CHEMICAL REVIEWS

REVIEW

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From 2000 to Mid-2010: A Fruitful Decade for the Synthesis of Pyrazoles

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1. INTRODUCTION

In the past decade, interest in pyrazole chemistry has significatively increased mainly due to the discovery of the interesting properties exhibited by a great number of pyrazole derivatives. Pyrazole, a five-membered heterocycle containing two adjacent nitrogen atoms (Scheme 1), is a motif found in a number of small molecules that possess a wide range of agricultural and pharmaceutical activities.[1] Moreover, some pyrazoles are used in supramolecular and polymer chemistry, in the food industry, and as cosmetic colorings and UV stabilizers, while some have liquid crystal properties.[2] Remarkably, the 1-arylpyrazole motif is present in drugs such as cyclooxygenase-2 (Cox-2) inhibitors and protein kinase inhibitors, as well as in antifungal compounds and in complexes with phosphorescent properties. Some 1,5-diarylpyrazole derivatives exhibit inhibitory activities of the HIV-1 reverse transcriptase, whereas 1,3,5-triaryl-4-alkylpyrazoles are efficient ligands for the estrogen receptor. Substituted pyrazoles have also been applied as ligands for transition metal-catalyzed reactions.[3] Accordingly, agrochemical, pharmaceutical, and chemical industries have a great interest in their synthesis.

Conventional approaches for the preparation of substituted pyrazoles involve either the construction of two C−N bonds by condensation of hydrazines with 1,3-dicarbonyl compounds or their 1,3-dielectrophilic equivalents (Scheme 1, via a) or the generation of one C−N bond and one C−C bond by intermolecular [3 + 2]-cycloadditions of 1,3-dipoles to dipolarophiles (Scheme 1, via b).[4] Each method has its own scope and efficiency limitations. However, in the past decade, general and efficient methodologies have been developed with the aim of increasing the regioselectivity in the preparation of substituted pyrazoles. Among them, those involving the creation of C−N and C−C bonds by cross-coupling reactions of aryl electrophiles with substituted pyrazoles have emerged as a promising alternative to conventional methodologies (see section 7).

This review covers the progress made in the preparation of substituted pyrazoles from 2000 to mid-2010 both in solution

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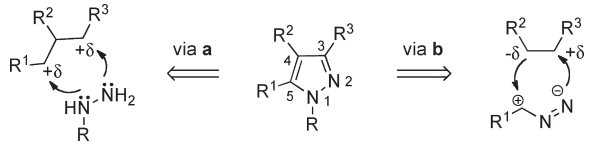
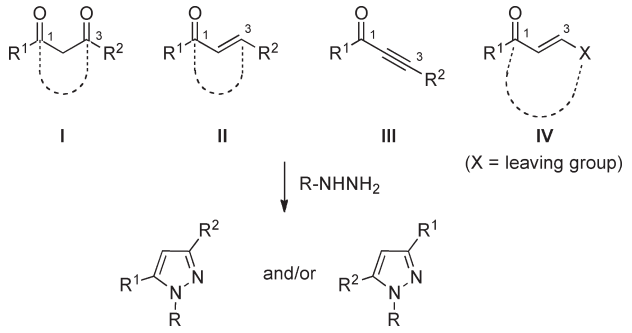
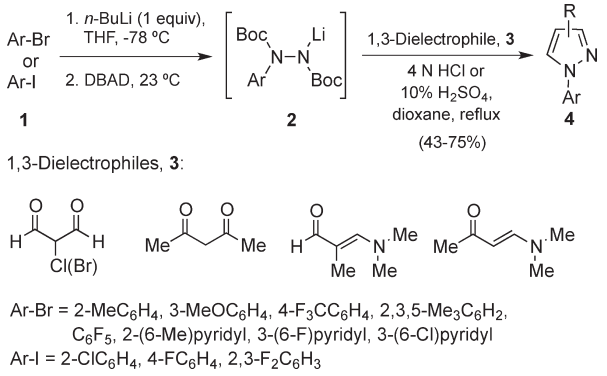
Scheme 1



Scheme 2



Scheme 3



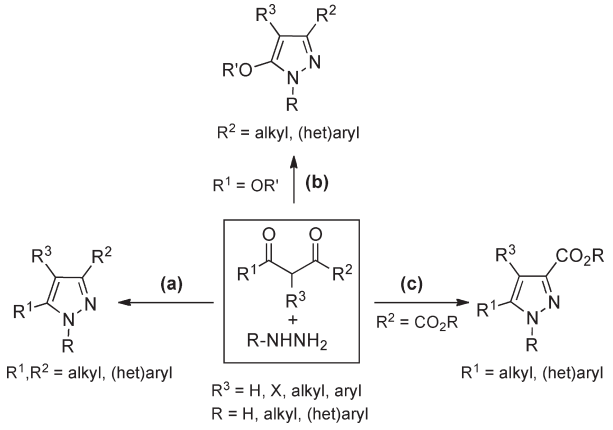
and on solid phase. It has been divided into two blocks: sections 2−6 include methods for the synthesis of alkyl-, (het)aryl-, fluoroalkyl-, alkoxy-, alkoxycarbonyl-, halogen-, thiyl-, and silyl-substituted pyrazoles from acyclic reagents; section 7 is dedicated to substitution reactions at either the nitrogen or carbon atoms of preformed pyrazoles by C−N and C−C cross-coupling reactions.

Conventional methods for the creation of the pyrazole ring have been reported.[4] In addition, we have recently published a revision of certain methodologies, including some conventional ones, which allow for the construction of the pyrazole ring from acyclic building blocks.[5] Moreover, recent developments in aminopyrazole chemistry have also been reported.[6]

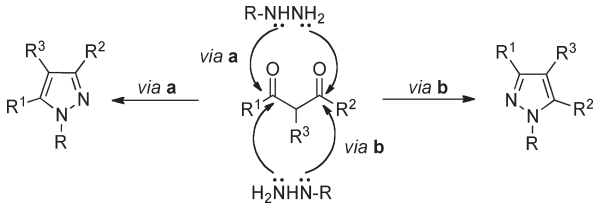
2. CYCLOCONDENSATION OF 1,3-DIELECTROPHILIC COMPOUNDS WITH HYDRAZINES

The most common synthetic method for the preparation of functionalized C-3 and C-5 pyrazoles involves the cyclocondensation of an appropriate hydrazine, which acts as a double nucleophile, with a three-carbon unit featuring two electrophilic carbons in a 1,3-relationship (Scheme 2), such as 1,3-dicarbonyl

Scheme 4



Scheme 5



(**I**), α,β-unsaturated carbonyl compounds (**II**, **III**), and β-enaminones or related compounds (**IV**).

However, this method suffers from certain limitations such as the access to 1,3-dielectrophilic building blocks and/or appropriately substituted hydrazines, mainly arylhydrazines.[7] To circumvent the last issue, the recently reported one-pot approach based upon cyclocondensation of 1,3-dielectrophilic compounds **3** with preformed bis-Boc protected arylhydrazines **2** could be a suitable alternative for the synthesis of some difficult-to-obtain *N*-arylpyrazoles (Scheme 3).[8] Intermediates **2** were generated by lithium−halogen exchange on arylbromides or iodines **1** followed by treatment with di-*tert*-butylazodicarboxylate (DBAD), and they were then in situ deprotected using 4 N HCl (or 10% H_2SO_4) in dioxane in the presence of dielectrophiles **3**, thus affording *N*-arylpyrazoles **4** in moderate to good yield. This procedure works efficiently with 1,3-dialdehydes, 1,3-diketones, β-aminoacroleines, and β-aminovinylmethylketones as the three-carbon synthons and with a variety of substituted phenyl and pyridyl halides. Moreover, it also allowed for the preparation of *N*-arylpyrazoles starting from activated arenes such as difluorophenyl derivatives instead of aryl halides, which were directly lithiated with LiHMDS and then reacted with 1,3-dielectrophiles.

2.1. 1,3-Dicarbonyl Compounds

The condensation of 1,3-diketones, β-ketoesters, and 2,4-diketoesters with hydrazines has been widely used in the preparation of *N*-substituted and *N*-unsubstituted 3,5- and 3,4,5-alkyl/(het)arylpyrazoles (Scheme 4, a), alkoxypyrazoles (Scheme 4, b), and pyrazole carboxylic acid esters (Scheme 4, c), respectively.

2.1.1. 1,3-Diketones: Synthesis of Alkyl/(Het)aryl-Substituted Pyrazoles. 1,3-Diketones can be efficiently condensed

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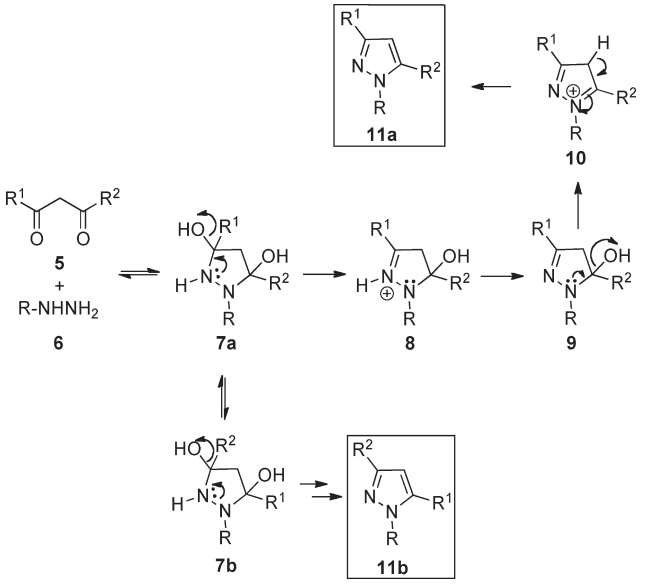
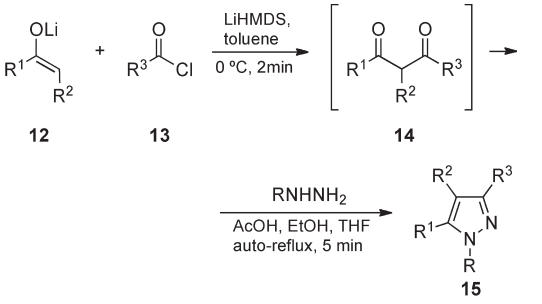
Scheme 6



Scheme 7



R = H : R^2 = H, R^1 or R^3 = *n*-C_5H_{11}, 4-Br/ MeO/ H_2N/ NC/ $EtO_2CC_6H_4$, 2,6-$(MeO)_2C_6H_3$, 4-pyridyl, 2-thienyl (49-89%)
R^2 = *n*-Pr or Ph, R^1 = 4-ClC_6H_4, R^3 = 4-$MeOC_6H_4$ (50-83%)
R^1/R^2 = $(CH_2)_4$, $CH_2CH_2OCH_2$, $CH_2CH_2N(Boc)CH_2$, R^3 = *n*-C_5H_{11}, 4-$MeOC_6H_4$ (50-83%)
R = Me : R^2 = H, R^1 = Ph, R^3 = 4-MeC_6H_4 (82%; ratio = 1:1)
R^1 = 4-BrC_6H_4, R^3 = 4-$MeOC_6H_4$ (83%; ratio = 3:1)
R = Ph : R^2 = H, R^1 = 4-$O_2NC_6H_4$, R^3 = 4-$MeOC_6H_4$ (43%; only one)

with hydrazines, affording simple pyrazoles bearing various alkyl or aryl substituents at the 3- and 5-positions. However, starting from unsymmetrical 1,3-dicarbonyl compounds ($R^1 \neq R^2$), mixtures of two regioisomers are often obtained in reactions with substituted hydrazines (R ≠ H). For R = H there is no regioisomerism due to the prototropic tautomerism of pyrazoles (Scheme 5).[4,9]

Elguero and co-workers have proposed a general mechanism for the reaction of unsymmetrical 1,3-diketones **5** with monosubstituted hydrazines **6** involving the initial formation of the 3,5-dihydroxypyrazolidine **7a**, as key intermediate, followed by the sequential loss of two water molecules (Scheme 6).[10] The formation of both N−C bonds of carbinolamine **7** is considered reversible, whereas the dehydration steps would be irreversible, with the first dehydration being the kinetics controlling step. When $R^1 \neq R^2$, both dihydroxypyrazolidines **7a** and **7b** would be in equilibrium. From the latter, regioisomer pyrazole **11b** would be obtained. They concluded that the orientation in the pyrazole formation was the result of the difference in the rates of dehydration of the two 3,5-dihydroxypirazolidines **7a** and **7b** in equilibrium (Scheme 6).

A systematic study correlating the regiochemistry in the synthesis of 1,5-diaryl-3-substituted pyrazoles with the reaction conditions and the electronic/steric factors of 1-(4-methoxyphenyl)-1,3-diketones **5** (R^1 = 4-$MeOC_6H_4$, R^2 = Me, CF_3, *n*-C_3H_7, 4-/ 2-pyridyl; Scheme 6) and aromatic hydrazines **6** (R = 4-MeO/O_2N/ $H_2NO_2SC_6H_4$, 2-HOH_2C-4-$Me(H_2N)O_2SC_6H_3$) (Scheme 6) was carried out by Singh, Rao, and co-workers.[11] In absolute ethanol, arylhydrazine hydrochlorides having electron-donating and weakly electron-withdrawing groups (R = 4-$MeOC_6H_4$, $H_2NO_2SC_6H_4$, 2-HOH_2C-4-$MeO_2SC_6H_3$) reacted with 1-(4-methoxyphenyl)-butane(hexane)-1,3-dione (R^2 = Me or *n*-C_3H_7) affording mixtures of **11a** and **11b** (ratio = 1:1 to 1:3); under the same reaction conditions, 4-nitrophenylhydrazine led to a 3:1 mixture of **11a** and **11b**. Nevertheless, either in a neutral or in a basic medium, all 1,3-diketones **5** afforded 1,5-diarylpyrazoles **11b** with excellent regioselectivity (96−100%).

On the other hand, the electronic effects in the regioselectivity of reactions of hydrazinopyridines with 1,3-diaryl-1,3-diketones in which the aryl rings were electronically dissimilar but sterically identical were also reported.[12]

2.1.1.1. Synthesis of 3,5- and 3,4,5-Alkyl/(Het)arylpyrazoles. In general, most of the 1,3-diketones used in the syntheses of pyrazoles have to be prepared in advance and purified and are often obtained as mixtures of condensation products. Moreover, most electrophilic functional groups do not survive these transformations. An efficient, rapid, and general one-pot synthesis of 3,5-, 1,3,5-, 3,4,5-, and fused ring-substituted pyrazoles **15** starting from enolizable ketones **12** and acid chlorides **13** was reported by Heller and Natarajan (Scheme 7).[13] 1,3-Diketones **14** were not isolated but converted in situ into pyrazoles by the addition of the appropriate hydrazine. A wide range of functional groups such as nitriles alkyl halides and electrophiles with enolizable α-protons were tolerated. By using methylhydrazine as nucleophile, mixtures of regioisomers (1:1 and 3:1 ratios) were obtained, whereas with phenylhydrazine, only one product was isolated. The reaction between cyclic saturated ketones and acid chlorides afforded fused pyrazoles in good yields. Moreover, both benzyl *p*-chlorophenyl ketone and *n*-butyl *p*-chlorophenyl ketone were coupled with *p*-methoxybenzoic acid chloride to give the corresponding 1,3-diketones, which were then condensed with hydrazine to afford the corresponding 3,4,5-substituted pyrazole derivatives.

Usually, cyclocondensation reactions between hydrazines and 1,3-diketones are carried out in polar, protic solvents such as alcohols or acetic acid. However, excellent yields and regioselectivities were obtained in reactions of 1-arylbutane-1,3-diones **16** with arylhydrazine hydrochlorides **17** in *N*,*N*-dimethylacetamide (DMAc), an aprotic solvent with strong dipole moment and dielectric constant. The addition of 10 N HCl_{aq} (50 mol %) resulted in increased yields, presumably by favoring the second dehydration step on the intermediate.[14] 1,5-Diaryl-3-methylpyrazoles **18** were the major or only regioisomers (Scheme 8). When analogue reactions were performed in refluxing ethanol as solvent, lower regioselectivities were observed (80:20 to 86:14).

In recent years, organic reactions carried out under operationally convenient conditions[15] such as solventless or in aqueous media have become highly desirable, thanks to the reduction of harmful effects of organic solvents on the environment and to their improved economic and safety profiles. Solventless reactions are often rapid and occur in high yields. Thus, for example,

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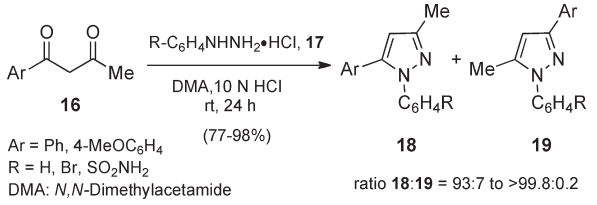
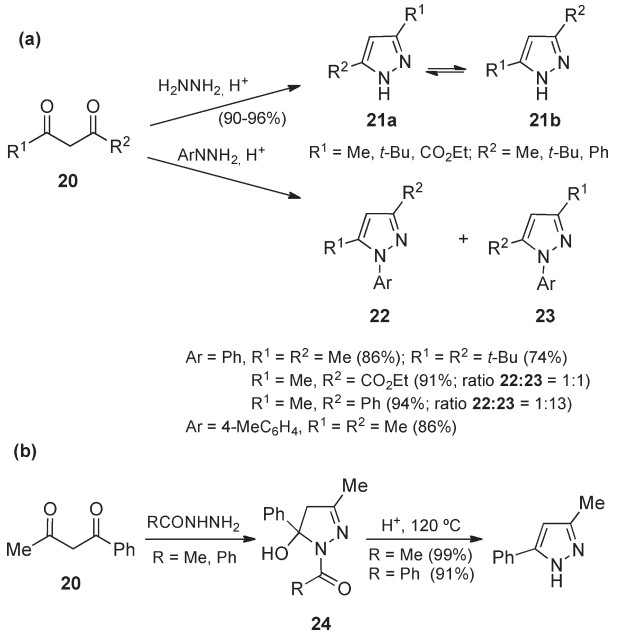
Scheme 8



Scheme 9

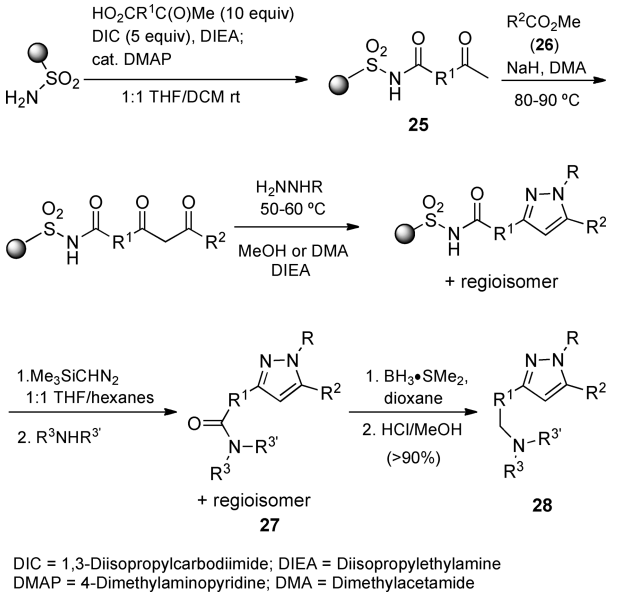


the solventless condensation of 1,3-diketones **20** with hydrazine in the presence of a catalytic amount of sulfuric acid at room temperature afforded 3,5-disubstituted pyrazoles **21** in high yields (Scheme 9a).[16] Reactions were carried out in a mortar, by mixing the diketone and the hydrazine hydrate with a drop of concentrated sulfuric acid. With unsymmetrical 1,3-diketones, either a single product (R^1 = CO_2Et, R^2 = Me) or a mixture of tautomers **21a**, **21b** (R^1 = Me, R^2 = Ph) was observed.

Under the same reaction conditions, the condensation between unsymmetrical 1,3-diketones **20** and phenylhydrazine afforded mixtures of the two regioisomers **22** and **23** (Scheme 9a).[16] Yields were good to excellent except for 2,2,6,6-tetramethylheptan-3,5-dione (R^1 = R^2 = *t*-Bu; 74%), probably due to the steric hindrance of the *t*-Bu groups. On the other hand, reactions of 1-phenylbutane-1,3-dione **20** (R^1 = Me, R^2 = Ph) with acylhydrazines (R = Me, Ph) led to *N*-acyl-4,5-dihydro-5-hydroxypyrazole derivatives **24** with complete regioselectivity (Scheme 9b). These were thermally dehydrated and deacylated in the presence of a catalytic amount of sulfuric acid.

A versatile and efficient synthesis of a broad library of 1,3,5-substituted pyrazoles in solid-phase from commercially available starting materials was reported by Shen et al.[17] Condensation of aromatic or aliphatic esters **26** with resin-supported acetyl carboxylic acids **25**, followed by condensation with aliphatic and aromatic hydrazines, activation of the linker, and subsequent

Scheme 10



cleavage by amines, afforded pyrazole amides **27** (Scheme 10 and Table 1). However, reaction conditions must be carefully controlled to improve regioselectivity. The best results in the cyclocondensation reaction were obtained using hydrazines as hydroclorides in methanol or dimethylacetamide (DMA) as solvents and diisopropylethylamine (DIEA) as an additive. A postcleavage reduction with borane converted **27** into amines **28** in high yields (>90%) and purities (>95%).

When aroyl carboxylic acids ($HO_2C-R^1-CH_2COAr$) were used instead of their acetyl analogues and were then condensed with alkyl formates (HCO_2R), solid-supported β-hydroxy-α,β-unsaturated ketones were obtained, which were then condensed with hydrazines yielding mixtures of 1,4,5- and 1,3,4-substituted pyrazole amides in a 5:1 to 10:1 ratio. These procedures provide ready access to well over 10^9 compounds from commercially available starting materials.

