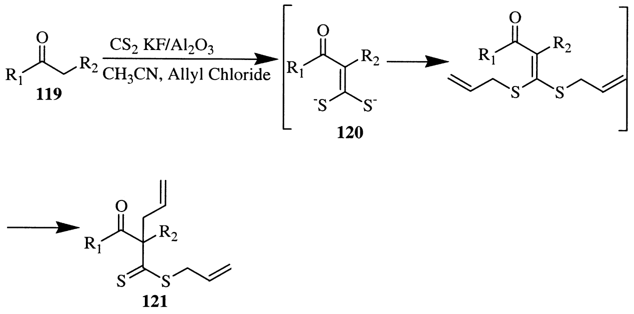
Entry	R	Yield (%)
1	Ethyl	94
2	*n*-Butyl	93
3	Phenyl	95

Table 45. KF/Al_2O_3 Mediated sigmatropic rearrangement of allylic alcohols



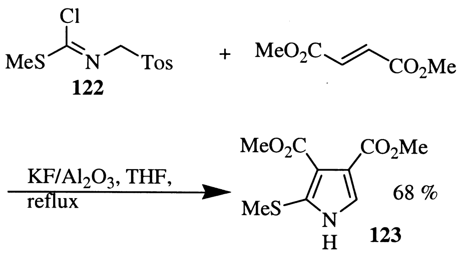
Entry	Alcohol	Yield (%)	Entry	Alcohol	Yield (%)
1	2-Buten-1-ol	85	4	Geraniol	69
2	3-Methyl-2-buten-1-ol	65	5	Farnesyl alcohol	65
3	Cinnamyl alcohol	78	6	3-Penten-2-ol	90

Table 46. KF/Al_2O_3 Mediated sigmatropic rearrangement of allylic thioethers



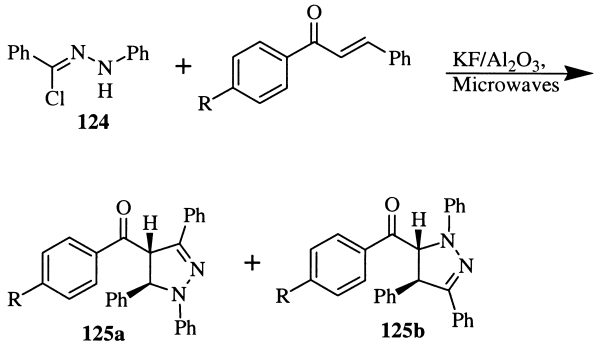
Entry	R_1	R_2	Yield (%)
1	Me	Bn	95
2	Ph	Bn	40
3	Ph	Me	80

the 4-nitroimidazoles (**115**) by heating them in the 2-ethoxyethanol in the presence of KF/Al_2O_3. Previously reported method for the preparation of 4-nitroimidazoles have been shown to produce mixtures of the 4- and 5-isomers (Table 44).[63]



Scheme 15.

Table 47. KF/Al_2O_3 Mediated 1,3-dipolar cycloaddition of diphenylnitrilimine



Entry	R	Time (min)	Temperature (°C)	Yield (%)	Ratio
1	H	12	123	90	91/9
2	Br	12	130	92	90/10
3	Cl	12	131	93	95/5
4	Me	12	125	89	88/12
5	OMe	12	126	83	95/5

The one pot conversion of allylic alcohols to amides via a KF/Al_2O_3 mediated sigmatropic rearrangement has also been reported. Initial condensation of an allylic alcohol (**116**) with trichloroacetonitrile at room temperature produces the intermediate trichloroacetimidate (**117**), which undergoes further rearrangement to the allyl amide (**118**). Other methods to perform the same chemistry have been reported, but they generally involve harsher conditions (strong bases and high temperatures) (Table 45).[64]

An additional example of a KF/Al_2O_3 mediated sigmatropic rearrangement of an allylic system has been disclosed by Villemin et al. in their synthesis of allylketodithioesters. Initial condensation of a suitable ketone (**119**) with carbon disulfide in the presence of KF/Al_2O_3 was followed by allylation of the initial intermediated (**120**) with allyl chloride. Sigmatropic rearrangement of the allyl thioether to the desired product (**121**) occurs at room temperature (Table 46).[65]

Two examples of KF/Al_2O_3 mediated 1,3-dipolar cycloadditions have been reported. In both cases, the basicity of KF/Al_2O_3 facilitates the preparation of a reactive intermediate used in the synthesis of a heterocycle. Morel et al. have reported the preparation and subsequent cycloadditon of thiocyanate ylides from imino chlorosulfides (**122**) to prepare pyrroles (**123**) in refluxing THF in the presence of KF/Al_2O_3 (Scheme 15).[66]

In a related example, it has been reported that KF/Al_2O_3 can induce the formation of diphenylnitrilimine from 1,3-diphenylhydrazonoyl chloride (**124**) and its subsequent 1,3-dipolar cycloaddition with the aid of microwave irradiation under solvent free conditions. Near quantitative yields were reported and a high degree of regioselectivity was observed. It is interesting to note that the desired product (**125**) was not observed when conventional heating was used instead of microwave irradiation (Table 47).[67]

6. Conclusions

The application of KF/Al_2O_3 to organic synthesis has provided new methods for a wide array of organic reactions, many of which are staples of synthetic organic chemistry. In many cases, the use of these new methods provides milder conditions and simpler procedures than previously reported examples. Investigations in this area, and the more general application of solid supported reagents will continue to provide simpler and more efficient methods for synthetic organic chemistry.

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Biographical sketch

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