Fully substituted pyrazoles have received a great deal of attention since they exhibit useful pharmacological and agrochemical properties. Specifically, 4-alkyl-1,3,5-triaryl and 5-alkyl-1,3,4-triarylpyrazoles have been widely investigated as ligands for the estrogen receptor.[18] Methodologies to prepare libraries of these compounds, involving syntheses both in solution and on solid phase, have been developed.[18,19] Initially, tetrasubstituted pyrazoles **31** were synthesized through the classical 1,3-diketone–hydrazine condensation route. To this end, two strategies were developed to introduce the C-4 alkyl group in pyrazole derivatives, either alkylation at C-2 of the 1,3-diketone precursor[20] or by using an appropriate alkylphenone as building block. The former was reported by Marzinzik and Felder[19a] on solid phase but lacked generality, whereas the latter was reported by Katzenellenbogen's group[18b,c] and allowed for the introduction of a variety of alkyl groups both in solution and on solid phase. In solution,[18b] the synthetic sequence involved a crossed-Claisen condensation between an appropriate 4-methoxy alkylphenone **29** and 4-nitrophenyl 4-methoxybenzoate, followed by the reaction of C2-alkylated 1,3-diketone **30** with an arylhydrazine (Scheme 11). Harsh conditions were required for the formation of sterically

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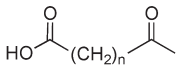
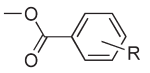
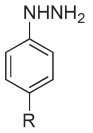
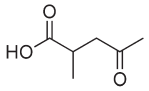
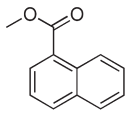
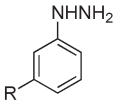
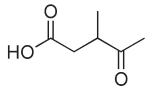
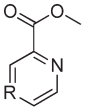
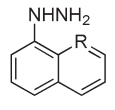
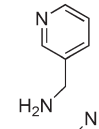
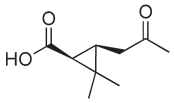
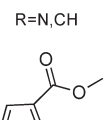
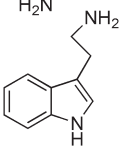
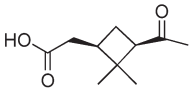
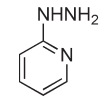
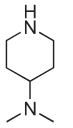
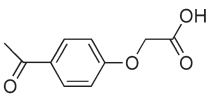
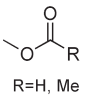
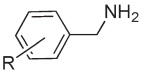
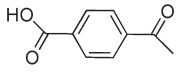
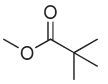
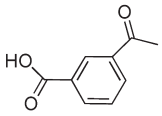
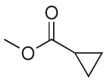
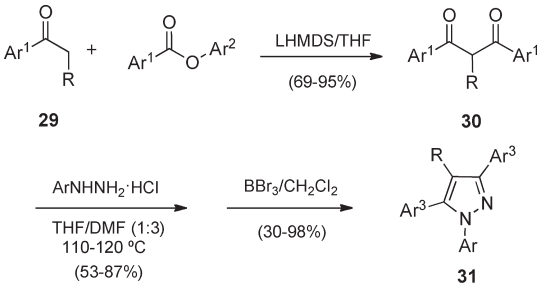
Table 1. Representative Substrates Used for Pyrazole Synthesis According to Scheme *10*

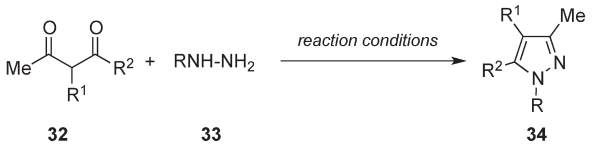
Keto acid	Ester	Hydrazine	Amine
 n=2-6	 R=2-, 3-, or 4-H, Me, F, Cl, Br, OMe, CF_3	 R=H, Me, F, Cl, OMe, CF_3, OCF_3	Me_2NH
			$Ph(CH_2)_nNH_2$ n=1, 2, 3, 4
			
	 R=N,CH	R=N, CH	
			
	 R=H, Me	H_2NNH_2	 R=3- or 4-CH_2NH_2
		$MeNHNH_2$	$H_2N(CH_2)_nNH_2$ n=5, 6
		$PhCH_2NHNH_2$	D-ArgOMe
		$CF_3CH_2NHNH_2$	L-ArgOMe

Scheme 11



R = Me, Et, *n*-Pr, *i*-Bu, *n*-Bu; Ar = Ph, 4-HOC_6H_4
Ar^1 = 4-$MeOC_6H_4$; Ar^2 = 4-$O_2NC_6H_4$; Ar^3 = 4-HOC_6H_4
LHMDS = Lithium hexamethyldisilamide

Scheme 12



reaction conditions:
Method I: 20% PSSA/H_2O, rt, 1-2 min (72-92%)
R^1 = H; R^2 = Me; R = Ph, 4-ClC_6H_4, MeCO, PhCO, 2-furyl-CO, 2-thienyl-CO
R^1 = Cl; R^2 = Me; R = Ph, 4-ClC_6H_4, MeCO, 2-furyl-CO, 2-thienyl-CO
R^1 = Et; R^2 = Me; R = Ph, 4-ClC_6H_4, 2-furyl-CO, 2-thienyl-CO
Method II: $H_3PW_{12}O_{40}$ (1 mol%), H_2O, rt, 6-60 min (81-96%)
R^1 = H, Me; R^2 = Me; R = H, Ph, 4-MeC_6H_4, 4-ClC_6H_4, MeCO

crowded tetrasubstituted pyrazoles. When this methodology was applied to unsymmetrical 1,3-diketones, a complete lack of regioselectivity was observed.

The same authors adapted both the synthetic sequence and reaction conditions to the solid-phase synthesis of libraries of 4-ethyl- and 4-isobutyl-1,3,5-triarylpyrazoles.[18c] Merrifield's resin was used as solid support, and the corresponding tetrasubstituted pyrazoles were obtained under milder reaction conditions than in solution. This method allowed for the introduction of molecular diversity in the target pyrazoles by means of alkylphenone, ester, or hydrazine components. However, mixtures of regioisomers were obtained with unsymmetrical 1,3-diones, which could be separated by means of high-performance liquid chromatography (HPLC).

In aqueous medium, polystyrene-supported sulfonic acid (PSSA)[21] (Scheme 12) or 12-tungstophosphoric acid ($H_3PW_{12}O_{40}$)-catalyzed[22] condensation between 2,4-pentanedione derivatives **32** and hydrazines/hydrazides **33** afforded symmetrical substituted pyrazoles **34** in high yields, at room temperature (methods

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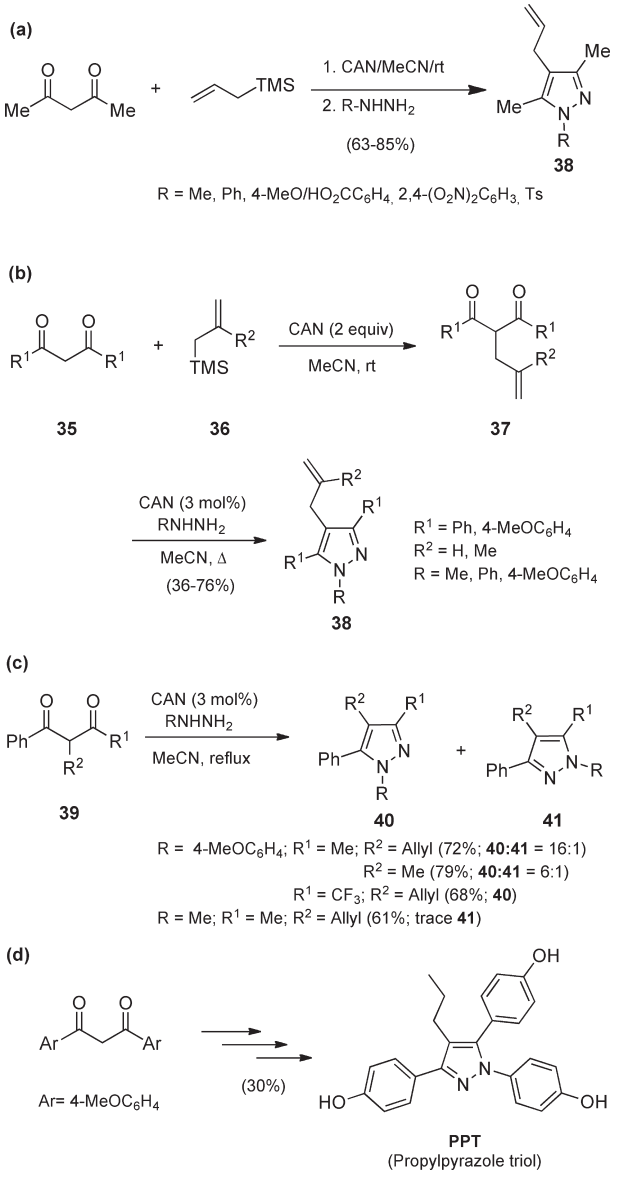
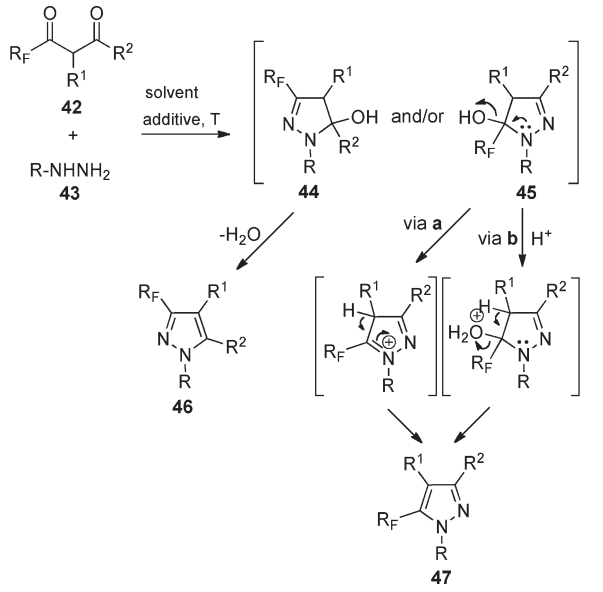
Scheme 13



Scheme 14



I and II; Scheme 12). PSSA-catalyzed condensations were much faster (1−2 min) than the corresponding $H_3PW_{12}O_{40}$-catalyzed ones (8−60 min).

Recently, a new route to 1,3,4,5-alkyl/aryl-substituted pyrazoles has been reported.[23] The method involves the treatment of 1,3-diketones **35** and allyltrimethylsilanes **36** with cerium ammonium nitrate (CAN) followed by cerium-catalyzed addition of substituted hydrazines (Scheme 13). Thus, 4-allyl-3,5-dimethyl-1-substituted pyrazoles **38** were obtained in 63−85% yield in a one-pot procedure from pentane-2,4-dione by reaction with CAN in the presence of allyltrimethylsilane followed by the addition of a range of monosubstituted hydrazines (Scheme 13a). However, starting from symmetrical aryl β-diketones, the isolation of the 2-substituted 1,3-diketone intermediates **37** was necessary to obtain pyrazole derivatives in adequate yields (Scheme 13b). The regioselectivity of the reaction was also studied using 1-phenyl-2-allyl/methyl-1,3-diketones **39** under the same reaction conditions. In this case, 5-phenylpyrazole derivatives **40** were obtained as either the single or major isomer (Scheme 13c). Results were consistent with product formation arising from steric interactions upon initial attack of the hydrazine on the diketone. Finally, this approach was applied to the synthesis of propylpyrazole triol (PPT), an agonist of the estrogen receptor. The product was obtained in four steps starting from 1,3-bis(4-methoxyphenyl)-1,3-propanedione in 30% overall yield (Scheme 13d).

2.1.1.2. Synthesis of Fluorinated Pyrazoles. Many pyrazoles containing fluorine or fluorocarbon groups are either in use or under active investigation in the fields of agrochemistry and medicine. Among fluorinated pyrazoles, trifluoromethyl derivatives are most frequently mentioned in the literature because of their important biological properties.

There are two main methods for the synthesis of fluorine-containing organic compounds, namely, the direct replacement of hydrogen by fluorine and the application of fluoro-containing building blocks; the second approach is, however, the most commonly applied one in the synthesis of fluorinated pyrazoles. Thus, condensation of fluoroalkyl 1,3-dicarbonyl compounds with hydrazines constitutes the main synthetic approach to fluoroalkyl 3,5-substituted pyrazoles. In the past decade, several research groups have applied this methodology to prepare a series of fluorinated pyrazole derivatives with important biological activities.[24]

The influence of the electronic/steric demands of the reagents and the reaction conditions on the regioselectivity of the condensation reaction between fluorinated 1,3-diketones **42** and monosubstituted hydrazines **43** has been widely studied (Scheme 14). As expected, mixtures of the two pyrazole regioisomers **46** and **47** are generally obtained. However, when reactions are performed in neutral alcoholic media, either at 0 °C,[25] at room temperature, or even at reflux, 5-fluoroalkyl-5-hydroxypyrazoline intermediates **45** were isolated instead of the 5-fluoroalkyl pyrazole final product **47**. This observation can be explained on the basis of the influence of the fluoroalkyl group adjacent to the hydroxyl group that stabilizes the hydroxypyrazoline **45**, rendering a very slow dehydration (Scheme 14, via a). Moreover, the dehydration involves a cationic intermediate,

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Table 2. Synthesis of Fluoroalkyl Pyrazoles by Condensation between Fluoroalkyl 1,3-Diketones and Monosubstituted Hydrazines

entry	R_F	R^1	R^2	R	conditions	ratio **46**/**45** or **46**/**47**	yield (%)	ref
1	CF_3	H	Me, 2-thienyl	C_6F_5, HC_6F_4 ClC_6F_4	EtOH; rt or reflux	0:100−1:2	57−72	26
2	CF_3	H	Me, Et, *i*-Pr, *i*-Bu, *t*-Bu,*n*-hexyl, Ph, 2-Me/MeO/F/$O_2NC_6H_4$, 4-Me/MeO/F/NCC_6H_4, 2-naphthyl/pyrrolyl/furyl/ thienyl/pyridyl	Ph	EtOH; rt or reflux; H_2SO_4	100:0−1:1	60−100	27
3	CF_3	H	2-$MeOC_6H_4$, 3-Me/MeO/ NCC_6H_4, 4-Me/Et/FC_6H_4, 2-/3-/4-pyridyl	4-MeC_6H_4	Si-TsOH; EtOH; μW; 160 °C; 5 min		42−95	28
4	CF_3 CHF_2	H, Et	Ph, 4-MeO/Br/$O_2NC_6H_4$	Ph, 4-Br/$H_2NO_2SC_6H_4$	DMAc, 10 N HCl, rt, 24 h	86:14 → 99.8:0.2	59−98	14
5	CF_2Br	H	Ph, 4-Me/$MeOC_6H_4$, 3-thienyl	Ph, 4-O_2N/H_2NSO_2/ $MeHNSO_2Bn$	DMF, conc. H_2SO_4; 100 °C; 2−7 h	94:6−99:1	69−86	30
6	CF_3 CHF_2	H	Ph	Ph[a]	*i*-PrOH,85 °C 1−6 days	3:1−8:1	97−100	31
				Ph, 4-methanosulfonyl pyridin-2-yl	*i*-PrOH,85 °C H_2SO_4 1 h	15:2−100:0	65−98	
7	CF_3	H	Ph, 4-MeO/F/Cl/Br/$O_2NC_6H_4$	Ph, 4-$O_2NC_6H_4$, 6-(Me/F)benzothiazol-2-yl, 4methylquinol- in-2-yl	EtOH, reflux	R = Ph: 2.5:1−100:0 Remaining hydrazines: 1:1.5−0:100	75−82	32
					EtOH, H_2SO_4, reflux	1.5:1−100:0	69−87	
8	CF_3	H	2-thienyl	Me	AcOH-EtOH, reflux	100	60	33
9	CF_3 CF_2Me CF_2CF_3	H	Me, Ph, 4-MeO/ClC_6H_4, 2,4-$(Cl)_2C_6H_3$, 2-furyl	Me, Ph	EtOH, rt, 45 min	1:1−6:1	52−99	34
					TFE, rt, 45 min	3:1−99:1	40−99	
					HFIP, rt, 45 min	4:1 → 99:<1	61−99	

[a] R = 4-methanosulfonylpyridin-2-yl, R_F = CF_3 (only **44**; 48%); R_F = CHF_2 (ratio **44**/**46** = 15:2; 99%).

whose formation could explain why, when R is an electron-withdrawing group, the dehydration does not occur or occurs with difficulty. However, in an acidic medium, the hydroxypyrazoline **45** is not observed, probably because the dehydration follows a different mechanism (Scheme 14, via b). Table 2 summarizes the syntheses of fluoroalkyl pyrazoles reported in the literature by condensation of fluorinated 1,3-diketones with monosubstituted hydrazines.

In neutral ethanolic medium, the condensation of 1,1,1-trifluoro-2,4-pentanedione or 4,4,4-trifluoro-1-(thien-2-yl)-1,3-butanedione **42** (Table 2, entry 1) with very electron-deficient per(poly)fluorophenylhydrazines **43** led to 5-trifluoro-5-hydroxypyrazolines **45** as the major or only product.[26] The authors explained these results on the basis of the proportion of the two enol forms of the 1,3-diketone being in equilibrium.

In contrast, in ethanol under acidic conditions (H_2SO_4), the 3-trifluoromethylpyrazole regioisomer **46** (Table 2, entry 2) was the major or the only product observed in the condensation of phenylhydrazine with trifluoromethyl-1,3-diketones **42** bearing aryl, heteroaryl, and alkyl substituents (for R^2 = Me; ratio **46**/**47** = 1:1).[27] The formation of the 5-trifluoro-5-hydroxypyrazoline intermediate **45** was not detected under the reaction conditions. When small alkyl groups were attached to the diketone, mixtures of regioisomers **46** and **47** were obtained, whereas when either bulky alkyl or aryl groups were present, the major product was usually 3-trifluoromethyl regioisomer **46**, suggesting that the attack of the NH_2 at the less sterically encumbered carbonyl is favored. However, electronic effects were also said to be operating because the 5-trifluoromethyl regioisomer **47** was the major regioisomer formed (ratio **46**/**47** = 1:4; 35% yield) in the reaction of the more deactivated nucleophile 2,4-dinitrophenylhydrazine with 1,1,1-trifluoro-2,3-pentanodione **42** (R^2 = Me).

By changing the acid source to silica-supported *p*-toluenesulfonic acid, a series of 1,5-diaryl-3-trifluoromethylpyrazoles **46** (Table 2, entry 3) were prepared through the microwave-assisted addition of 4-methylphenylhydrazine to aryltrifluoromethyl-1,3-diketones **42** in ethanol.[28] Reactions were completed in 5 min, and no workup was necessary to isolate the targeted pyrazoles. The required starting materials **42** were obtained in 10 min by microwave-assisted condensation of commercially available arylmethylketones and ethyl trifluoroacetate.

Excellent regioselectivities in the condensation reaction of fluorinated 1,3-diketones with arylhydrazines were obtained using polar aprotic solvents such as *N*,*N*-dimethylacetamide (DMAc), instead of ethanol, in the presence of 10 N HCl_{aq} (50 mol %) (Table 2, entry 4).[14] Reactions between fluorinated 1-aryl-1,3-diketones **42** and arylhydrazine hydrochlorides **43** were run on gram-scale at room temperature for 24 h and 0.25 M in DMAc, yielding 1,5-diaryl-3-fluoroalkylpyrazoles **46** as major products in high yields. Analogous reactions performed in ethanol at room temperature generally gave poor regioselectivity.[29]

More recently, Wu and co-workers[30] reported a highly regioselective condensation reaction between 1-aryl-4-bromo-4,4-difluorobutane-1,3-diones **42** (R_F = CF_2Br, R^1 = H; Table 2, entry 5) and aryl hydrazines **43** in dimethylformamide (DMF) at 100 °C in the presence of concentrated sulfuric acid. In all cases, the main

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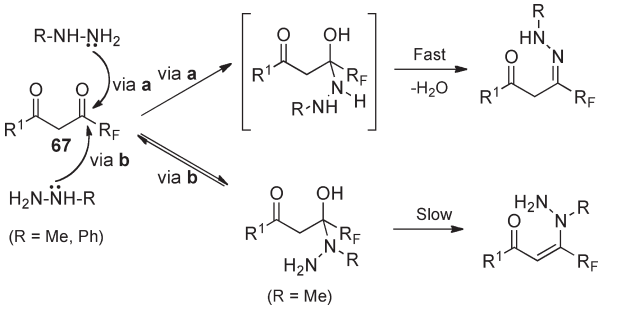
regioisomer obtained was 3-bromodifluoromethylpyrazole derivative **46**.

Norris et al.[31] studied the regioselectivity in the heterocyclization of 4,4,4-trifluoro- and 4,4-difluoro-1-phenyl-1,3-butanediones **42** with phenyl and 4-methanosulfonylpyridin-2-yl hydrazine in refluxing 2-propanol under neutral and acidic conditions (Table 2, entry 6). Surprisingly, under neutral conditions, all cyclization reactions took several days to complete. The condensation of **42** ($R_F = CF_3$) with the two hydrazines under study led to variable mixtures of up to three of the following products: 3-trifluoromethylpyrazole **46**, its 5-trifluoromethyl regioisomer **47**, the 5-hydroxy-5-phenylpyrazoline **44**, and its 5-trifluoromethyl-5-hydroxypyrazoline regioisomer derivative **45** depending on the electron-withdrawing character of the hydrazine. To explain the formation of hydroxypyrazoline **45**, the authors proposed a significant concentration of the enol form of **42**, which would result in the initial hydrazone formation at the phenyl carbonyl group and subsequent dehydration. The use of **42** ($R_F = CHF_2$) led to comparable results. From these results the authors concluded that, when only one electron-withdrawing group is present, the reaction proceeds to the pyrazole product, whereas with two electron-withdrawing groups, the major isolated product was the pyrazoline. Cyclizations were much faster (1−2 h) when carried out in boiling 2-propanol in the presence of sulfuric acid. In all cases, 3-fluoroalkyl pyrazole regioisomer **46** was the predominant product. However, whereas the cyclization of **42** ($R_F = CHF_2$) was promoted by a catalytic amount (10 mol %) of sulfuric acid, 150 mol % was required for **42** ($R_F = CF_3$). It is noteworthy that the observed regioselectivity in the reaction of the latter 1,3-dione with 4-methanosulfonylpyridin-2-ylhydrazine under neutral conditions is the complete reversal to that observed in acidic medium.

Qualitatively similar results were obtained by Elguero and coworkers in their study on the regioselectivity of the reaction of aryl trifluoromethyl 1,3-diketones **42** with aryl and heteroarylhydrazines **43** in refluxing ethanol under neutral and acidic conditions giving rise to variable mixtures of 3-trifluoromethylpyrazoles **46** and 5-hydroxy-5-trifluoromethylpyrazoline **45** (Table 2, entry 7).[32] The **46**/**45** ratio obtained was dependent on the substitution at both reactants, as well as on the reaction conditions (either neutral or acidic). The authors concluded that (i) on going from neutral to acidic conditions, the proportion of 3-trifluoromethylpyrazoles **46** always increases; (ii) as the electron-withdrawing effect of the substituent on the hydrazine gets higher, the proportion of 5-hydroxypyrazoline **45** increases; and (iii) the more electron-withdrawing the substituent on the phenyl ring of the 1,3-diketone, the larger is the proportion of 5-hydroxypyrazoline. Pyrazolines were converted into their respective pyrazoles by refluxing in EtOH under acidic conditions.

Condensation reactions of fluorinated 1,3-diketones with methylhydrazine are scarce in the literature. Yonetoku et al.[33] reported that the reaction of 4,4,4-trifluoro-1-(2-thienyl)butane-1,3-dione with methylhydrazine in boiling AcOH−EtOH regioselectively leads to 3-trifluoromethyl-1-methyl-5-(2-thienyl)pyrazole in 60% yield (Table 2, entry 8). More recently, an elegant study on the regioselectivity in the synthesis of fluorinated 1-methyl and 1-phenylpyrazoles from fluoroalkyl 1,3-diketones and methyl- and phenylhydrazine using either ethanol or fluorinated alcohols as solvents was reported by Fustero et al. (Table 2, entry 9).[34] The condensation reactions between fluoroalkyl 1-aryl-1,3-diketones **42** and hydrazines in ethanol at room temperature were completed in <1 h, affording mixtures of 3-fluoroalkylpyrazoles **46** and 5-fluoroalkyl-5-hydroxypyrazolines **45** in good to excellent yields

Scheme 15



(52−99%) but generally poor regioselectivities (1:1 to 1:3). Pyrazolines **45** were then converted into their respective 5-trifluoromethylpyrazoles **47** in almost quantitative yields through treatment with 3 M HCl in refluxing tetrahydrofuran (THF). The regioselectivity improved to 99:1 (61−99% yield) in favor of **46** when reactions were carried out in the more acidic alcohols trifluoroethanol (TFE) and hexafluoroisopropanol (HFIP) as solvents at room temperature. An NMR experiment involving addition of an excess of CD_3OH to an NMR sample tube containing **42** (R^2 = 2-furyl, $R_F = CF_3$) revealed the formation of a mixture of the adduct at the $COCF_3$ carbonyl (hemiketal) and the diketone starting material in an 8:1 ratio, whereas when TFE-d_3 or HFIP-d_2 was added to the same 1,3-diketone, the corresponding adduct was not detected. From these results, the authors concluded that the low regioselectivities observed in EtOH were due to the competition between the two nucleophiles, hydrazine and alcohol, toward the more reactive fluorinated carbonyl group. Non-nucleophilic TFE and HFIP did not compete with the hydrazine in the attack to the fluorinated carbonyl group, and thus, the regioselectivity increased. A step-by-step pathway was proposed for this process. Interestingly, 3-fluoroalkylpyrazole analogues **46** ($R_f = CF_3$) were obtained as major regioisomers either with methyl- or phenylhydrazine in spite of the fact that NH_2 is the more nucleophilic nitrogen in phenylhydrazine but the less nucleophilic one in methylhydrazine. This apparent anomaly in the case of methylhydrazine was explained by considering that the attack of the more nucleophilic NH group on the more reactive carbonyl group led to a hemiaminal that does not dehydrate easily to yield a hydrazone and can revert to the starting materials (Scheme 15). This dehydration is disfavored because of the presence of the fluoroalkyl group. In contrast, the NH_2 group of methylhydrazine attacks the fluoralkylated carbonyl group, leading to the irreversible hydrazone formation, in agreement with Elguero's observation that the kinetic controlling step is the first dehydration.[10]

Finally, this approach was applied to the regioselective synthesis of fluorinated analogues of Tebufenpyrad, a commercial acaricide, **48** (Scheme 16). Some of these analogues displayed a strong acaricidal activity that was either comparable to or better than that of the commercial compound.[1b]

2.1.2. β-Ketoesters: Synthesis of Alkoxypyrazoles. The condensation reaction between β-ketoesters and hydrazines affords either pyrazol-3/5-ones as the only products or mixtures of pyrazol-3/5-ones and 3/5-alkoxypyrazoles depending on the reaction conditions. Pyrazol-5-one derivatives **51** were obtained in 50−80% yield by reaction of ethyl fluoroalkyl-β-ketoesters **49** with 2-pyridylhydrazine derivatives **50** in refluxing EtOH or

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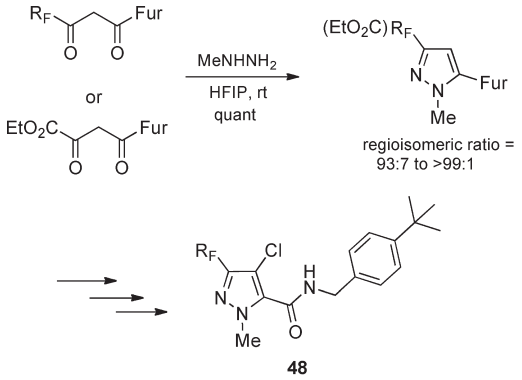
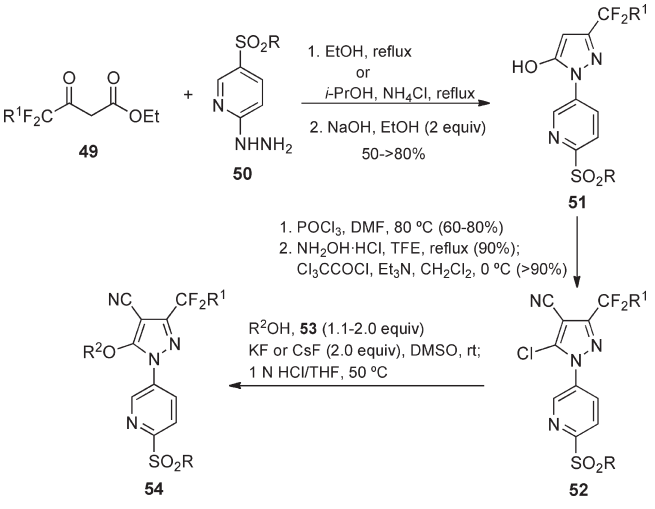
Scheme 16



R_F = CF_3, CF_2CF_3,CF_2CH_3, CH_2CF_3, CH_2CHF_2, CH_2CH_2F, $CHFCH_3$, $CHFCF_3$

Scheme 17



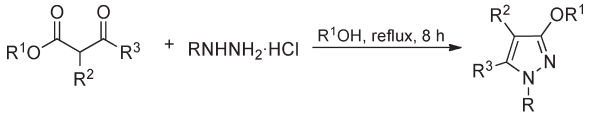
R = Me (24-68%); R^1 = H, F; R^2 = *Cy*$PrCH_2$, *cy*Bu, *cy*$BuCH_2$, *cy*Hept, *cy*Hex-3-enCH_2, (4-methylen)*cy*$HexCH_2$, (2-/3-Me)*cy*Hex, (4-ethyl)*cy*Hex, 1,2-$(Me)_2$Pr

R = NH_2 (5-47%); R^1 = F; R^2 = *Cy*Hept, (3-Me)*cy*Hex, (4-Et)*cy*Hex, (4,4-F_2)*cy*Hex, *cy*$PentCH_2$, 2,2-$(Me)_2$Pr

i-PrOH, followed by treatment with sodium hydroxide (Scheme 17).[35] Pyrazolones **51** were then used as building blocks for the synthesis of 5-alkoxypyrazole derivatives **54** through a sequence of reactions involving substitution of the hydroxy group at C-5 by a chlorine atom, introduction of a cyano group at C-4, and fluoride-mediated nucleophilic substitution of the chlorine atom with alcohols **53**.

A direct, simple approach for selectively preparing 3-alkoxypyrazoles **57** by condensation between alkyl acetoacetates **55** and hydrazine monochlorides **56** was reported by Janin and coworkers[36] (Scheme 18). The best yields were obtained by reacting 1.0 equiv of **57** and 1.05 equiv of hydrazine monohydrochloride, either at reflux in the corresponding alkyl alcohol for 8 h or overnight at room temperature. Ethyl or isopropyl acetoacetates gave higher yields than methyl- or benzyl acetoacetates. Ethyl or benzyl substituents as well as a fluorine atom at the Cα of ethyl acetoacetate did not hinder the reaction. On the other hand, the six-membered cyclic β-ketoesters [R^2/R^3 = $(CH_2)_4$]

Scheme 18



55					56				57
R^1	R^2	R^3	R	57 (%)	R^1	R^2	R^3	R	57 (%)
Et	H	Me	H	55	Et	$(CH_2)_4$		H	54
Bn	H	Me	H	22	Et	F	Me	H	40
Me	H	Me	H	25	Et	Me	CO_2Et	H	39
i-Pr	H	Me	H	55	Et	H	CF_3	H	25
t-Bu	H	Me	H	Mixture	Allyl	H	Me	H	48
Et	Et	Me	H	56	Et	$(CH_2)_3$		H	Mixture
Et	Bn	Me	H	55	Et	CO_2Et	Bn	H	Mixture[a]
Et	H	Ph	H	40	*i*-Pr	H	Me	Me	69

[a] 3-Ethoxypyrazole derivative (27%) + pyrazol-3-one derivative (34%).

(Scheme 18) gave the corresponding 3-ethoxytetrahydroindazole in good yield, but the five-membered analogue [R^2/R^3 = $(CH_2)_3$] led to an inseparable mixture of products. When methylhydrazine monohydrochloride was used in the reaction with isopropyl acetoacetate, the corresponding 5-isopropoxy-1,3-dimethylpyrazole was regioselectively obtained in 69% yield (Scheme 18). Compounds **57** were then *N*-arylated by cross-coupling reactions with arylboronic acids (see section 7). Under the same reaction conditions, the condensation between diethyl phenylacetylmalonate and hydrazine hydrochloride afforded a mixture of 5-benzyl-3-ethoxy-4-ethoxycarbonylpyrazole (27%) and its respective pyrazol-3-one (34%)[36b] (Scheme 18), in desagreement with previously reported results.[37] The 3-ethoxypyrazole derivative was then decarboxylated to the corresponding 3,5-substituted pyrazole. The condensation of ethyl acetoacetate with monosubstituted hydrazines was also carried out in water using PSSA[21] or $H_3PW_{12}O_{40}$[22] as catalyst, giving rise to 5-ethoxypyrazole derivatives in high yields, at room temperature in the former case (R = Ph, 4-ClC_6H_4) and at 50 °C in the latter one (R = Ph, 4-ClC_6H_4, 4-MeC_6H_4).

An interesting solution-phase parallel synthesis of a series of 11 1,3-substituted pyrazol-5-ones (40−60% yield) was carried out by Botta and co-workers by condensation between appropriate ethyl β-ketoesters **55** (R^2 = H; R^3 = Me, *i*-Pr, CF_3, Ph) and phenylhydrazines **56** (R = Ph, 4-F/Cl/Br/Me/*i*-PrC_6H_4) in refluxing EtOH.[38] The C-4 acyl derivatives of these pyrazolones were tested as inhibitors of *Mycobacterium tuberculosis*.

2.1.3. 1,3-Diketoesters: Synthesis of Pyrazole 3(5)-Carboxylic Acid Derivatives. The [3 + 2]-cyclization reaction between hydrazines and 1,3-diketoesters has been the most frequently used approach to synthesize pyrazole-3(5)-carboxylic acid esters. In this regard, a complete revision concerning the synthesis of 3/5-pyrazole carboxylic acids in the last 120 years has been recently reported.[39]

Claisen condensation of ketone enolates **58** with diethyl oxalate is the most general method used to prepare 1,3-diketoesters **59** (Scheme 19), which constitute the building blocks of most of the pyrazole-3(5)-carboxylic acid derivatives **60** reported in the literature. Some of these compounds display important pharmacological activities.[40]

2.2. α,β-Unsaturated Carbonyl and Related Compounds

2.2.1. Enones and Related Compounds. In general, the condensation of hydrazines with α-enones regioselectively leads to pyrazolines, which must then be oxidized to obtain the corresponding pyrazoles.[41]

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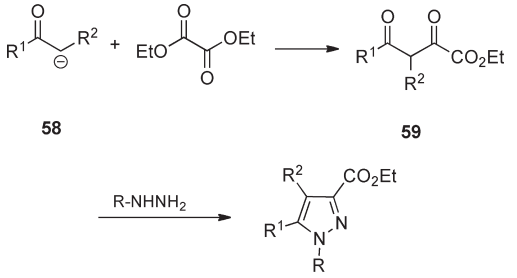
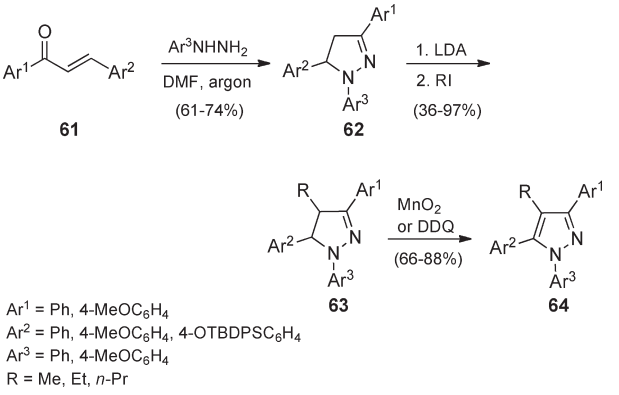
Scheme 19



Scheme 20

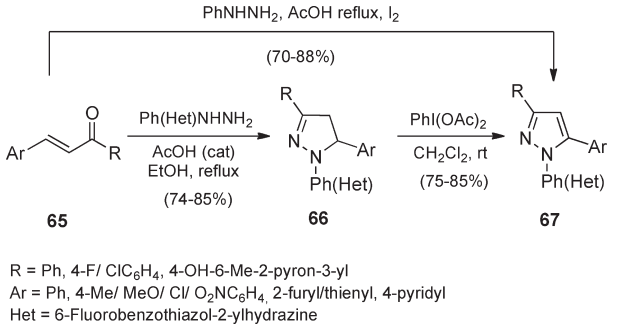


Chalcones (1,3-diaryl-2-propen-1-ones), which can be easily obtained in high chemical yields by a Claisen−Schmidt condensation of functionalized acetophenones and benzaldehydes, are adequate building blocks to prepare 3,5-diarylpyrazoles. A series of 4-alkyl-1,3,5-triarylpyrazoles **64** were regioselectively obtained by oxidation of pyrazolines **63**. These were in turn prepared by means of a cyclocondensation reaction between phenyl and 4-methoxyphenylhydrazine and chalcones **61**, followed by alkylation at the C-4 position of the pyrazoline ring in **62** (Scheme 20).[42]

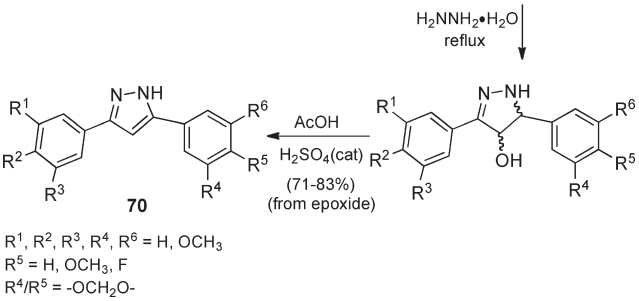
On the other hand, chalcones **65** underwent a regioselective cyclocondensation with phenyl- or 6-fluorobenzothiazol-2-ylhydrazine in the presence of a catalytic amount of glacial acetic acid in refluxing ethanol, leading to the corresponding pyrazolines **66**, which were subsequently oxidized with iodine(III) to pyrazoles **67** in good yields (Scheme 21).[43] Starting from chalcones **65**, 1-phenyl-3,5-triarylpyrazoles **67** were also obtained in a one-pot procedure (70−88% yield) by reaction with phenylhydrazine in refluxing AcOH in the presence of 1 equiv of elemental iodine.[44]

The synthesis of 3,5-diarylpyrazoles via epoxide intermediates allows one to obtain a relatively large number of compounds in an easy manner. An effective procedure was reported by Bhat et al.[45] through the transformation of chalcones **68** into chalcone epoxides **69** (Scheme 22). The condensation of hydrazine hydrate with epoxides **69**, followed by dehydration, led to products **70**. Epoxidation reactions took place in high yields (85−94%), and the two subsequent steps were carried out in a one-pot reaction.

Scheme 21



Scheme 22



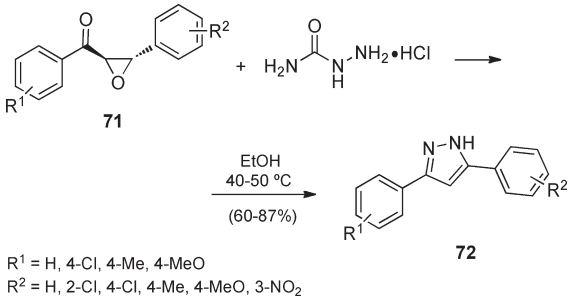
This strategy has been applied by several authors to prepare arrays of this class of compounds with potential pharmacological activities, such as analogues of the combretastatins,[46a] cytotoxic agents,[46b] or inhibitors of monoamine-oxidase-A.[46c]

The easier-to-handle and safe semicarbazide hydrochloride salt was used instead of the highly toxic hydrazine hydrate in the preparation of a series of 3,5-diaryl-1*H*-pyrazoles **72** from α-epoxyketones **71** (Scheme 23).[47] Reactions were performed in 15−45 min under mild conditions. Products **72** were obtained in good yield without separation and purification of intermediates.

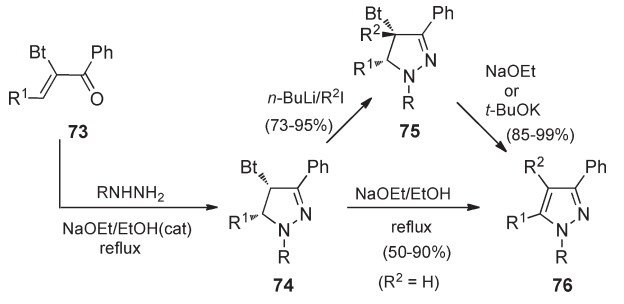
The condensation of hydrazines with α-enones bearing a leaving group leads straight to pyrazoles through an elimination reaction on the pyrazoline intermediate. Katritzky et al. reported the synthesis of 1,3,5-substituted pyrazoles **76** (R^2 = H; Scheme 24) by means of the regioselective condensation of α-benzotriazolyl-α,β-unsaturated ketones **73** with methyl- and phenylhydrazines via intermediate pyrazolines **74**.[48] No products resulting from the alternative regiochemistry of addition were detected. Pyrazolines **74** were converted into pyrazoles in high yields by treatment with a mild base. This approach also allowed for the preparation of 1,3,4,5-substituted pyrazoles **76** ($R^2 \neq$ H; Scheme 24) in excellent yields and complete regioselectivity via C_α alkylation of 4-benzotriazolylpyrazolines **74** and subsequent elimination reaction. The presence of the benzotriazolyl substituent renders the α-hydrogen acidic, thus

dx.doi.org/10.1021/cr2000459 |*Chem. Rev.* 2011, 111, 6984–7034

Scheme 23



Scheme 24



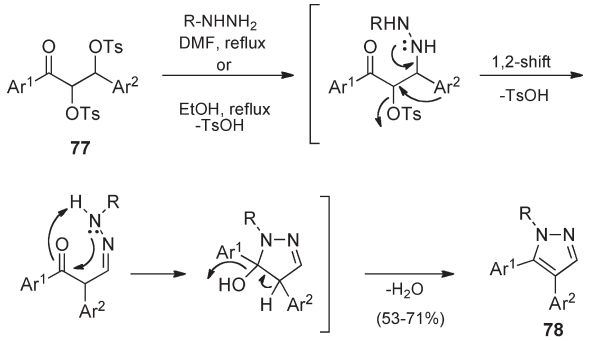
allowing for its replacement through the use of an electrophilic reagent.

Starting from previously prepared α,β-chalcone ditosylates **77**, very scarce 1,4,5-substituted pyrazoles were obtained (Scheme 25). Treatment of **77** with phenylhydrazine hydrochloride (R = Ph) in refluxing dimethylformamide afforded 4,5-diaryl-1-phenylpyrazoles **78** as the only products in moderate yields (52−68%).[49] This approach also allowed for the preparation of 4,5-diaryl-1-(thio)carboxamides (R = CO(S)NH$_2$) by condensation of **77** with semicarbazide hydrochloride or thiosemicarbazide, respectively, in refluxing ethanol. The proposed mechanism involves a 1,2-aryl migration, closely related to a pinacol rearrangement.

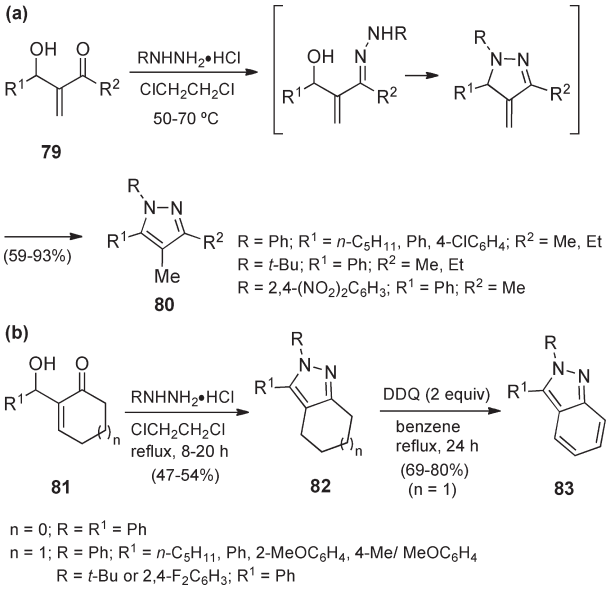
Tetrasubstituted pyrazoles **80** were regioselectively synthesized in good yields by means of the reaction between Baylis−Hillman adducts **79** and monosubstituted hydrazine hydrochlorides in 1,2-dichloroethane (for the reaction with 2,4-dinitrophenylhydrazine, *p*-toluenesulfonic acid was used as catalyst).[50a] The formation of pyrazoles could be explained through the formation of a hydrazone intermediate followed by acid-catalyzed cyclization and subsequent 1,3-hydrogen transfer (Scheme 26a). When Baylis−Hillman adducts derived from 2-cyclopenten- and 2-cyclohexen-1-one **81** were used, the corresponding 3,4-annulated-1,5-diarylpyrazoles **82** were obtained in moderate yields.[50b] Products **82** derived from 2-cyclohexen-1-one were subsequently oxidized to 2*H*-indazole derivatives **83** in good yields (Scheme 26b).

2.2.2. Ynones. Syntheses of 1,3- and 1,5-substituted pyrazoles by condensation of ynones and substituted hydrazines have

Scheme 25



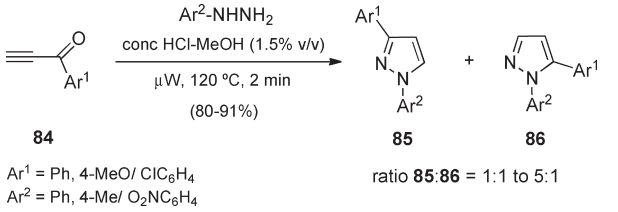
Scheme 26



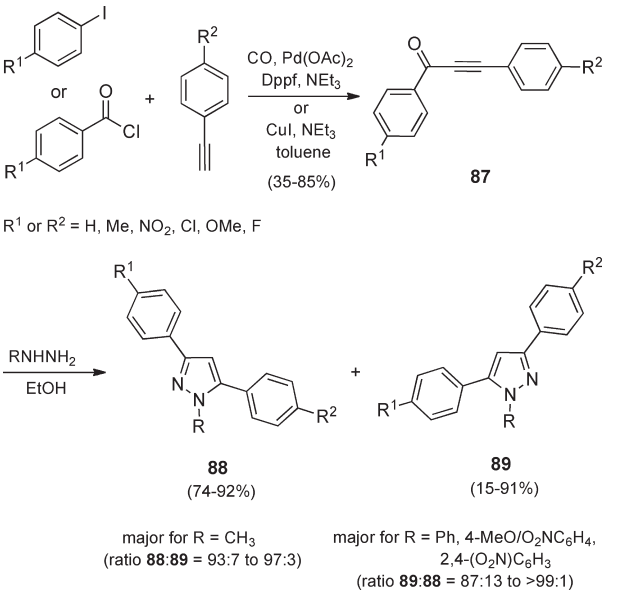
been reported by several authors. However, the regioselectivity of this reaction was often contradictory. Depending on the reaction conditions, only one isomer or mixtures of both regioisomers were observed.[51] A reinvestigation carried out by Bagley et al.[52] by reacting propynone and phenylhydrazine, in the reaction conditions previously related by other authors, showed the formation of mixtures of 1,3- and 1,5-diphenylpyrazoles in all cases, with the former obtained preferentially when the cyclocondensation was performed in acidic medium (high yield and 7:1 ratio was achieved in concentrated HCl−MeOH (1.5% v/v) at 0 °C). Under these reaction conditions, microwave irradiation of mixtures of alkynyl ketones **84** and arylhydrazines at 120 °C for 2 min afforded mixtures of 1,3- and 1,5-diarylpyrazoles **85** and **86**, respectively, in high yields but, in general, with low regioselectivity (Scheme 27). When nonterminal ynones were condensed with hydrazines, 1,3,5-substituted pyrazoles were obtained.

dx.doi.org/10.1021/cr2000459 |*Chem. Rev.* 2011, 111, 6984–7034

Scheme 27

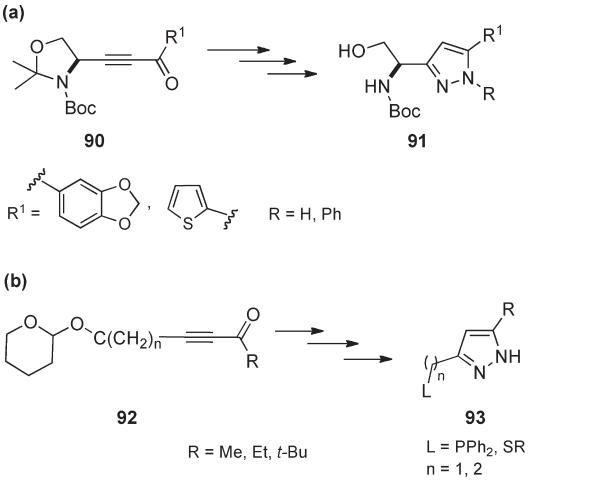


Scheme 28



This methodology was applied to the regioselective preparation of 1-methyl- and 1-aryl-3,5-diarylpyrazoles **88** and **89**, respectively, from β-aryl,aryl-ynones **87** and methyl- and arylhydrazines.[53] Reactions were carried out in neutral medium with ethanol as solvent (Scheme 28). Compounds **87** were previously prepared either via the Pd-catalyzed carbonylative coupling of phenyl acetylenes with aryl iodides or by the Cu-catalyzed coupling of aryl acid chlorides with phenyl acetylenes. Reactions of **87** with methylhydrazine occurred at room temperature, whereas refluxing ethanol was required to reach complete conversions in the case of arylhydrazines. In all cases, high levels of regiocontrol were achieved, independently of the aryl substituents present in the substrates. In general, high yields were obtained in reactions with methyl-, phenyl-, *p*-methoxyphenyl-, and *p*-nitrophenylhydrazines, whereas 2,4-dinitrophenylhydrazine afforded low yields (15−22%) of the expected pyrazoles. The observed regioselectivity was explained as a result of an initial 1,4-conjugate addition of the more nucleophilic nitrogen (methyl-substituted in methylhydrazine and unsubstituted in arylhydrazines) to the triple bond of the ynone system, followed by cyclization of the other hydrazine nitrogen onto the carbonyl group in a favored 5-exo-trig process and subsequent dehydration. This method allowed for the preparation of regioisomeric pyrazole through selection of the appropriate substitution pattern in the ynone substrates.

Scheme 29



The palladium-catalyzed preparation of ynones and their further condensation with hydrazine and methyl- and phenylhydrazine has recently been adapted to a modular flow reactor.[54] This technique makes it possible to perform these reactions in continuous flow to give 3,5- and 1,3,5-substituted pyrazoles in excellent purity (>95%) with good to excellent regioselectivity and good yields in two steps without the necessity of chromatographic purification. Reactions were conducted in EtOH at 100 °C for 20−30 min. Glass tubes containing appropriate scavenger materials ensured the quality of the final products, which were obtained by simple evaporation of the solvent.

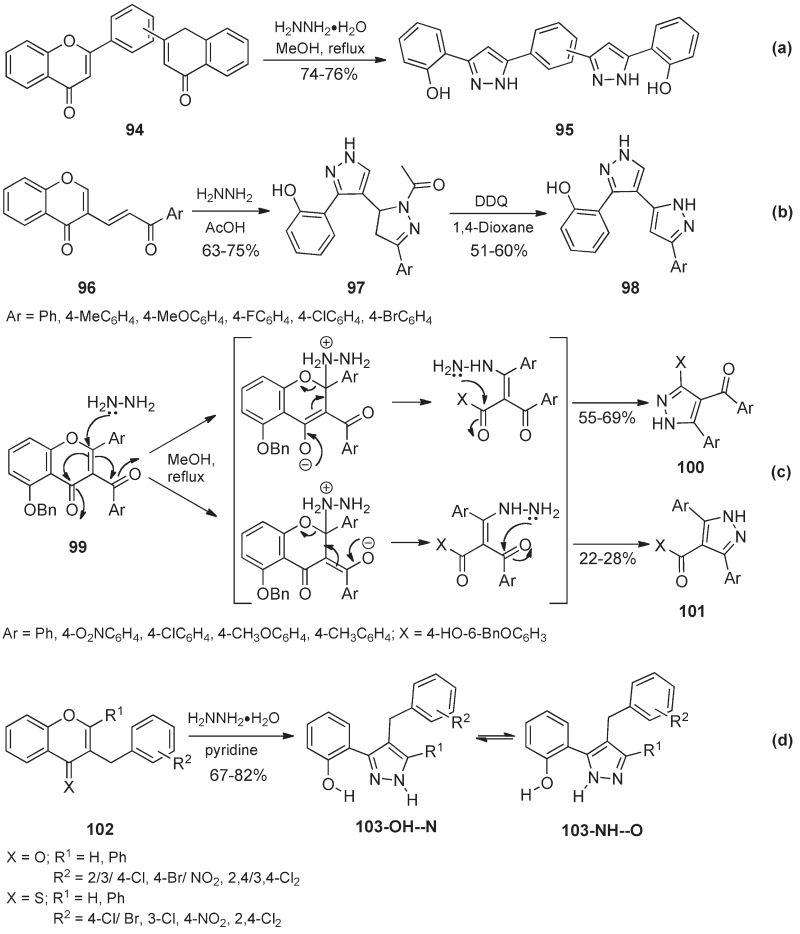
Starting from chiral oxazolidine ynones **90**, enantiopure pyrazolyl-β-amino alcohols **91** bearing heterocyclic residues were regioselectivity prepared in high yields and ee ≥ 95% (Scheme 29a).[55] On the other hand, sulfur- and phosphorus-containing pyrazole-based ligands **93** were obtained by condensation of tetrahydropyranyloxy ynones **92** with hydrazine followed by alcohol deprotection, conversion to pyrazole hydrochlorides, and nucleophilic substitution (Scheme 29b).[56]

2.3. α,β-Unsaturated Carbonyl Compounds Bearing a Leaving Group at the β-Carbon

2.3.1. Synthesis of Alkyl/(Het)aryl Pyrazoles. The alkoxymethylene, aminomethylene, and (dimethylamino)methylene groups act as synthetic equivalents of a formyl group; therefore, compounds containing these substructures have been used in the synthesis of a variety of pyrazole derivatives. Thus, Silva and co-workers prepared new derivatives of (2-hydroxyphenyl)pyrazoles **95**, **98**, **100**, **101**, and **103** through conjugate addition of hydrazine to bis(chromone) **94** (Scheme 30a),[57] 3-(3-aryl-3-oxopropenyl)chromen-4-ones **96** (Scheme 30b),[58] 3-aroyl-5-benzyloxyflavones **99** (Scheme 30c)[59] and 3-benzylchromones **102** (R^1 = H, X = O), and 3-benzylflavones (R^1 = Ph, X = O) and their 4-thio analogues (X = S) (Scheme 30d).[60] The condensation of **99** with hydrazine occurred through two possible pathways, leading to a mixture of pyrazoles **100** and **101** (2:1 to 3:1) (Scheme 30c). On the other hand, an ^{1}H NMR study in [d_6]dimethyl sulfoxide ([d_6]DMSO) showed that pyrazoles **103** existed as mixtures of tautomers, owing to the presence of intramolecular hydrogen bonds in each tautomer (**OH—N** and **NH—O**). When R^1 = H, the **OH—N** tautomers were more abundant (63%), whereas when

dx.doi.org/10.1021/cr2000459 |*Chem. Rev.* 2011, 111, 6984–7034

Scheme 30

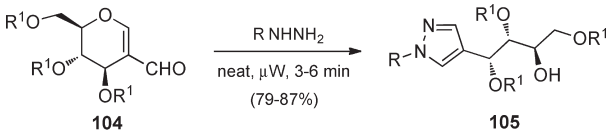


R^1 = Ph, the **NH—O** tautomers were the major form (59%) (Scheme 30d). This approach was applied to the preparation of a series of 3,4-diaryl-5-methylpyrazoles starting from previously obtained functionalized chromen-4-ones. Some of these compounds were Hsp90 inhibitors that displayed inhibition of cell proliferation.[61]

Yadav et al.[62] prepared an array of enantiomerically pure 4-substituted pyrazoles **105** from 2-formyl glycols **104** and arylhydrazines under solvent-free conditions (Scheme 31). Both reaction rates and yields were substantively enhanced by microwave irradiation when compared to thermal conditions: 3−6 min versus 6−9 h, and 79−87% versus 65−78%. The in situ formation of the hydrazone and subsequent cyclization followed by intramolecular pyran ring-opening was proposed to explain the regioselectivity observed.

4,5-Fused cycloalkanone 1-substituted pyrazoles **108a,b** were obtained under microwave irradiation in an aqueous one-pot synthesis from 1,3-cycloalkanediones **106a,b** and dimethylformamide dimethyl acetal (DMFDMA) via β-enaminediones **107a,b** (Scheme 32a).[63] Regioisomers **108a,b** were mentioned as the only formed products in all cases. The short reaction time required (2 min, 200 °C) and convenient purification through precipitation of the products in aqueous media make this procedure operationally convenient. Fused cycloheptanone 1-substituted pyrazoles **108b** were also obtained as major or

Scheme 31



only regioisomers in the condensation reaction of the previously prepared enaminedione **107b** with methyl, ethyl, benzyl, and phenylhydrazine in methanol as solvent (Scheme 32b).[64] When benzyl and phenylhydrazine were used, only regioisomeric pyrazoles **108b** were observed (61−85% yield). However, in the case of methyl and ethylhydrazine, both yields (56−91%) and regioselectivities (**108b**/**109b** = 1:3 to >19:1) were temperature-dependent (−78 to 65 °C); the lower the temperature, the higher are the yields, and the higher the temperature, the higher are the ratios. Regioisomers **109a,b** were obtained in acceptable yield in a one-pot procedure by reversing the order of addition of the reagents, namely, forming the hydrazone from the monosubstituted hydrazine and the cycloalkyl-1,3-dione, followed by cyclization with DMFDMA (Scheme 32c). This procedure was applied to the syntheses of 2-pyridyl-substituted

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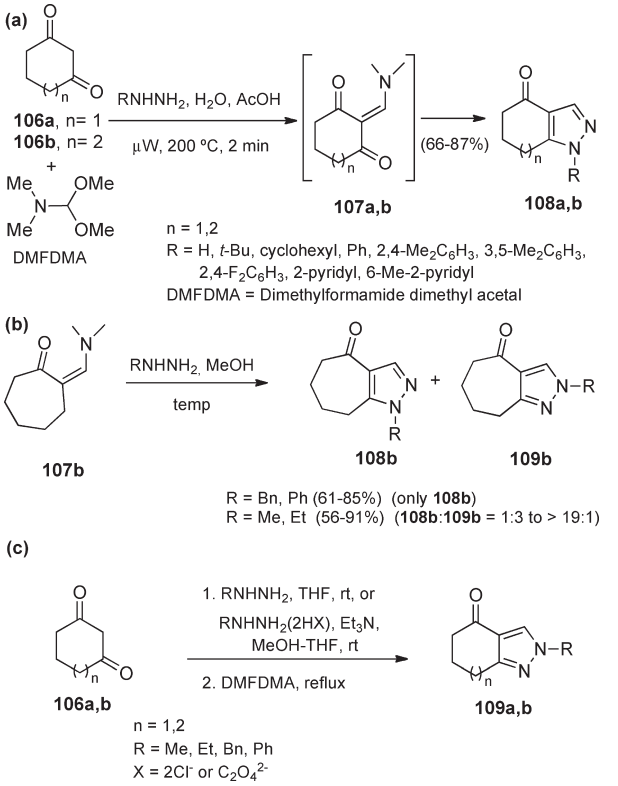
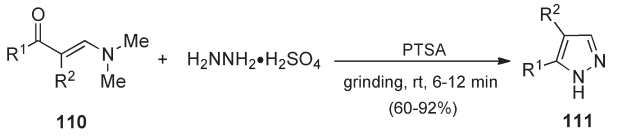
Scheme 32

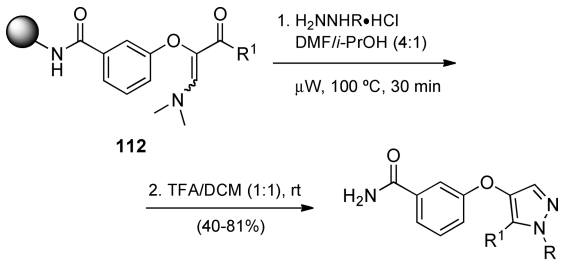


Scheme 33



R2 = H; R1 = Ph, 4-Me/ F/ Cl/ Br/ O2NC6H4, 3-MeOC6H4, 2-furyl, 2-thienyl (65-90%)
R2 = 2-MeOC6H4; R1 = Me (92%)
R1/R2 = -(CH2)3C(O)- (60%)

Scheme 34



R1 = Ph, 3-/4-BrC6H4, 3-MeOC6H4, 4-PhC6H4, 4-(N-pyrrolidinyl)C6H4
R = H, Ph, 2-pyridyl

pyrazoles as transforming growth factor-β type 1 receptor kinase inhibitors,[65a] a potent and highly selective ROS1-tyrosine kinase inhibitor,[65b] and 6,7-dihydroindazolones with potential atypical antipsychotic activity.[65c]

A series of 5-(het)aryl N*H*-pyrazoles **111** were synthesized by reaction of β-dimethylaminovinylketones **110** and hydrazine sulfate in solid state by grinding, using *p*-toluenesulfonic acid (PTSA) as a catalyst under solvent-free conditions (Scheme 33).[66] Reactions proceeded smoothly at room temperature in shorter reaction times (6−12 min vs 2−6 h) and better yields (60−92% vs 50−83%) when compared to conventional heating in ethanol in the presence of PTSA as catalyst. This procedure also allowed for large-scale preparation of the N*H*-pyrazoles **111**.

β-Enaminone scaffold **112** was used in the condensation with hydrazine and phenyl- and 2-pyridylhydrazine for the preparation of a small library of 5-aryl-4-carbamoylphenoxypyrazole derivatives **113** in solid-phase using Rink amide resin (Scheme 34).[67] The use of microwave irradiation reduced reaction times and improved both yields and purity of the final products.

2.3.2. Synthesis of Pyrazole−3/4/5-Carboxylic Acid Derivatives. Persson and Nielsen developed an efficient approach to pyrazole-3-carboxylates from Weinreb amides, hydrazines, and ethyl propynoate.[68] Weinreb amides **114** were reacted with the sodium acetylide of ethyl propynoate in an acyl substitution−conjugate addition sequence to furnish (*E*)-β-ethoxycarbonyl-*N*-methoxy-*N*-methyl-β-enaminones **115**, which regioselectively condensed with methyl- and phenylhydrazines in a microwave-assisted reaction to afford target pyrazoles **116** (Scheme 35).

4-Alkoxycarbonylpyrazoles can be regioselectively obtained starting from α-alkyloxycarbonyl-β-enaminones. This procedure was applied to the synthesis of Zoniporide, a potent and selective inhibitor of the NHE-1 isoform of sodium−hydrogen exchangers, which contains an acylguanidine group at C4 of 5-cyclopropyl-1-(5-quinolinyl)pyrazole. The 4-ethoxycarbonylpyrazole precursor was prepared in 88% yield by condensation between the appropriate α-ethoxycarbonyl-β-enaminone and 5-quinolinylhydrazine hydrochloride at reflux in EtOH.[69]

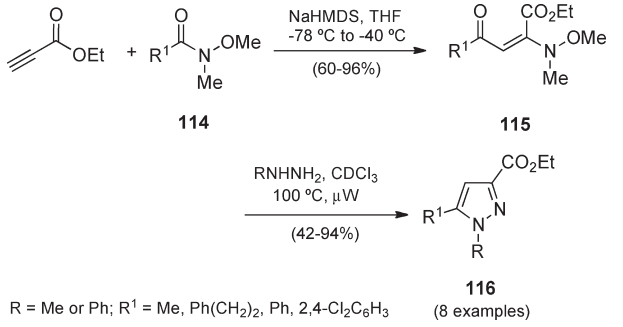
A small library of 1,5-substituted-4-pyrazole esters and amides **120** was prepared in solution through a three-step procedure starting from Meldrum's acid, which was initially acylated with acyl chlorides to give derivatives **117** (Scheme 36 and Table 3). These in turn underwent ring-opening with a variety of aliphatic, aromatic, and heterocyclic alcohols and amines to afford substituted β-keto esters (X = O) and β-keto amides (X = N) **118** (Table 3). Further reaction with DMFDMA yielded the desired precursors **119**. Subsequent condensation with monosubstituted hydrazines (Table 3) regioselectively afforded pyrazoles **120** with high purities and yields.[70] Scavenger resins were used in the first step, whereas the use of microwave irradiation allowed for complete conversion of the starting materials in the other two steps.

This approach was applied to the preparation of 1-substituted 5-[2-(acylamino)ethyl]pyrazole-4-carboxamides, pyrazole analogues of histamine, in a seven-step synthesis starting from *N*-Boc-β-alanine via an α-alkoxycarbonyl-β-enaminone as a precursor of 4-alkoxycarbonyl pyrazoles by condensation with a variety of monosubstituted hydrazines.[71]

An array of differently substituted pyrazole-4-carboxylates **124** was regioselectively obtained in good to excellent yields by condensation of α-ethoxycarbonyl-β-enaminones **123** with hydrazine and phenylhydrazine in the presence of a catalytic

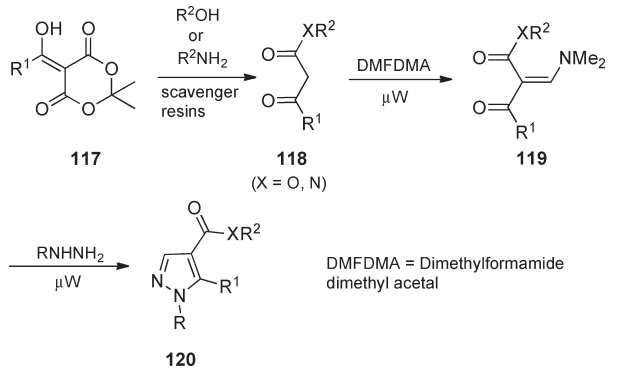
dx.doi.org/10.1021/cr2000459 |*Chem. Rev.* 2011, 111, 6984–7034

Scheme 35



114 **115** **116**

Scheme 36



117 **118** **119** **120**

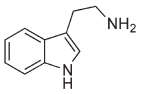
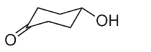
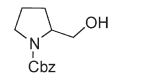
amount of *p*-TsOH.[72] Precursors **123** were previously prepared in 45−95% yield by chemoselective tandem acylation of Blaise reaction intermediates **122** obtained from readily available nitriles **121** (Scheme 37). A mechanism involving a regioselective Michael-type addition followed by dehydrative cyclization was proposed.

The condensation of previously prepared β-alkoxyvinyl trichloromethyl ketones **125** with hydrazine hydrochloride in EtOH, or phenylhydrazine in MeOH or EtOH, afforded 5(3)-alkoxycarbonylpyrazole derivatives **126** in good yields (Scheme 38).[73] The alkoxycarbonyl group was generated by alcoholysis of the trichloromethyl group.

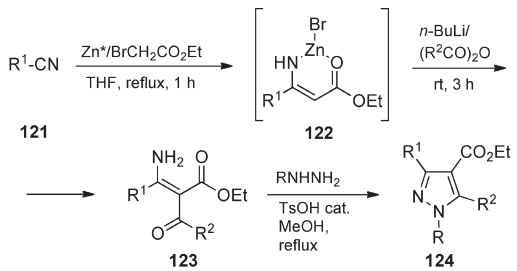
Martins and co-workers reported a straightforward and highly regioselective synthesis of 4-acylpyrazole-5-carboxylates **128** from unsymmetrical ethyl enaminodiketoesters **127**.[74] Observed regioselectivities were independent of the structure of the R^1 substituent present in the β-enaminodiketone (Scheme 39). The proposed mechanism would start with a Michael-type addition of the hydrazine followed by elimination of dimethylamine, affording the intermediate presenting the R^1CO group in a trans relationship to the bulky *tert*-butylhydrazino group. The subsequent heterocyclization of the *cis*-β-hydrazino unsaturated ketone would yield the products. When enaminodiketones **127** were reacted with carboxymethylhydrazine (R = CO_2Me) at room temperature, 1*H*-pyrazoles **128** (R^2 = H) were regioselectively obtained.

2.3.3. Thio-, Silyl-, and Halopyrazoles. These compounds are interesting building blocks in heterocyclic chemistry owing to the easy substitution of thio-, silyl-, and halo-groups by carbon or heteroatomic substituents. Thiopyrazoles have mainly been synthesized by reaction of α-oxoketene-*S*,*S*-acetals, as 1,3-bielectrophilic

Table 3. Substrates Used for Pyrazole Syntheses According to Scheme *36*

Acid chloride (R^1)	Alcohol	Amine	Hydrazine
Me	EtOH	$PhCH_2NH_2$	$PhNHNH_2$
Me_2CH	CH_2=$CHCH_2OH$	4-MeO-$C_6H_4CH_2NH_2$	4-$O_2NC_6H_4NHNH_2$
Me_2CHCH_2	CbzNHCH_2CH_2OH	$PhCH_2CH_2NH_2$	$H_2NCONHNH_2$
$PhCH_2CH_2$	Me_2CHOH	CH_2=$CHCH_2NH_2$	
Et(Ph)CH	$PhCH_2OH$		
	$PhCH_2CH_2Oh$		
	t-Bu-OCH_2MeCHOH		
			
			
			

Scheme 37



121 **122** **123** **124**

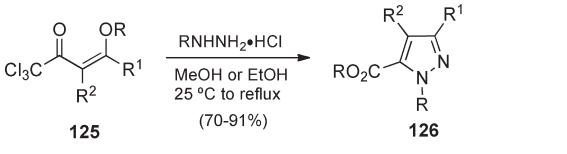
R^1	R^2	123 (%)	124 (%) R=H	124 (%) R=Ph	R^1	R^2	123 (%)	124 (%) R=H	124 (%) R=Ph
Ph	Me	82	85	91	Ph	4-$MeOC_6H_4$	89	95	--
Me	Ph	81	--	88	Ph	4-$F_3CC_6H_4$	84	--	83
Ph	*i*-Pr	45	96	--	4-$F_3CC_6H_4$	Ph	89	--	88
Ph	*sec*-Bu	94	90	87	Me	Et	82	--	91
sec-Bu	Ph	90	--	85	Et	Me	86	--	90
Ph	CF_3	81	70	71	Bn	Me	95	76	95
Ph	Ph	80	91	60					

synthons, with hydrazines.[75] This approach was applied to the synthesis of methylsulfanylimidazo-[4,5-*c*]pyrazoles **130** by piperidine-mediated condensation of the easily prepared 2-thiohydantoin ketene dithioacetals **129** with hydrazine or phenylhydrazine in refluxing ethanol (Scheme 40).[76]

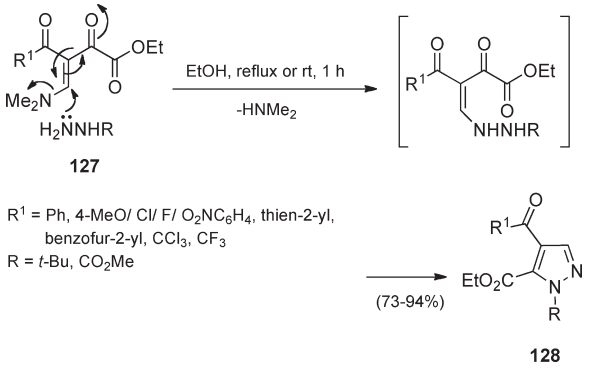
A highly regioselective synthesis of 1-aryl-3,4-substituted/annulated-5-(methylthio)pyrazoles **132** and 1-aryl-3-(methylthio)-4,5-substituted/annulated pyrazoles **135** via cyclocondensation of arylhydrazines with α-oxoketene dithioacetals **131** and β-oxodithioesters **134**, respectively, was reported by Ila, Junjappa, and co-workers (Scheme 41).[77] Both precursors **132** and **135** were easily accessible from active methylene ketones. Reactions of **131** with phenyl- and 4-fluorophenylhydrazine were conducted in the presence of potassium *tert*-butoxide in refluxing *tert*-butyl alcohol with elimination of methylmercaptan, whereas condensations of **134** with the same hydrazines occurred in refluxing ethanol with elimination of H_2S. Raney-Ni desulfurization regioselectively led to 1-aryl-3,4-substituted/annulated pyrazoles **133** and 1-aryl-4,5-substituted/annulated pyrazoles **136** in high yield. The 3- and 5-methylthio functionalities in compounds

dx.doi.org/10.1021/cr2000459 |*Chem. Rev.* 2011, 111, 6984–7034

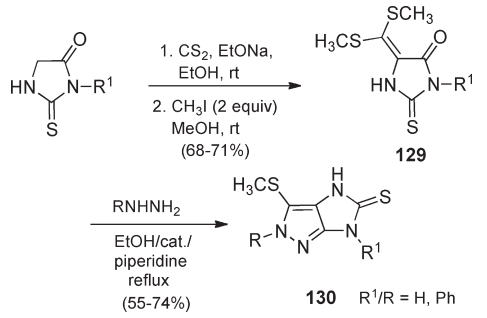
Scheme 38



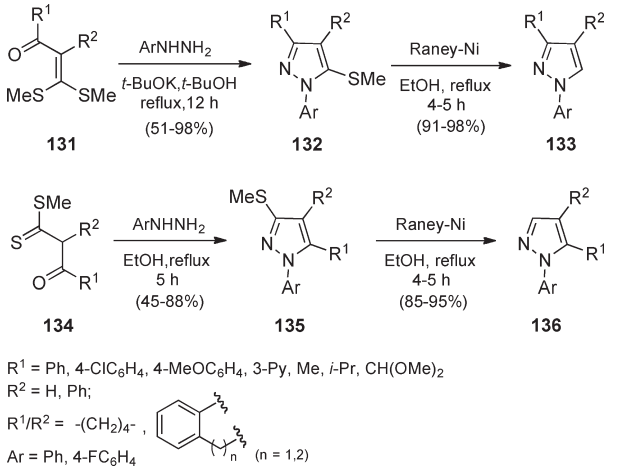
Scheme 39



Scheme 40



Scheme 41



132 and **135** were also further elaborated for the highly regioselective introduction of either 3/5-alkyl or aryl groups (see section 7).

Arylmethylsilanes are synthetic equivalents of silicon-stabilized carbanions offering broad synthetic opportunities. An approach to 3-/5-silyl and 3-/4-/5-silylmethylpirazoles involved the condensation of hydrazines with silyl β-enaminones **138**, previously prepared in excellent yields by catalytic hydrogenation of silyl and silylmethylisoxazoles **137** (Scheme 42).[78] Reactions were carried out in ethanol at room temperature or reflux. Acylsilane derivatives **138** (R^3 = Me_3Si, Me_2PhSi, Ph_2t-BuSi) reacted with methylhydrazine to give mixtures of 3- and 5-silylpyrazoles **139** and **140**. However, the reaction of these substrates with other hydrazines (R = Et, *t*-Bu, $CONH_2$, Ph) afforded only the corresponding 5-silylpyrazoles **139**. Similar results were obtained in the condensation of silyl β-enaminones **138** (R^3 = Me_3SiCH_2, $Me_2PhSiCH_2$, Ph_2t-$BuSiCH_2$) with the same hydrazines. Silylated β-aminoenone **138** (R^1 = R^3 = Me; R^2 = Me_3SiCH_2) also condensed regioselectively with phenylhydrazine and semicarbazide giving 4-trimethylsilylmethylpyrazoles. Finally, γ-silyl-β-enaminone **138** (R^1 = Ph_2t-$BuSiCH_2$; R^2 = H; R^3 = Ph) reacted with phenyl- and *tert*-butylhydrazine, giving rise to the corresponding 3-*tert*-butyldiphenylsilylmethylpyrazoles regioselectively in moderate yields.

The presence of a halogen substituent at the pyrazole ring offers considerable synthetic potential and diversity via substitution and coupling processes. However, methods to prepare halopyrazoles from accessible starting materials or in adequate yields are scarce.[79] An array of 3-alkyl/aryl-5-chloro/bromo-1-methylpyrazoles **144** was prepared in good yields by reaction of readily accessible β,β-dichloroenone **141** (X = Cl) and 1,1-dimethylhydrazine at room temperature (Scheme 43).[80] A variety of solvents such as hexane, benzene, lower alcohols, diethyl ether, or acetonitrile was used. A mechanism involving initial formation of a β,β-dichloroenone dimethylhydrazone **142** (X = Cl), followed by an intramolecular nucleophilic attack by the dimethylamino group on the β-carbon atom of the vinyl group, and subsequent demethylation of *N*,*N*-dimethylpyrazolium chloride **143** (X = Cl) thus formed was proposed. Interestingly, the byproduct 1,1,1-trimethylhydrazinium halide was insoluble in the organic solvent and could be separated by filtration. This procedure can be applied to large-scale production of pyrazoles **144**. As an extension of this approach, Taylor and co-workers employed β,β-dibromoenone **141** (X = Br) in condensation with methylhydrazine to prepare 5-bromo-1-methylpyrazole derivatives **144**. Synthons **141** were obtained in a one-pot procedure from aryl, heteroaryl, and aliphatic α-hydroxyketones by means of a tandem MnO_2-mediated oxidation−Ramírez olefination sequence using dibromethylphosphonium bromide.[81] Alternatively, compounds **141** were converted into 1-methyl-3,5-substituted pyrazoles in a one-pot, tandem condensation/Suzuki cross-coupling process (see section 7).

3. 1,3-DIPOLAR CYCLOADDITIONS

The 1,3-dipolar cycloaddition reaction has been employed as one of the most powerful synthetic tools to provide substituted pyrazoles.[82] Three main classes of 1,3-dipoles have been used as

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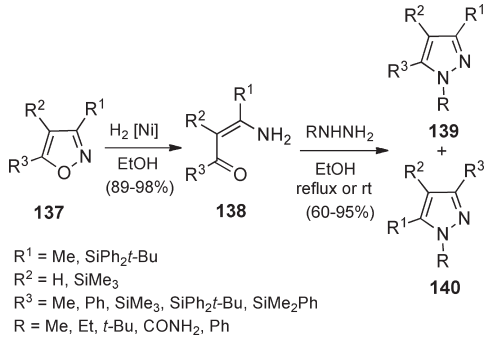
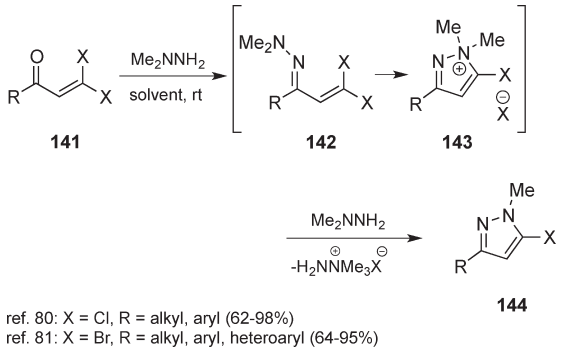
Scheme 42



Scheme 43



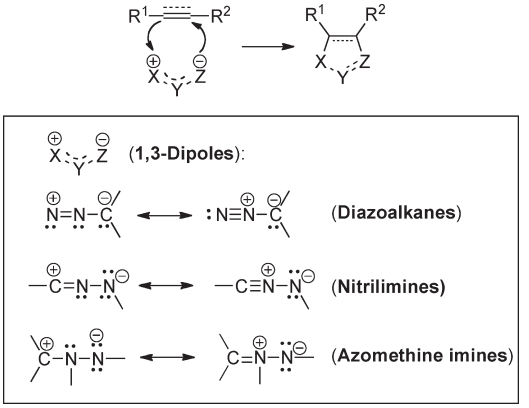
[*CNN*] syntons, namely, diazoalkanes, nitrilimines, and azomethine imines; the [*CC*] fragment would come from alkenes or alkynes (Scheme 44).[4a,b] Hydrazones have also been reported to undergo 1,3-dipolar cycloadditions with activated alkenes or alkynes to afford pyrazolidines or pyrazoles, respectively, probably proceeding via thermal or Lewis acid-promoted tautomerization of hydrazone−azomethine imines.[83]

Compared to the classical cylocondensation reaction between hydrazines and 1,3-diketones, in which the regioselectivity relies on the different reactivity of the two carbonyl groups, 1,3-dipolar cycloadditions are intrinsically more highly regioselective owing to the significant electronegative difference between the *N* and *C* atoms of the substrate.

3.1. Diazoalkanes as 1,3-Dipoles

The 1,3-dipolar cycloaddition of electron-rich diazo compounds with alkynes can be conducted efficiently under thermal conditions. However, diazo compounds are dangerous to prepare and handle because of their toxicity and potentially explosive nature. A method for generating aryldiazomethanes from stable tosylhydrazone derivatives has been developed to overcome these problems. Thus, an operationally convenient one-pot procedure for the preparation of 3(5)-arylpyrazoles **148** from aromatic aldehydes **145** has been reported (Scheme 45).[84] Diazo compounds **146**, generated in situ from tosylhydrazones, were reacted with *N*-vinylimidazole—an acetylene equivalent bearing a leaving group—affording pyrazoles **148**, generally in moderate yields. With phenyl and 3-pyridyl acetylenes as dipolarophiles, 3,5-substituted pyrazoles **148** were obtained with excellent 3,5/3,4 regioselectivity. This procedure

Scheme 44



was applied to the preparation of 3,4,5-substituted-1*H*-pyrazoles **148** and **149** by 1,3-dipolar cycloaddition of vinylidenecyclopropane (VDCP)-diesters **147**—synthetic equivalents of alkynes—with aromatic diazomethanes generated in situ from the corresponding aromatic aldehydes **145** and tosylhydrazine (Scheme 45).[85] Reactions of unsubstituted VDCP diesters (R^1 = H) with aryl diazomethanes led to mixtures of 3,5- and 3,4-substituted pyrazoles in a 2:1 ratio in high yields; however, when R^1 was an aryl group, only the 3,5-diaryl regioisomer was obtained.

Aoyama and co-workers[86] prepared di- and trisubstituted pyrazoles **152** via the [3 + 2]-cycloaddition reaction between 2-diazo-2-(trimethylsilyl)ethanol derivatives **151** and ethyl propiolate or dimethyl acetylenedicarboxylate (Scheme 46). This method allowed for the synthesis of polysubstituted pyrazoles from aldehydes and ketones as compounds **151** were prepared in nearly quantitative yields from aldehydes or ketones **150** by reaction with diazo(trimethylsilyl)methylmagnesium bromide.

1,3-Dipolar cycloadditions between diazocarbonyl compounds and alkynes usually require a Lewis acid to lower the energy of the lowest unoccupied molecular orbital (LUMO) of the dipolarophile and, thus, promote the reaction. In this context, Jiang and Li[87] reported the first intermolecular 1,3-dipolar cycloaddition reaction between acyclic and cyclic α-diazocarbonyl compounds **153** and alkynones or alkynoates **154** catalyzed by $InCl_3$ in water at room temperature. This methodology allowed for the synthesis of carbonyl or ethoxycarbonyl pyrazoles **155** (Scheme 47). The reaction proceeded by a domino 1,3-dipolar cycloaddition−hydrogen(alkyl or aryl) migration. However, the cycloaddition products from the reaction of methyl propiolate with both the *β*-hydroxy and *β*-amino α-diazocarbonyl compounds [R^1 = CH(OH)Ph, CH(NHTs)Ph] underwent a spontaneous retro-aldol reaction, affording the same 3,5-bis(alkoxycarbonyl)pyrazole as the one obtained in the reaction with ethyl diazoacetate (R^1 = H). Electron-rich acetylenes, e.g., phenylacetylene, failed to give the desired product. The use of water as solvent played a crucial role in the reaction outcome, as the reaction carried out in dichloromethane or toluene only led to traces of the target products. The catalyst, which remained in the aqueous phase after workup, could be reused in two additional runs without loss of catalytic activity.

This procedure was subsequently conducted under both catalyst- and solvent-free conditions.[88] Reactions were performed

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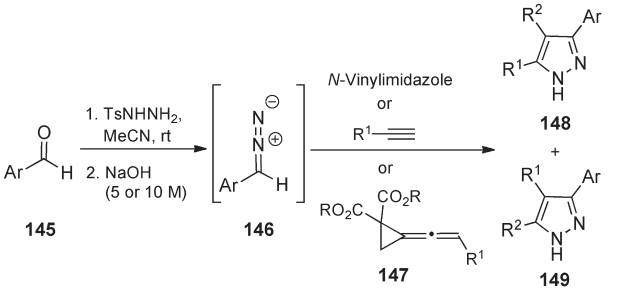
Scheme 45

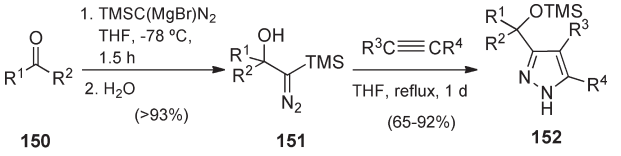


R^2 = H (ref. 84)
R^2 = 2,2-*bis*(alkoxycarbonyl)cyclopropyl; R = Me, Bn (ref. 85)

ref. 84			ref. 85		
Ar	R^1	Yield (%) (ratio 148:149)	Ar	R^1	Yield (%) (ratio 148:149)
Ph	H	56[a]	Ph	H	72 (2:1)
Ph	Ph	61 (99.8:0.2)	4-MeC_6H_4	H	80 (2:1)
Ph	3-Pyridyl	36 (97:3)	4-ClC_6H_4	H	82 (2:1)
2-MeC_6H_4	H	47[a]	Ph	Ph	80[a]
4-$MeOC_6H_4$	H	62[a]	Ph	4-MeC_6H_4	76[a]
4-$MeOC_6H_4$	Ph	51[a]	4-MeC_6H_4	Ph	85[a]
4-$MeOC_6H_4$	3-Pyridyl	54 (99.8:0.2)	Ph	4-ClC_6H_4	82[a]
4-NCC_6H_4	H	79	4-BrC_6H_4	Ph	88[a]
4-NCC_6H_4	Ph	67 (99.8:0.2)	3-$MeOC_6H_4$	Ph	79[a]
4-NCC_6H_4	3-Pyridyl	19 (99.8:0.2)	2-ClC_6H_4	Ph	85[a]
4-ClC_6H_4	H	71[a]	2,3-$Cl_2C_6H_3$	Ph	72[a]
2-Furyl	H	33[a]	3-Pyridyl	Ph	81[a]
2-Thienyl	H	32[a]	Ph	Bn	10[a]
3-Pyridyl	H	32[a]			
3-Pyridyl	Ph	33 (97:3)			
3-Pyridyl	3-Pyridyl	24 (95:5)			

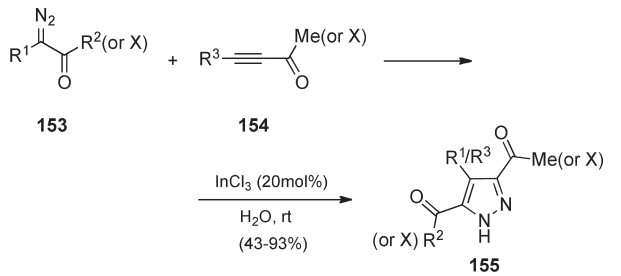
[a] Only **148**

Scheme 46



R^1 = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, $PhCH_2CH_2$, *t*-Bu
R^2 = H, Me
R^3 = R^4 = CO_2Me; R^3 = H, R^4 = CO_2Et

Scheme 47



R^1 = H, Me, CH(OH)C_6H_4, CH(NHTs)C_6H_4, Ph, 3/4-$MeOC_6H_4$, 4-FC_6H_4, 3-Br/ $CF_3C_6H_4$
R^2 = Me, Et
X = OMe, OEt
R^3 = H, CO_2Et

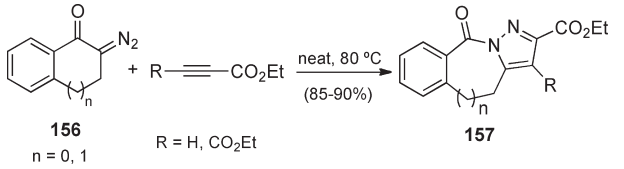
with 1.1 equiv of the most volatile reagent, i.e., diazocompound or alkyne, at 80 °C. After evaporation of the reagent in excess, pyrazoles were obtained in excellent purities and yields in most cases. Under these conditions, the poorly reactive trimethylsilylacetylene and phenylacetylene reacted readily with ethyl diazoacetate in high yields (90 and 93%, respectively). In addition, trimethylsilyldiazomethane, a stable analogue of diazomethane, reacted with ethyl propiolate, diethyl acetylene dicarboxylate, and phenylacetylene, leading to 3(5)-phenylpyrazole in good yield. Moreover, cyclic compounds **156**, derived from 1-indanone and α-tetralone, reacted with ethyl propiolate and diethyl acetylene dicarboxylate, leading to tricylic condensed pyrazole derivatives **157** in high yield (Scheme 48). It is noteworthy that in this reaction a ring expansion took place. In addition, this protocol was proven efficient on a multigram scale.

The scope of this reaction was extended to a wide range of alkynes. Thus, a variety of 3,5-disubstituted pyrazoles **160** were synthesized by cycloaddition of diazocarbonyl compounds **159** with in situ generated copper acetylides from alkynes **158** (Scheme 49; method I). This constitutes an example of a dipolar cycloaddition reaction with inverse electron demand.[89] Both electron-poor and electron-rich arylacetylenes and alkyl-substituted terminal alkynes performed well in the reaction. The formation of copper acetylide was proposed to narrow the energy gap between the highest occupied molecular orbital (HOMO) of the alkyne and the LUMO of the diazo compound. This 1,3-cycloaddition reaction was also promoted by $Zn(OTf)_2$ solventless at 100 °C.[90] Aryl alkynes performed significantly better than alkyl alkynes (Scheme 49; method II).

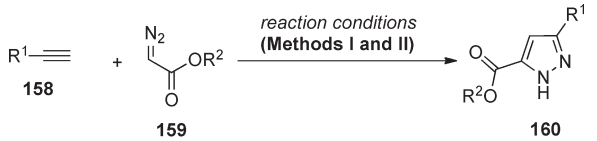
Xie et al.[91] employed electron-poor α-carbethoxy-1-nitrostyrenes **161** as dipolarophiles in the regioselective synthesis of 3,4,5-substituted 1*H*-pyrazoles **163** by means of a catalysis-free one-pot tandem reaction with ethyl diazoacetate (Scheme 50). Reactions were carried out at room temperature with spontaneous elimination of the nitro group. Electron-withdrawing substituents on the aryl ring led to better yields than electron-donating ones. Starting from 3-nitrocoumarines **162**, the reaction with ethyl diazoacetate led to cycloadducts **164** in 71−91% yield. Nitrostyrenes bearing a better leaving group than the nitro group, e.g., an α-bromine atom, afforded nitropyrazole derivatives in moderate yields. However, simple nitroolefins exhibited low reactivity with ethyl diazoacetate in the same reaction conditions. Similar 1,3-dipolar cycloaddition of the anion of diethyl 1-diazomethylphosphonate **166** with conjugated (het)arylnitroalkenes **161** (R^2 = H) provided regioisomerically pure phosphonylpyrazoles **167** in moderate to good yield (Scheme 50).[92] 1,3-Dipole **166** was generated in situ from 1-diazo-2-oxopropylphosphonate (Bestman-Ohira reagent, BOR) **165**. Reactions were carried out in the presence of a nucleophilic base (NaOEt) in a protic solvent (EtOH) at room temperature, with the base-mediated acyl cleavage of BOR taking place prior to cycloaddition with nitroalkene **161** (Scheme 50). Pyrazoles **167** were formed in one pot via spontaneous elimination of the nitro group. However, nitropyrazoles were obtained starting from α-bromonitroalkenes

dx.doi.org/10.1021/cr2000459 |*Chem. Rev.* 2011, 111, 6984–7034

Scheme 48



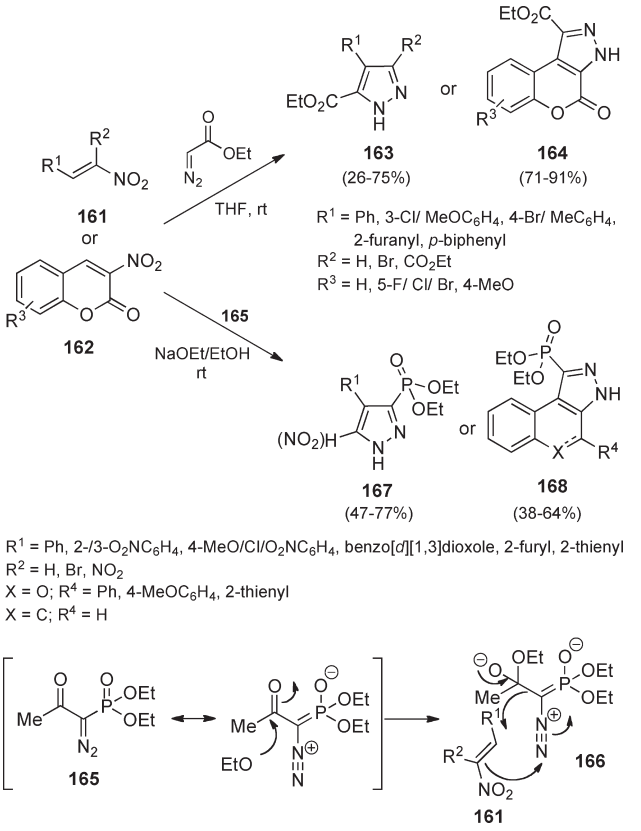
Scheme 49



Method I				Method II	
R^1	R^2 Yield (%)			R^1	R^2 = Et Yield (%)
	Bn	*t*-Bu	Et		
Ph	80	65	74	Me_3Si	53
4-MeC_6H_4	72	70	66	$EtCH_2$	45
3-FC_6H_4	85	78	78	$Et(CH_2)_3$	47
3,5-$(CF_3)C_6H_4$	75	85	82	$EtOCH_2$	44
$NC(CH_2)_3$	73	69	64	$AllylOCH_2$	28
2-(6-MeO)Naphtyl	81	--	--	$PhCOOCH_2$	48
4-(*N*-Morpholyn)$(CH_2)_4$	76	--	--	$HO(Me)_2C$	31
3-$Cl(CH_2)_3$	74	--	--	Ph	89
4-$BnO(CH_2)_4$	51	--	--	4-MeC_6H_4	71
c-Hex	64	--	--	4-BrC_6H_4	89
c-$PentCH_2$	61	--	--	4-$O_2NC_6H_4$	81
n-Bu	60	--	--	2-Ethynylpyridyl	87
Bn	76	--	--		
$Ph(CH_2)_3$	73	--	--		
EtO_2C	62	--	--		

Method I: 1. *n*-BuLi, THF, -78 ºC; CuCN.6LiCl, -17 ºC, THF. 2. **159**, rt, 2-4 h.
Method II: $Zn(OTf)_2$, NEt_3, 100 ºC, 8 h.

Scheme 50



(R^2 = Br). The same strategy was employed for the synthesis of various fused phosphonylpyrazoles **168**.

Recently, Maguire and co-workers [93] have reported a systematic study on the dipolarophilic behavior of β-chloroacrylamides **169** at sulfide and sulfoxide oxidation levels toward diazoethane, diazomethane, trimethylsilyldiazomethane, and phenyldiazomethane (Scheme 51). In all instances, the cycloaddition reactions proceeded in a highly regioselective manner, with the carbon terminus of the diazoalkane adding to the β-carbon of the β-chloroacrylamide. The isolated products—pyrazolines **170** and **172**, desulfinated pyrazoles **171**, and rearranged pyrazoles **173**—were dependent on the dipole, the level of oxidation and the nature of the substitution at the sulfur center, and the nature of the amide group of the β-chloroacrylamide. The formation of either pyrazoles **171** or rearranged pyrazoles **173** was rationalized through the initial formation of pyrazoline cycloadducts **170** and **172**, respectively, followed either by elimination of PhSOCl or by loss of chloride with generation of a sulfur-stabilized carbocation and subsequent trimethylsilyl migration (or hydride shift) in the sulfonium ion intermediate.

Pyrazoline cycloadducts **170** and **172** (R^2 = Me) derived from the diazoethane cycloadditions were the most stable ones, and the pyrazoles **171** were only isolated from the cycloadditions with the benzenesulfinyl-β-chloroacrylamides (Scheme 52); no rearranged pyrazoles **173** were observed. Cycloadditions with diazomethane and phenyldiazomethane led to less stable pyrazolines **170** and **172** (R^2 = H, Ph), and therefore pyrazoles **171** and **173** were formed. When trimethylsilyldiazomethane was employed as the dipole, the pyrazoline cycloadduct was not isolated in any case, with elimination of the sulfoxide group observed for the sulfinyl derivatives **171** (R^2 = H) and migration of the sulfur group observed for thio derivatives **173** (Scheme 52).

Methods for preparing 4-trifluoromethylpyrazoles from acyclic precursors are very scarce. 4-Trifluoromethyl-5-substituted pyrazoles **176** (Scheme 53) were efficiently and regioselectively obtained by in situ addition of diazomethane to unpurified tributyl(3,3,3-trifluoro-1-propynyl)stannane **174**, followed by functionalization at the C-5 of 3(5)-tributylstannyl-4-trifluoromethylpyrazole **175** by coupling with a variety of reagents (see section 7).[94]

Similar procedures have been developed for preparing 4-fluoropyrazole derivatives **179** (see section 7) from 5-tribuylstannyl-4-fluoropyrazole (X = Bu_3Sn) and 4-fluoro-5-trimethylsilylpyrazole (X = Me_3Si) **178**.[95] Precursors **178** were obtained as the only products through a 1,3-dipolar cycloaddition of diazomethane and in situ prepared fluoro(tributylstannyl/trimethylsilyl)acetylenes **177** (Scheme 54). Treatment of either tributylstannylpyrazole **178** (X = Bu_3Sn) with *n*-BuLi in THF at −78 °C followed by acid hydrolysis or trimethylsilylpyrazole (X = Me_3Si) with tetrabutylammonium fluoride (TBAF) afforded 4-fluoropyrazole **179** (R = H) in 68 and 84% yield, respectively; whereas the reaction of **178** (X = Bu_3Sn) with iodine in THF at room temperature led to 4-fluoro-3/5-iodopyrazole **179** (R = I) in 95% yield.

3.2. Nitrilimines as 1,3-Dipoles

Nitrilimines are in situ generated by treatment of hydrazonoyl halides with a base. The 1,3-dipolar cycloaddition of nitrile imines to alkenes has been employed for the synthesis of

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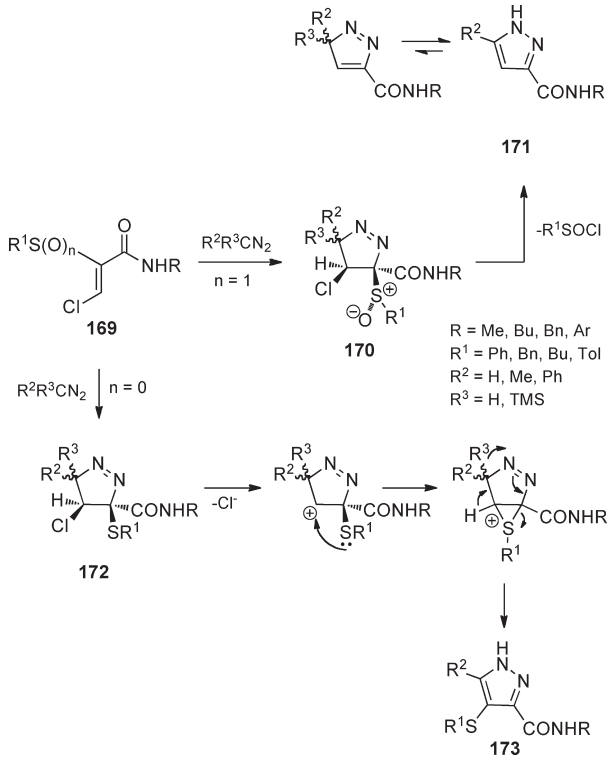
substituted pyrazoles in solution for several decades.[96] This approach has been applied to the regioselective synthesis of selective inhibitors of COX-2 as celecoxib, as well as the cannabinoid type-1 rimonabant.[97]

On solid phase, the cycloaddition reaction between nitrile imines **181** and resin-bound piperazine enamines of arylacetaldehydes **180** leads to pyrazoline intermediates **182**, which can be directly cleaved from the resin under mild acidic conditions to afford 1,4-diarylpyrazole-3-carboxylates **183** regioselectively, in good yield and in high purity (Scheme 55).[98] Resin-bound enamines of aliphatic aldehydes such as hexanal and (*R*)-(+)-citronellal also led to the respective 4-alkyl-1-arylpyrazole adducts but in low yield.

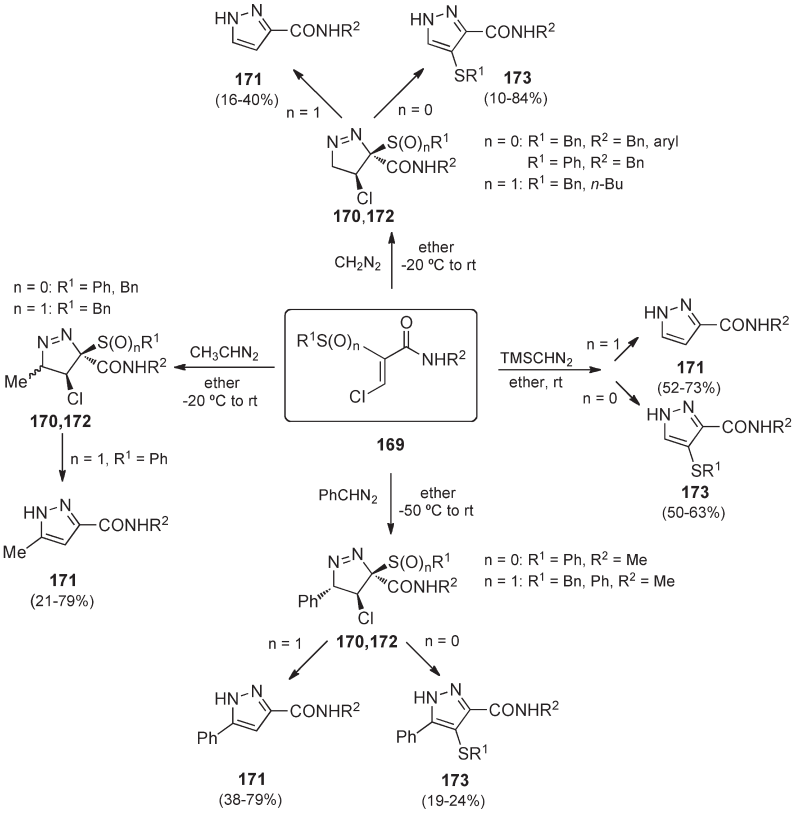
Polymer-supported vinylsulfones **184** have also been employed as dipolarophiles in the regioselective 1,3-cycloaddition reaction with nitrile imines **185** for the synthesis of a library of 1,3-diarylpyrazole derivatives **187**/**188** via elimination of the *p*-toluensulfonyl group with 1,8-diazabicycle[5.4.0]undec-7-ene (DBU) in the pyrazoline intermediates **186** (Scheme 56).[99]

However, pyrazoles can be directly obtained when reactions are performed with dipolarophiles bearing a group prone to an in situ elimination under the cycloaddition reaction conditions.[100] This was observed in the 1,3-cycloaddition reaction of hydrazonyl bromides **189** with active methylene compounds **191** and **194** affording 1,3,4,5-substituted pyrazoles **193** and **196**, respectively, in moderate to good yields (Scheme 57).[101] Reactions of compounds **191** dibenzoylmethane (R^1 = Ph, R^2 = COPh), acetylacetone (R^1 = Me, R^2 = COMe), ethyl acetoacetate (R^1 = Me, R^2 = CO_2Et), phenacyl cyanide (R^1 = Ph, R^2 = CN), and acetoacetanilide (R^1 = Me, R^2 = CONHPh) took place by the addition of nitrile imine **190** generated from hydrazonyl bromide **189** to the enol tautomer of the active methylene compound **191**, followed by loss of one water molecule from

Scheme 51



Scheme 52



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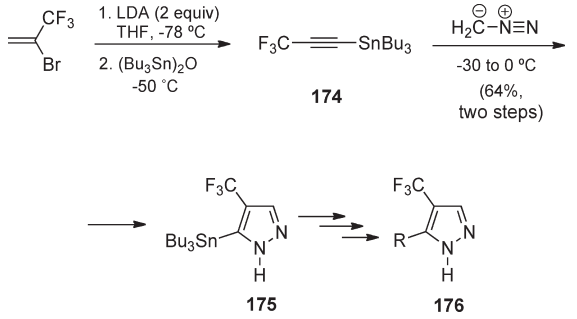
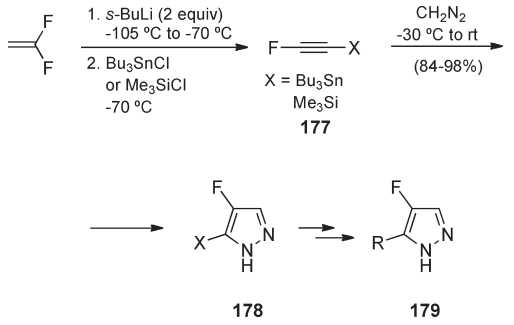
Scheme 53



Scheme 54



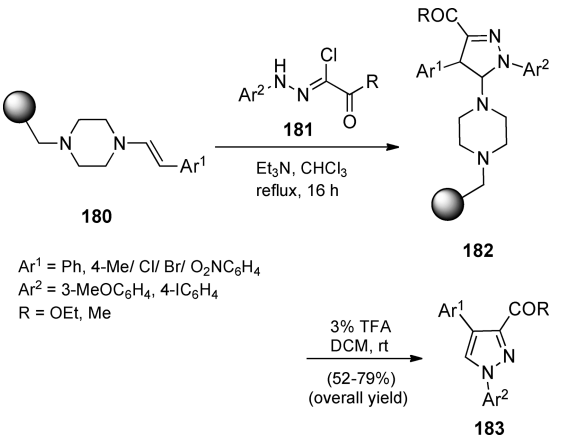
the 5-hydroxypyrazoline intermediate **192**. Reactions with ethyl cyanoacetate (R^3 = OEt) and cyanoacetamide (R^3 = NH_2) **194** occurred through imine tautomer **195**, affording 5-aminopyrazole derivatives **196**.

Tetrasubstituted pyrazoles **198** were also obtained in high yield through the regioselective 1,3-dipolar cycloaddition of α-bromocinnamaldehyde to *C*-aryl-*N*-phenyl nitrile imines **197** at room temperature (Scheme 58).[102]

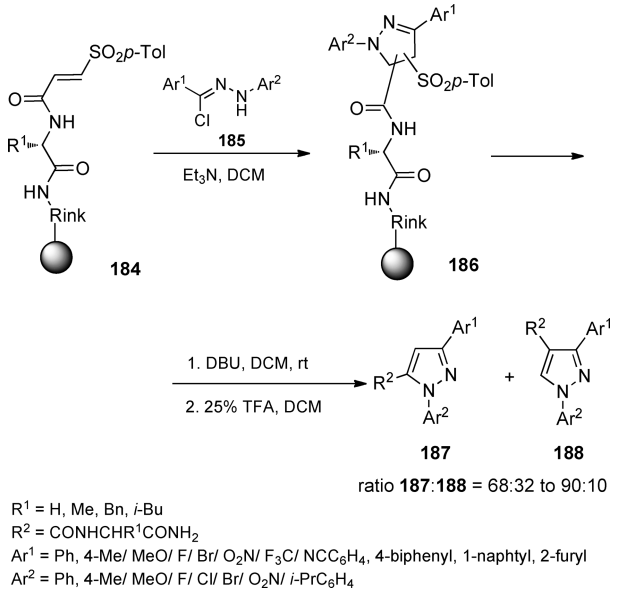
Cycloaddition reactions between nitrile imines and alkyne derivatives have been studied to a lesser extent. Mixtures of 4- and 5-substituted pyrazoles are usually obtained. Recently, a study on the regioselectivity of the 1,3-dipolar cycloaddition of *C*-carboxymethyl-*N*-aryl- and *C*-aryl-*N*-arylnitrile imines **199** and **200**, respectively, with benzyl propiolate and *N*-phenylpropiolamide under both uncatalyzed and $Sc(OTf)_3$-catalyzed conditions has been reported (Scheme 59).[103] Although regioisomeric mixtures were obtained in all cases, the results allowed concluding that *N*-phenylpropiolamide was a better substrate than benzyl propiolate for the preparation of 5-substituted pyrazoles **201** under uncatalyzed reaction conditions. On the other hand, reactions of **199** under $Sc(OTf)_3$-catalyzed conditions afforded 4-substituted regioisomers **202** as the major products with both alkyne derivatives.

The carboxylate group has been replaced by a phosphonate moiety in the preparation of several pharmacologically active compounds.[104] *N*-Phenyl-5-substituted-3-dimethoxyphosphonopyrazoles **206**, which have been investigated as possible *N*-methyl D-aspartate (NMDA) antagonists, were obtained with high regioselectivity but in low yields by a 1,3-dipolar cycloaddition of nitrile imine **204** to monosubstituted alkynes **205**.[104] Compound **204** was generated in situ by reacting hydrazonoyl bromide **203** with sodium bicarbonate (Scheme 60).

Scheme 55



Scheme 56



Cycloadditions of **204** to alkenes **208** regioselectively led to 5-substituted pyrazoline derivatives **209**, which were converted into pyrazoles in high yields by oxidation with 15-fold excess of pyridinium dichromate (PDC) in DMF at room temperature. The phosphonic ester group in pyrazoles and pyrazolines was quantitatively further transformed into the corresponding phosphonic acid group by treatment with a 10-fold excess of trimethylsilyl bromide. The observed regioselectivity was explained on the basis of the Frontier orbital theory, where the dominant interaction involves the LUMO of the 1,3-dipole and the HOMO of the dipolarophile.

3.3. Sydnones as Azomethine Imine-type 1,3-Dipoles

Sydnones are relatively stable mesoionic compounds that can react as azomethine imine-type dipoles. They can be readily obtained by cyclodehydration of *N*-substituted-*N*-nitrosoamino acids with reagents such as acetic anhydride. These compounds undergo a 1,3-dipolar cycloaddition with electron-deficient acetylenes, giving rise to pyrazoles by carbon dioxide extrusion.[105]

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Preliminary studies in this area by using unsymmetrically substituted alkynyl esters revealed that those reactions proceeded in moderate yields and with low levels of regiocontrol (e.g., cycloadditions of methyl propiolate to 3,4-disubstituted sydnones led to ~3:1 mixtures of 3- and 5-carbomethoxypyrazoles). This selectivity was improved up to 6.56:1 in the condensation of methyl propiolate with 3-phenylsydnone by using near- or supercritical carbon dioxide as solvent.[106] In addition, the cycloaddition of *N*-(4-ethoxyphenyl)-4-cyanosydnone **211** to ethyl propiolate **212** (R = Et) led to mixtures of 3- and 4-ethoxycarbonyl-5-substituted pyrazoles **213** and **214** in good yield and variable regiocontrol.[107] The regioisomeric ratio was significantly improved with the size of the ester substituent since only the 3,5-disubstituted regioisomer **213** was detected in the reaction of **211** with diphenylmethyl propiolate **212** (R = $CHPh_2$) (Scheme 61). This approach was applied to the synthesis of dihydroorotate dehydrogenase (DHODase) inhibitors.[107]

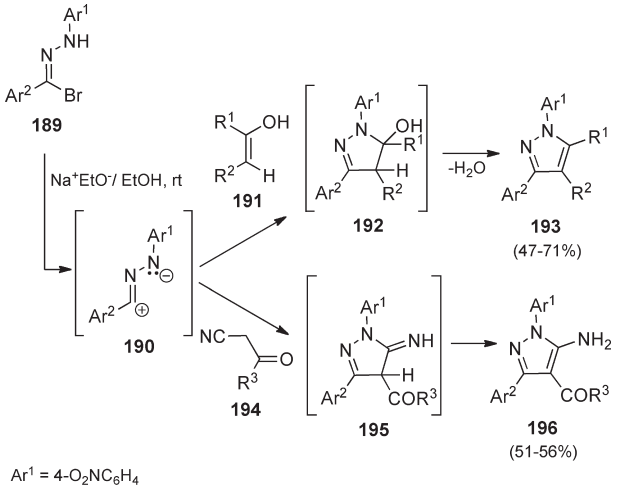
Previously prepared polymer-bound sydnones **215** were reacted with alkyl propiolates and dimethyl acetylenedicarboxylate (DMAD), under microwave irradiation in the presence of acetic anhydride as dehydrating agent. The resulting polymer-bound pyrazoles **216** were cleaved from the resin under mild conditions, affording *N*-unsubstituted 5-alkylpyrazole-3,4-dicarboxylates **217** or inseparable mixtures of 3- and 4-carboxylic acid derivatives **218** and **219**, with the former being the major regioisomer (Scheme 62).[108]

Highly functionalized unsymmetrical α,β-acetylenic phenones bearing a 5-nitrofurane unit **221** (X = O) were employed as dipolarophiles in 1,3-dipolar cycloadditions with *N*-arylsydnones **220** for the regioselective preparation of a series of 1-aryl-3-(5-nitro-2-furyl)-4-aroylpyrazoles **222** in high yields (Scheme 63).[109] Similar results were obtained when replacing the furan ring by thiophene. The resulting pyrazoles were further tested for their antibacterial and antifungal activities.[110]

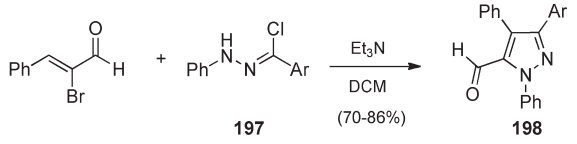
Harrity and co-workers[111] have investigated the use of alkynylboronates **224** as dipolarophiles in regiocontrolled cycloaddition reactions with sydnones **223** as a direct method of accessing pyrazole boronic esters, further employed in cross-coupling reactions (Scheme 64a). Results indicated that 4-unsubstituted sydnones **223** (R^2 = H) underwent a highly regioselective cycloaddition with phenyl-substituted and terminal alkynylboronates **224** (R^3 = Ph, H), whereas variable selectivities were observed when using alkynylboronates **224** bearing alkyl or silyl substituents (R^3 = Bu, Me_3Si). In contrast, with 4-substituted sydnones **223** (R^2 = Me, *i*-Pr, Ph), excellent levels of regiocontrol were observed in all cases. The selectivity was largely independent of the sydnone *N*-substituent. This methodology was applied to the regioselective synthesis of all three Withasomnine natural products (Scheme 64b).[112]

The variety of R^2 substituents at the C-4 position of sydnone was extended by means of Pd-catalyzed cross-coupling reactions of the readily obtained *N*-phenyl-4-bromosydnone **225**

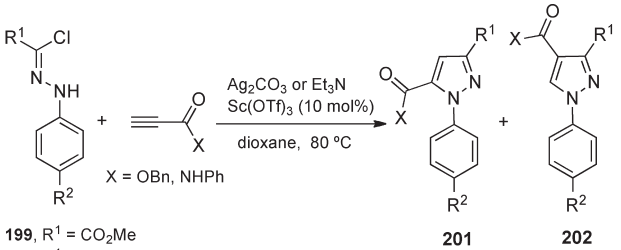
Scheme 57



Scheme 58



Scheme 59



Nitrile imine	Yield (%)[a] (201:202) ---	Yield (%)[a] (201:202) $Sc(OTf)_3$	Yield (%)[b] (201:202) ---	Yield (%)[b] (201:202) $Sc(OTf)_3$
199a	61 (3:1)	90 (1:4)	66 (4:1)	94 (1:9)
199b	58 (1:1)	88 (1:4)	63 (3:1)	89 (1:1.5)
199c	84 (1:1)	92 (1:9)	90 (7:1)	95 (1:2)
200a	76 (2:1)	70 (1:1)	56 (3:1)	60 (2:1)
200b	63 (5:1)	65 (1.5:1)	71 (2:1)	68 (1:1)
200c	65 (1:1)	61 (3:1)	60 (3:1)	58 (3:1)

[a] With benzyl propiolate. [b] With *N*-phenylpropiolamide. [c] No catalyst

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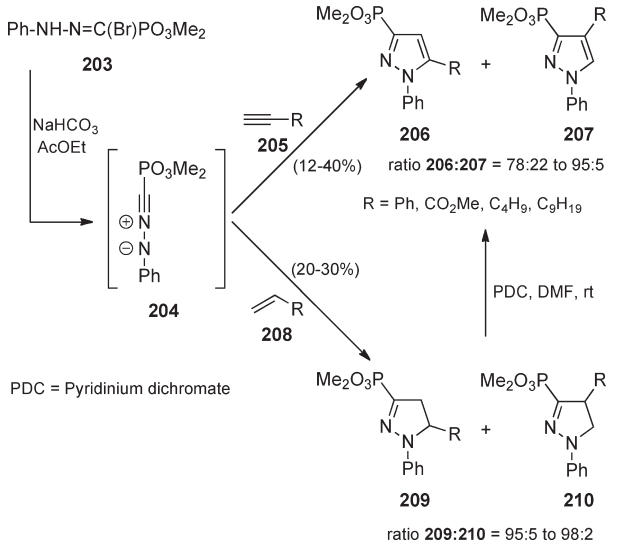
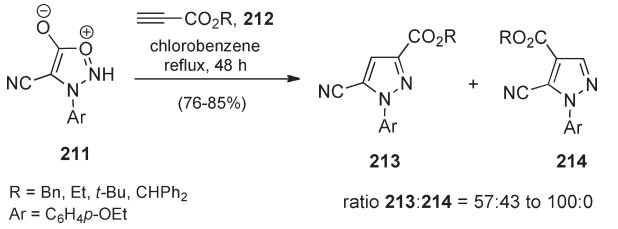
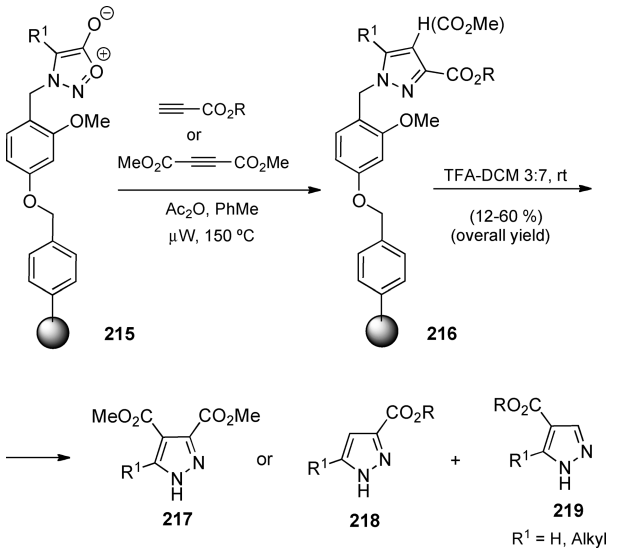
Scheme 60



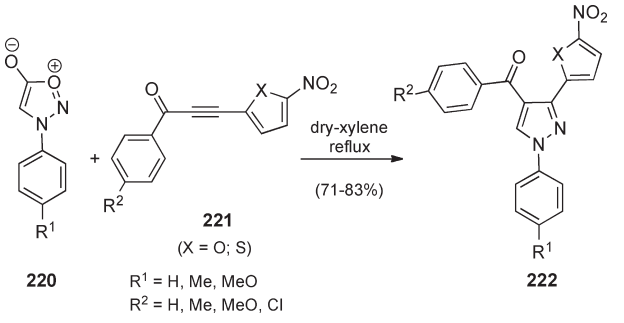
Scheme 61



Scheme 62



Scheme 63



with styryl- and (het)aryl boronic acid derivatives **226** under microwave irradiation (Scheme 65).[113] Subsequent cycloaddition of *N*,4-diphenylsydnone **227** (R^1 = Ph) to terminal alkynes **228** led to trisubstituted pyrazoles **229** in moderate to very good yields.

More recently, the same authors prepared a variety of 5-iodo-1-(*p*-nitrophenyl)-3-substituted pyrazoles **232** in good yields by cycloaddition of nonactivated terminal alkynes **231** and PNP-protected sydnones **230** bearing an iodine atom at the C-4 position (Scheme 66).[114] The resulting 5-iodo pyrazoles **232** (R = TMS, cyclopropyl, phenyl) were then coupled with a variety of arylboronic acids (see section 7) to afford the corresponding 1,3,5-substituted pyrazoles in very good yields. Alternatively, the iodine atom of pyrazoles **232** was replaced with other substituents via lithium−iodine exchange and subsequent in situ reaction with different electrophiles, thus affording functionalized pyrazoles **233** in good yields (Scheme 66a). Remarkably, an amine group could be introduced at the 5-position through a sequence involving the formation of pyrazolyl-5-boronic ester **233** (E = BPin), followed by copper-catalyzed azidation and subsequent reduction of the azide group (Scheme 66b).

A novel strategy for the synthesis of 3,5-bis(het)aryl pyrazoles **239** based on the introduction of distinguishable halides (Br and I) at the C-3 and C-5 positions of *N*-substituted pyrazoles has recently been reported by Monteiro, Balme, and co-workers (Scheme 67).[115] Reaction of 4-methoxyphenyl(PMP)-protected 4-iodosydnone **235** with ethyl bromopropiolate in refluxing xylenes led to a 3:1 mixture of 3-bromo-5-iodo- and 4-bromo-5-iodopyrazole carboxylates **236** and **237**, respectively, which were easily separated. Decarboxylation of major isomer **236** by treatment with 50% aqueous sulfuric acid at reflux afforded *N*-PMP-3-bromo-5-iodopyrazole **238**, which was selectively coupled with a variety of (het)arylboronic acids to give pyrazoles **239** (see section 7).

Silyl- and stannylacetylenes **241** were employed as an alternative to alkynylboronates in cycloaddition reactions with *N*-phenylsydnone **240** for the regioselective synthesis of *N*-phenyl-3-silylpyrazoles **242** (Scheme 68).[116] In general, excellent levels of regiocontrol were observed except when R^1 was a silyl or an acetyl group. In these cases selectivities dropped to 2:1 and 5:1, respectively.

4. INTRAMOLECULAR NITROGEN ADDITION TO ALKYNES

Metal-activated alkynes can undergo 5-exo-/endo-dig cyclizations by intramolecular nucleophilic addition of nitrogen derivatives leading to pyrazoles. A general and efficient methodology to access 3(5)-, 3,5-, and 3,4,5-substituted pyrazoles **247** was reported by Buchwald and co-workers.[117] The target

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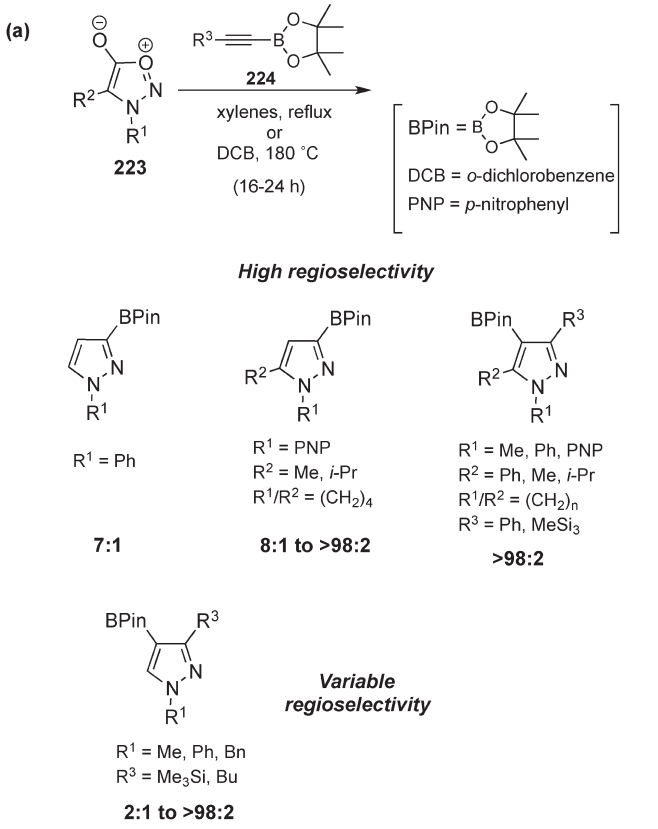
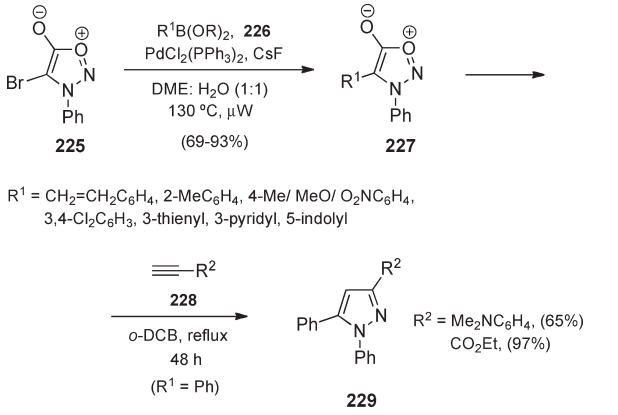
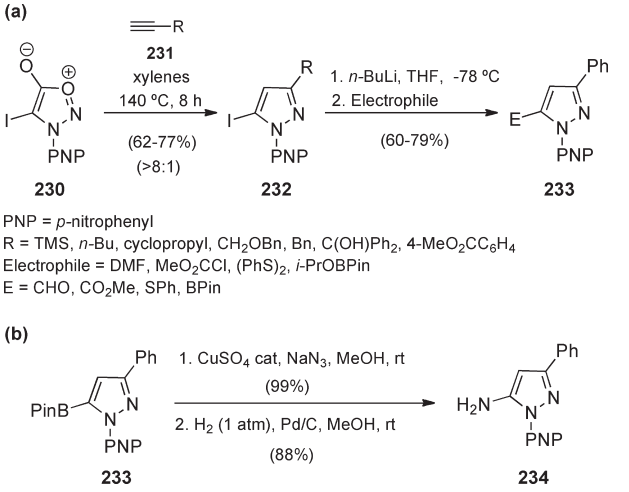
Scheme 64



Scheme 65



Scheme 66



compounds were exclusively obtained in good to excellent overall yields through a copper-catalyzed domino amidation of haloenynes **244** followed by 5-exo-dig hydroamination of the in situ formed alkyne **245** to give intermediates **246** (Scheme 69). Bis(Boc)hydrazine was used as nucleophile, and the Boc protecting groups were finally removed by treatment with trifluoroacetic acid. This methodology is highly flexible, and many functional groups, such as alkyl halides, esters, benzyl ethers, and even silyl ethers, are tolerated despite the final acidic treatment. The transformation constitutes a straightforward alternative to the existing methodologies for the preparation of pyrazoles.

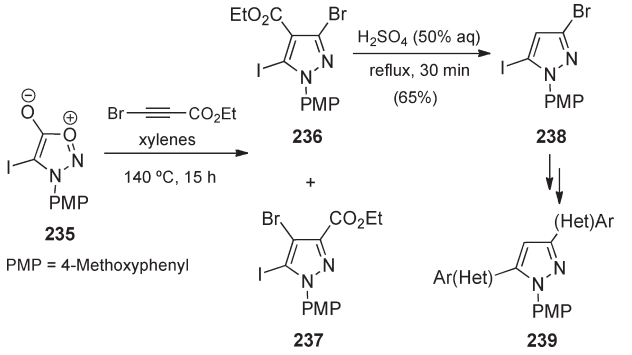
A silver nitrate-catalyzed highly regioselective 5-endo-dig cyclization of alkynyl nitrosamines **248** at room temperature was reported by Hayes et al.[118] Intermediate pyrazole derivatives **249** were obtained in essentially quantitative yields, and two of them were deoxygenated by treatment with PCl_3 in refluxing chloroform, affording 1,3,5-substituted pyrazoles **250** in excellent yields (Scheme 70). A mechanism involving a nucleophilic attack by the nitroso nitrogen on the alkyne−silver complex, followed by a hydride shift, was proposed.

Propargyl *N*-sulfonylhydrazones **251** were also used in the regioselective silver(I)-catalyzed synthesis of 1,3- and 1,5-substituted pyrazoles **252**.[119] Reactions were performed at room temperature in dry dichloromethane in the presence of 5 mol % of $AgSbF_6$ (Scheme 71). *N*-Monosubstituted pyrazoles **252** ($R^1 = R^2 = H$) were obtained in high yield from a variety of aryl, alkenyl, and styryl hydrazones. The introduction of a methyl group at the propargylic position in the styryl hydrazone **251** (R^1 = Me, R^3 = PhCH=CH_2) slightly decreased the yield of the reaction. Moreover, a 1,3,5-substituted pyrazole **252** was obtained in acceptable yield starting from 4-methoxystyryl hydrazone **251** (R^1 = Me, R^2 = Ph, R^3 = 4-$MeOC_6H_4$-CH=CH). The process involved an intermolecular migration of the sulfonyl group through the formation of a tosyl anion and an electron-deficient pyrazolyl iminium cation as an ion pair.

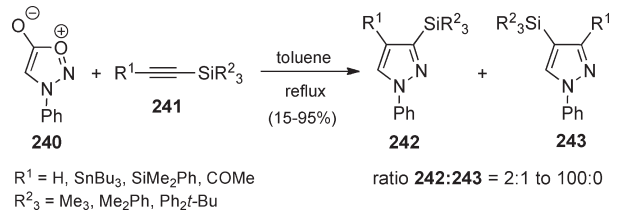
Recently, Wada and co-workers[120] have reported the regioselective synthesis of 5-alkyl/(het)aryl-4-iodopyrazoles **254** by a iodocyclization reaction of easily prepared propargylic hydrazides **253**. The best results were obtained when using *N*-iodosuccinimide (NIS) as the iodinating reagent,

dx.doi.org/10.1021/cr2000459 |*Chem. Rev.* 2011, 111, 6984–7034

Scheme 67



Scheme 68



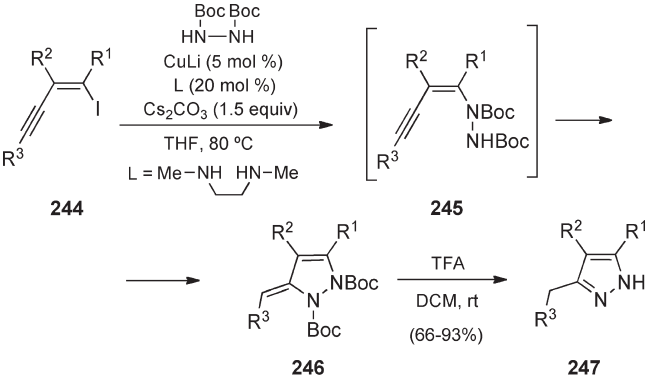
$BF_3 \cdot OEt_2$ as Lewis acid, and *N,N′*-isopropyloxycarbonyl hydrazides in dichloromethane at 0 °C (Scheme 72). Propargylic hydrazides bearing aryl and heteroaryl substituents, except for *p*-nitrophenyl, afforded pyrazoles in higher yields than the corresponding vinyl and alkyl derivatives. The iodine atom could be further substituted in cross-coupling reactions (see section 7). The mechanism proposed by the authors involved an electrophilic addition of I^+ to the alkyne, leading to a iodonium ion that would undergo a 5-endo cyclization to give a dihydropyrazole. Subsequent iodination followed by intramolecular ring-opening of the iodonium ion and elimination of HI would lead to a pyrazolium ion, which would be hydrolyzed at the less-hindered carbamate group, finally affording pyrazole **254** (Scheme 72).

5. MULTICOMPONENT REACTIONS IN SOLUTION

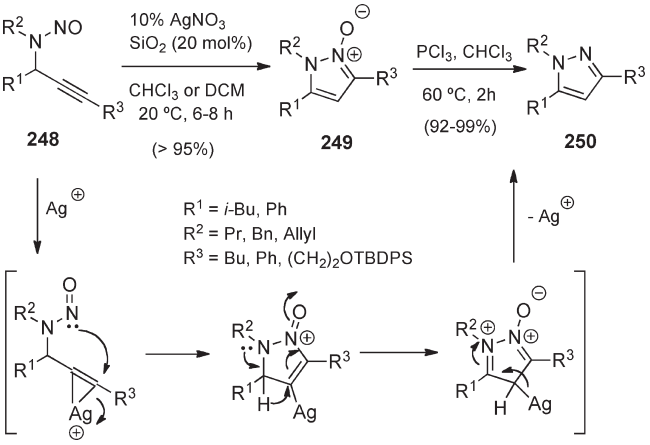
Multicomponent reactions (MCRs) are especially relevant because they enable more than two building blocks to be combined, leading to the desired products in a single step through the simultaneous formation of two or more bonds without isolating or purifying intermediates. Moreover, high levels of diversity can be achieved by varying the reacting components.

For instance, the alkyne−acid chloride coupling−cyclocondensation sequence reported by Bishop et al.[53] (see Scheme 28) was also carried out in a one-pot, three-component (acid chloride **255**, alkyne **256**, hydrazine **257**) procedure catalyzed by $Pd(PPh_3)_2Cl_2$/CuI (Scheme 73).[121] Reactions were performed either at room temperature using CH_3CN as cosolvent[121a] or under microwave irradiation at 150 °C in the presence of methanol and acetic acid. These pyrazoles are highly fluorescent, both in solution and in the solid state.[121b] In general, the second approach led to the

Scheme 69



Scheme 70



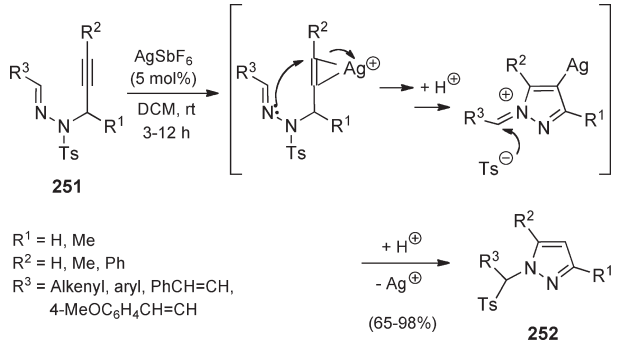
corresponding 3,5-diaryl-1*H*-pyrazoles **258** in higher yields than the first one. Moreover, when monosubstituted hydrazines (R ≠ H) were employed, only one regioisomer was preferentially formed (regioselectivity >98:<2).

Mori and co-workers also reported an efficient one-pot, four-component coupling of terminal alkynes **261**, aryl iodides **262**, methylhydrazine, and carbon monoxide to prepare 3,5-diarylpyrazoles **263** (R = Me) in the presence of a palladium catalyst.[122] The reaction proceeded at room temperature under 1 atm of carbon monoxide in aqueous solvent (Scheme 74). With aqueous hydrazine, the corresponding 3,5-diarylpyrazoles **263** (R = H) were also obtained. However, no reaction was observed with phenylhydrazine. In the presence of copper iodide as a cocatalyst, 1-octyne also reacted, affording the corresponding 1-methyl-3-aryl-5-hexylpyrazoles **263**. This reaction was found to be highly regioselective, with the substituent at the 5-position of the pyrazole ring coming from the terminal alkyne. This MCR was also carried out by using molybdenum hexacarbonyl instead of carbon monoxide.[123]

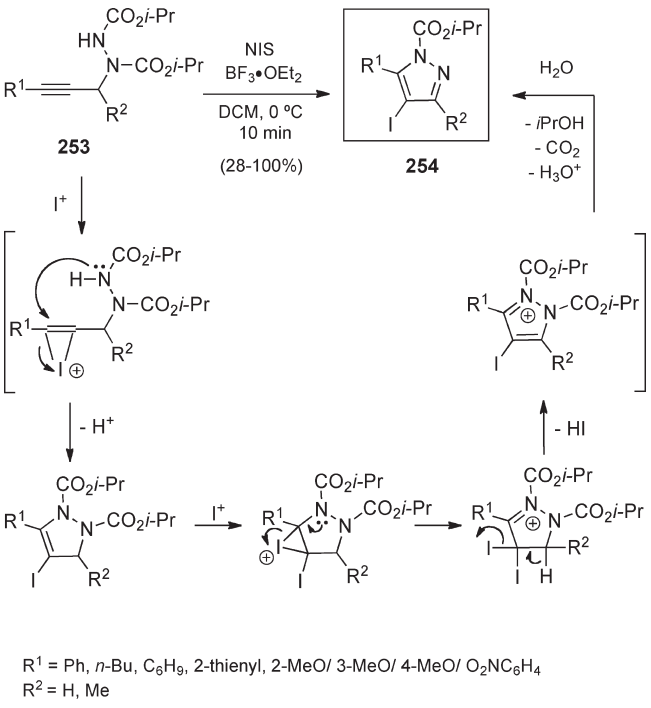
Rare earth metal-containing compounds have been used as powerful catalysts replacing conventional Lewis acids in various organic synthetic processes. In this context, Cao, Qian, and co-workers[124] employed ytterbium perfluorooctanoate

dx.doi.org/10.1021/cr2000459 |*Chem. Rev.* 2011, 111, 6984–7034

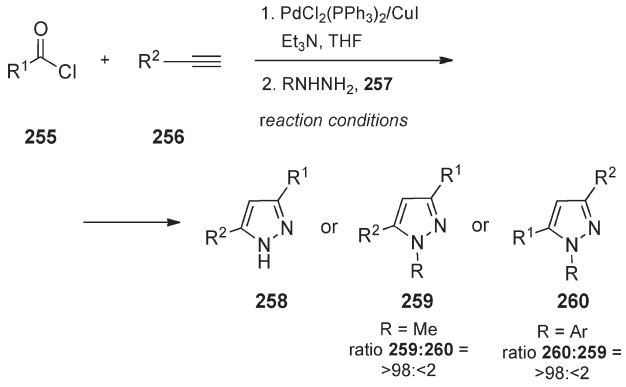
Scheme 71



Scheme 72



Scheme 73



ref. 121a, *reaction conditions* : MeCN, rt, 16 h (15-85%)
R^1 = Ph, 2-furyl, 4-MeC_6H_4, 4-$O_2NC_6H_4$, 2-thienyl, cyclohexyl
R^2 = Ph, 4-MeC_6H_4, 2-naphthyl, *n*-hexyl
R = H

ref. 121b, *reaction conditions* : MeOH, $MeCO_2H$, 10 min, 150 °C, μW (53-95%)
R^1 = 4-Me/ MeO/ *t*-Bu/ Cl/ F_3C/ NCC_6H_4, 2,4-$Cl_2C_6H_3$, 2-thienyl
R^2 = *n*-butyl, Ph, 4-Cl/ Br/ MeO/ O_2N/ NC/ $MeO_2CC_6H_4$,
4-(*N*-pyrrolidyl)C_6H_4, 10-hexylphenothiazin-3-yl
R = H, Me, Ph, 4-Br/ ClC_6H_4

$[Yb(PFO)_3]$ as catalyst in the coupling of aldehydes **264**, arylhydrazines **265**, and alkyl acetoacetate **266** (R^1 = Me, R = Et)[124a] or ethyl trifluoroacetoacetate **266** (R^1 = CF_3, R = Et)[124b] for the preparation of fully substituted alkyl *N*-aryl pyrazole-4-carboxylates **268** and **270**, respectively, in a one-pot reaction under solvent-free conditions (Scheme 75). When ethyl trifluoroacetoacetate was employed, methyl *N*-aryl pyrazoline-4-carboxylates **269** were the only products obtained, which were in situ oxidized with 2-iodoxybenzoic acid (IBX) to pyrazoles **270**. The key step of the process was the cyclization of the catalyst-activated hydrazone **267** with the catalyst-stabilized enol tautomer of **266**. With alkyl acetoacetate, a sequence involving cyclization to a 5-hydroxypyrazolidine dehydration, oxidation, further oxidation, and aromatization was proposed for explaining the formation of **268**, while air caused oxidative reactions (Scheme 75). The formation of a carbenium ion followed by 1,3-hydride migration and subsequent deprotonation was proposed to explain the formation of pyrazolines **269**. In general, the reaction proceeded more efficiently with aliphatic aldehydes than with aromatic ones, giving rise to the corresponding pyrazoles in good yields. Additionally, the catalyst could be easily recovered after three runs without loss of activity.

Isocyanide-based MCRs are especially relevant for the construction of heterocyclic scaffolds.[125] For example, Adib et al.[126] prepared dialkyl 5-(alkylamino)-1-arylpyrazole-3,4-dicarboxylates **274** in good yields by means of an MCR at room temperature (Scheme 76). A solution of an isocyanide **271** in dry acetone was added to a solution containing a dialkyl acetylenedicarboxylate **272** and a hydrazine carboxamide **273** in the same solvent. The proposed mechanism involved an initial addition of isocyanide **271** to dicarboxylate acetylene **272** and subsequent protonation of the resulting zwitterionic adduct. Next, addition of the conjugated base of **273** followed by intramolecular cyclization of the formed ketenimine would afford a 2,3-dihydropyrazole intermediate, which would then lead to the final pyrazoles **274** through the release of carbon monoxide and aniline (Scheme 76).

Methods to prepare 4,5-disubstituted pyrazoles are scarce. Odom and co-workers[127] have recently described the synthesis of an array of 1-aryl-4,5-disubstituted pyrazoles **278** in low to moderate yields by in situ cyclization of 1,3-diimines **277** with hydrazine or hydrazine derivatives in a one-pot procedure. Intermediates **277** were assembled by means of a titanium-catalyzed three-component coupling of terminal or internal alkynes **275**, *tert*-butyl isocyanide, and primary amines **276** (Scheme 77). In general, 10 mol % of $Ti(NMe_2)_2$(dpma) [dpma = *N*,*N*-di(pyrrolyl-α-methyl)-*N*-methylamine] was employed, although with internal alkynes, the more active $Ti(NMe_2)_2$(dpm) (dpm =5,5-dipyrrolylmethane) complex was used in 10 or 20 mol %. In addition, differences in regioselectivity were observed depending on the catalyst employed. In general, dpm favored 4-substitution when terminal alkynes were employed. The tridentate ligand dpma favored 4-substitution for

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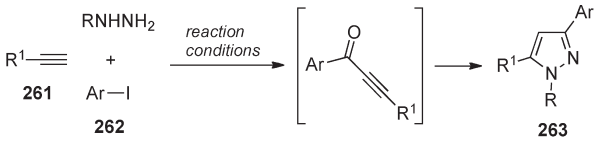
aromatic groups and 3- or 5-substitution for alkyl-containing alkynes (Scheme 77). This methodology was applied to the synthesis of the natural product withasomnine (see Scheme 64) in a six-step sequence starting from 4-pentyn-1-ol (24% overall yield).[127]

The Bestman-Ohira reagent (BOR) **165** was employed for the first time, together with aldehydes **281** and nitriles **282**, in an MCR involving a domino Knoevenagel condensation/1,3-cycloaddition sequence. This process gave rise to 5-phosphonylpyrazole derivatives **285** in a regioselective manner through the formation of two C−C bonds and one C−N bond (Scheme 78; see also Scheme 50).[128] The formal 1,3-dipolar cycloaddition reaction took place between the in situ methoxide-generated anion of BOR **166** and the initially formed Knoevenagel adduct **283** with a subsequent elimination of a cyano group from intermediate **284**. Phosphonylpyrazoles **285** were obtained in high to excellent yields by reacting aromatic, heteroaromatic, aliphatic, and ferrocenyl aldehydes, BOR, and either malononitrile or ethylcyanoacetate, cyanoacetamide, or *N*-benzyl-2-cyanoacetamide.

Scheme 74



ref. 122, *reaction conditions* = CO (1 atm), $PdCl_2(PPh_3)_2$, rt (59-93%)
R^1 = *n*-C_6H_{13}, Ph, 4-MeC_6H_4
R = H, Me
Ar = Ph, 4-Me/ $MeOC_6H_4$, 2-thienyl

ref. 123, *reaction conditions* = $Mo(CO)_6$, $Pd(OAc)_2$, CuI, P*t*-Bu_3, Cs_2CO_3, 80 °C, 18h (39-99%)
R^1 = Ph, 4-MeO/ ClC_6H_4, Bn, 3-thienyl/ pyridyl, CH_2O(tetrahydropyranyl)
R = H, Me, Ph
Ar = Ph, 4-Me/ ClC_6H_4, 3-pyridyl

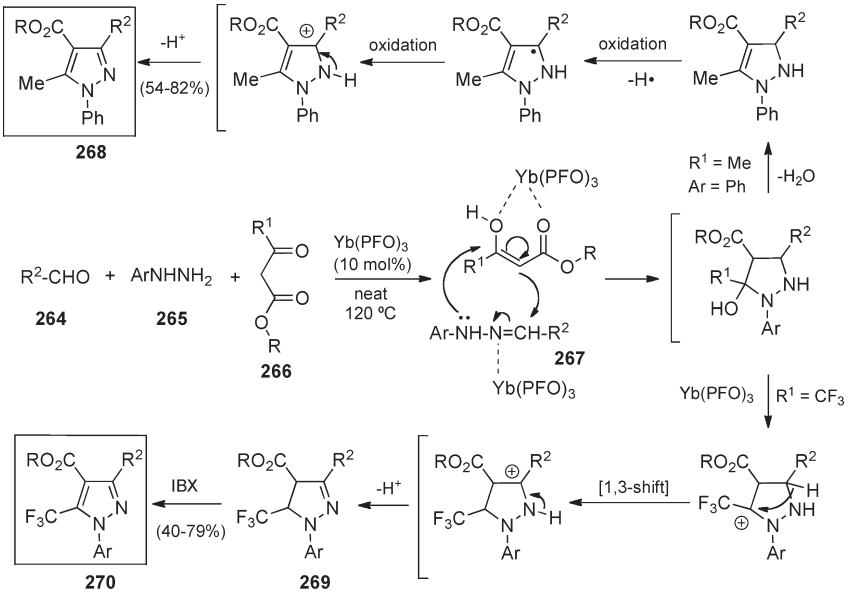
6. OTHER METHODS FOR CREATING THE PYRAZOLE RING

A variety of additional strategies have been developed for the regioselective construction of the pyrazole ring. Noteworthy are those leading to pyrazole carboxylic acid derivatives owing to the potential biological activity of these compounds. For example, highly functionalized pyrazole-4-carboxylic acid derivatives **289** were prepared in moderate to good yields by addition of Huisgen zwitterions **287**, previously obtained by reaction of PPh_3 with dialkyl azodicarboxylates **286**, to 4-substituted allenoates **288** (Scheme 79).[129] The proposed mechanism involved nitrogen-to-carbon migration of the carboalkoxy group, ring-closure, elimination of triphenylphosphine oxide, and double-bond isomerization.

Fully substituted pyrazole-4-carboxylates **293** were also regioselectively obtained by addition of zwitterionic intermediates **291**, in situ formed from PPh_3 and acetylenic esters **290**, to hydrazonoyl chlorides **292** (Scheme 80).[130] Subsequent ring-closure and PPh_3 release afforded the expected pyrazoles in high yields.

Very recently, Glorius and co-workers[131] have reported an efficient methodology for the regioselective synthesis of fully substituted pyrazole 4-carboxylates **296** from enamines **294** and nitriles **295** involving an oxidative C−C/N−N bond-formation cascade (Scheme 81). Reactions were performed using an excess of nitrile without any additional solvent, in the presence of $Cu(OAc)_2$ under air atmosphere, with copper acting as a Lewis acid activator and as an oxidizing agent. This approach has a wide substrate scope, allowing for the preparation of a variety of 1,3,4,5-substituted pyrazoles in high yields

Scheme 75



ref. 124a: Ar = Ph, R = Me, Et, R^1 = Me
R^2 = *n*-Pr, 4-Me/ MeO/ Br/ F_3C/ CF_3O/ $O_2NC_6H_4$, 2-F-5-MeC_6H_3, 3-(6-Cl-pyridinyl)

ref. 124b: Ar = Ph, 4-Me/ FC_6H_4, R = Et, R^1 = CF_3
R^2 = $MeCH_2$, Me_2CH, Me_2CHCH_2, Ph, 4-Me/ NC/ Br/ $F_3COC_6H_4$, 3-(6-Cl-pyridinyl)

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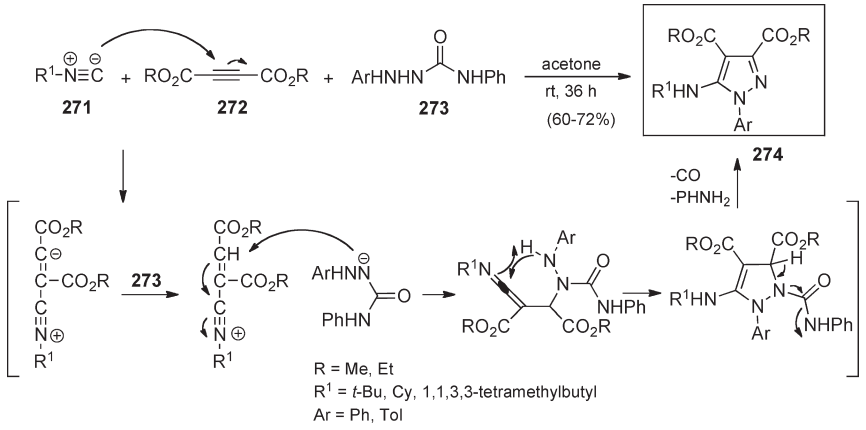
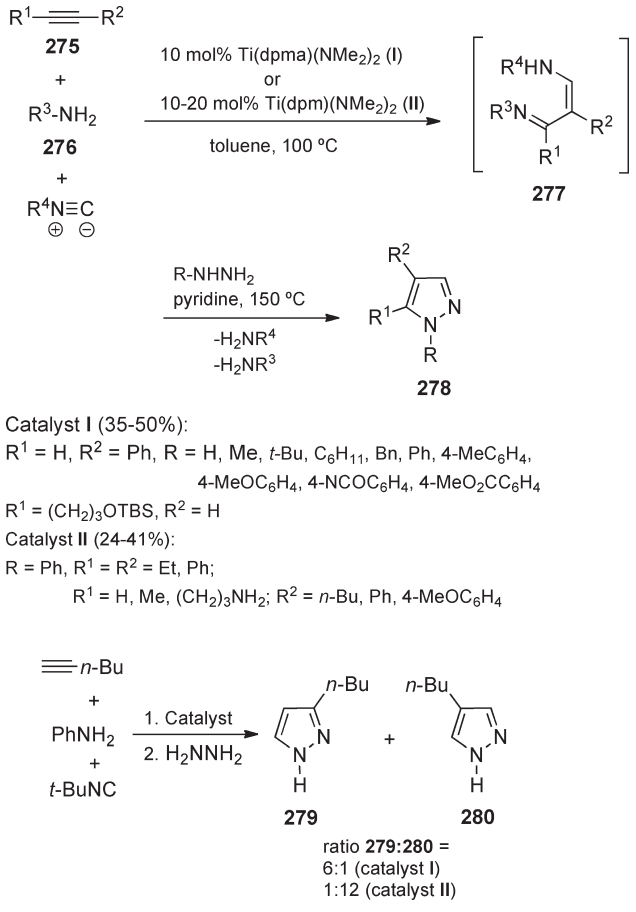
Scheme 76



Scheme 77



from both aliphatic and aromatic nitriles and enamines. In addition, two bispyrazoles were efficiently prepared in up to 73% yield. The mechanism proposed involved an initial activation of the nitrile by the Lewis acid, followed by nucleophilic attack of the enamine and reductive elimination in the 1,3-bisimine−Cu(II) complex formed.

Cyclizations of hydrazone dianions with esters, acid chlorides, and nitriles were described several years ago as convenient procedures for the preparation of pyrazole−carboxylic acid derivatives.[132] However, the first one-pot approach to pyrazole-5-carboxylates and pyrazole-1,5-dicarboxylates by cyclization of hydrazone 1,4-dianions with diethyl oxalate was reported by Langer and co-workers in 2007.[133] The reaction of diethyl oxalate with the dianion of an appropriate ketone hydrazone **297** resulted in the formation of the corresponding ethyl *N*-ethoxycarbonyl-4,5-dihydropyrazole-5-ol-5-carboxylate **298**, which in turn afforded pyrazoles **299** in the presence of *p*-TsOH at refluxing toluene (Scheme 82). By contrast, refluxing a dichloromethane solution of **298** in the presence of trifluoroacetyl (TFA) afforded pyrazole-1,5-dicarboxylates **300**. This methodology was found to be quite general and has been applied to a variety of aryl and alkyl ketones. Moreover, tetralone hydrazone gave the corresponding tricyclic pyrazoles, as well as hydrazones derived from cyclohexa-, hepta-, octa-, and dodecanone, which afforded their respective bicyclic pyrazoles under the same reaction conditions.

The same strategy was applied to the synthesis of a series of 5-alkyl-1,3,4-triarylpyrazoles **305** because the condensation of a 2-substituted 1,3-diketone with an arylhydrazine mentioned before[18d] (see Scheme 11) proved to be inappropriate. Compounds **305** were regioselectively prepared starting from acetophenone derivatives **301** through a five-step sequence (Scheme 83). After assembling hydrazones **302**, acylation of the corresponding lithiated dianions with alkyl anhydrides **303**, followed by cyclization, gave trisubstituted pyrazoles **304**. These were in turn iodinated at the C-4 position and subjected to Suzuki coupling conditions to introduce the third aryl substituent (Ar^2).[18d]

During the course of an investigation to develop novel antiviral agents, Dragovich et al.[134] observed the formation of a 5-hydroxy-3-pyrazole carboxylate by intramolecular addition of a methylene carbon of a malonyl fragment to an amide carbonyl carbon of an oxalyl fragment. This result suggested a novel procedure for the highly regioselective preparation of 1-substituted-5-hydroxypyrazoles **309** bearing ester moieties at the 3- and 4-positions (Scheme 84). These compounds were prepared in a three-step sequence involving coupling of monosubstituted benzyl carbazates **306** with methyl malonyl chloride, *N*-Cbz deprotection, and derivatization of the resulting hydrazides **308** with monomethyl oxalyl chloride. The pyrazole ring was formed by intramolecular addition of the methylene carbon in

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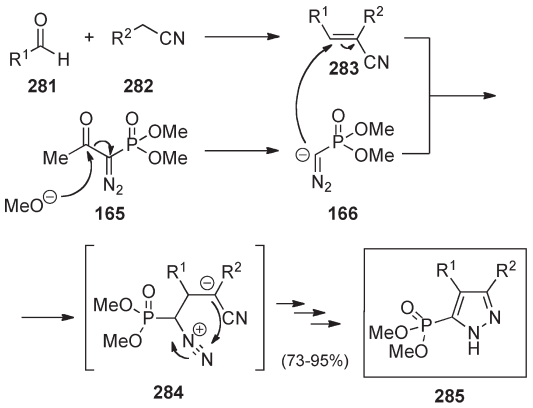
Scheme 78



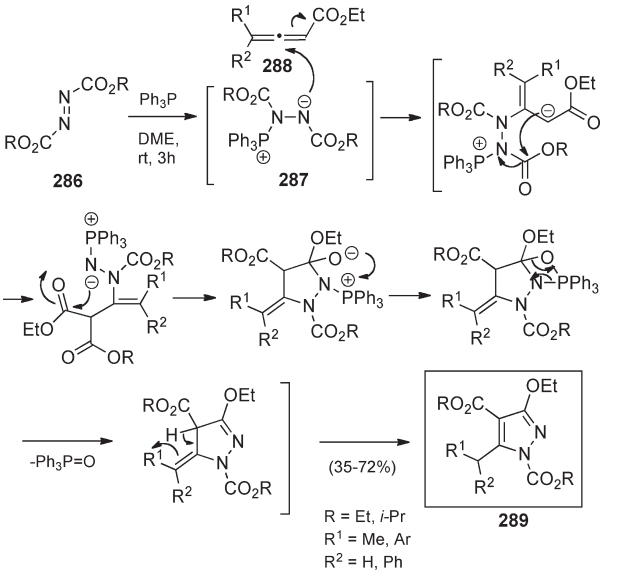
R^2 = CN, R^1 = 1-octenyl, cycloundecyl, Ph, 4-HO/ MeO/ Br/ $O_2NC_6H_4$, 2-O_2N/ $B(OH)_2C_6H_4$, 2,4-$Cl_2C_6H_3$, 1-pirenyl, 2-thienyl, ferrocenyl

R^2 = COOMe, R^1 = 4-(1,5,5-Me_3)cyclopentenyl, Ph, 4-BrC_6H_4

R^2 = $CONH_2$, R^1 = Ph, 2-thienyl

R^2 = $CONHCH_2Ph$, R^1 = Ph

Scheme 79

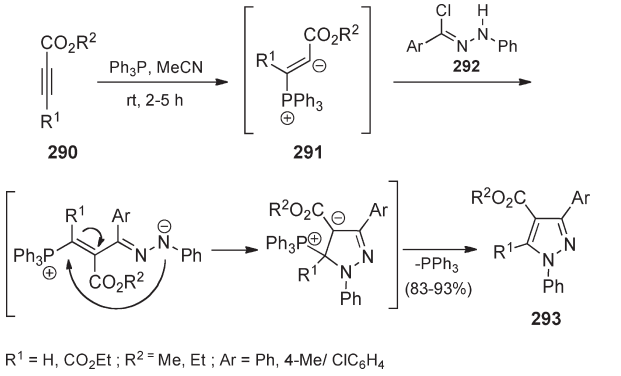


R = Et, *i*-Pr

R^1 = Me, Ar

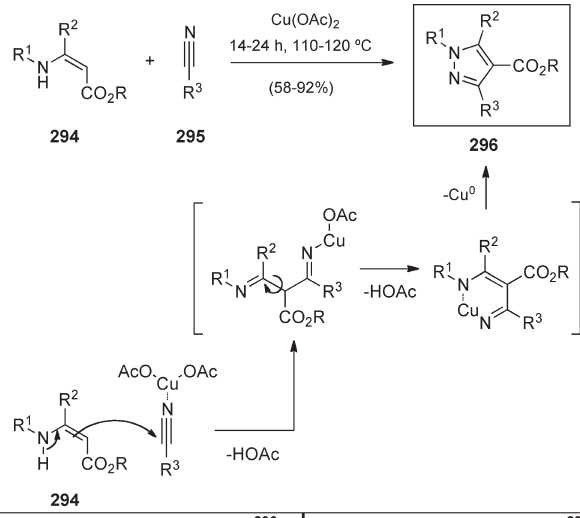
R^2 = H, Ph

Scheme 80



R^1 = H, CO_2Et ; R^2 = Me, Et ; Ar = Ph, 4-Me/ ClC_6H_4

Scheme 81



R	R^1	R^2	R^3	296 Yield(%)	R	R^1	R^2	R^3	296 Yield(%)
Me	Ph	Me	Me	81	Me	3-MeC_6H_4	Me	Et	72
Me	Ph	Me	Et	77	Me	2-MeC_6H_4	Me	Et	75
Me	Ph	Me	Ph	76	Me	4-$EtO_2CC_6H_4$	Me	Et	73
Me	Ph	Me	CO_2Me	72	Me	4-$EtOC_6H_4$	Me	Ph	87
Me	Ph	Et	Me	77	Me	4-$EtOC_6H_4$	Me	Et	88
Me	Ph	H	Ph	39	Me	4-$O_2NC_6H_4$	Me	Et	65
Me	4-FC_6H_4	Me	Me	87	Me	4-$O_2NC_6H_4$	Me	Ph	75
Me	4-FC_6H_4	Me	Et	83	Et	Ph	Ph	Me	88
t-Bu	4-FC_6H_4	Me	Et	73	Et	Ph	Ph	Et	87
Bn	4-FC_6H_4	Me	Et	84	Et	Ph	Ph	Ph	82
Me	4-FC_6H_4	Me	*i*-Pr	73	Et	2,4,6-$(Me)_3C_6H_2$	Me	Et	92
Me	4-FC_6H_4	Me	Ph	90	Et	2,4,6-$(Me)_3C_6H_2$	Me	Ph	83
Me	4-FC_6H_4	Me	3-$F_3CC_6H_4$	81	Et	2,6-(*i*-$Pr)_2C_6H_3$	Me	Ph	35
Me	4-MeC_6H_4	Me	Et	77					

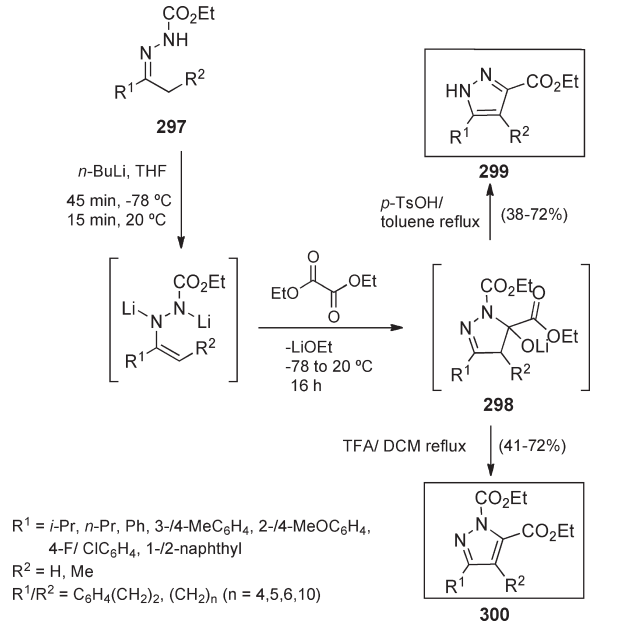
the malonyl fragment of **308** to the amide carbonyl carbon of the oxalyl fragment, followed by reaction with a second equivalent of methyl oxalyl chloride and subsequent elimination of monomethyl oxalyl acid ester. Hydroxypyrazoles **309** were then employed as building blocks in Suzuki cross-coupling reactions with boronic acids (see section 7).

The cycloaddition reaction between *N*-monosubstituted hydrazones **310** and nitroolefins **311** (Scheme 85) was reported by Deng and Mani for the first time.[135] These authors carried out a systematic study of this reaction under neutral (MeOH or ethylene glycol), acidic (TFA in CF_3CH_2OH), and basic conditions (*t*-BuOK in THF). Under both neutral and acidic conditions, the presence of air was necessary for the regioselective formation of 1,3,5- and 1,3,4,5-substituted pyrazoles **312** and **313**, respectively, in moderate to excellent yields (Scheme 85, conditions **A**, **B**, and **C**). The two sets of reaction conditions were complementary to each other in terms of functional group compatibility. However, under basic conditions, a reversal in regioselectivity was observed, and 1,3,4-substituted pyrazoles **314** were obtained in 11−88% yield. In this case, reactions were performed under N_2 atmosphere at −78 °C using TFA as quenching reagent (Scheme 85, condition **D**).

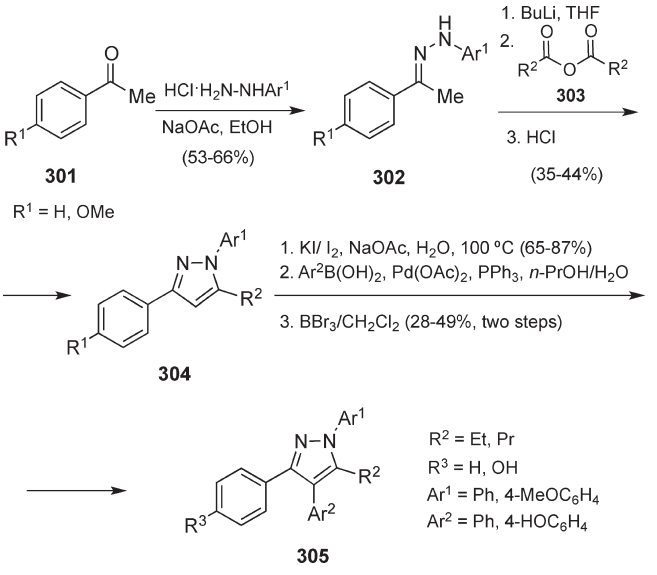
All these processes are quite broad in scope; either aryl or alkyl groups at the R^3 position of nitroolefins **311** afforded the corresponding pyrazoles in good yields. The substitution at the R^4 position to afford 1,3,4,5-substituted pyrazoles **315** was also well tolerated. On the other hand, the electronic properties of

dx.doi.org/10.1021/cr2000459 |*Chem. Rev.* 2011, 111, 6984–7034

Scheme 82



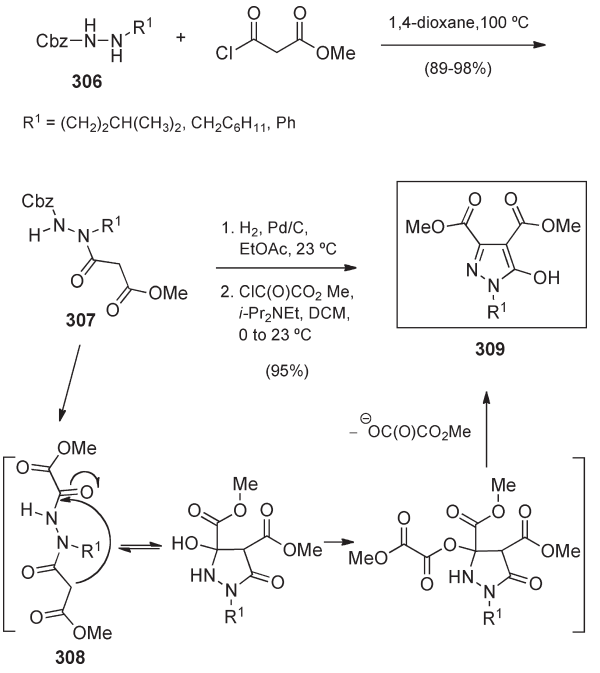
Scheme 83



the substituent (R^2) on the aldehyde counterpart of the hydrazone, as well as both the electronic and steric effects of the substituent (R) on the hydrazine, had a great influence on the reactivity.

The proposed stepwise cycloaddition mechanism involved an initial Michael-type addition of either a nitrogen (neutral or acidic conditions; via a Scheme 86) or a carbon (basic conditions; via b Scheme 86) nucleophile in hydrazones **310** to the nitroolefin **311** to afford the corresponding adducts. An intramolecular cyclization on these intermediates would provide pyrazolidines **A** and **B**. Next, the **A** species would undergo a slow oxidation by air, followed by a fast elimination of HNO_2 to give the corresponding pyrazoles. On the other hand, TFA would protonate **B** to afford a pyrazolidine intermediate that in turn would undergo elimination of HNO_2, followed by oxidative aromatization promoted by HNO_2 to furnish the final pyrazoles (Scheme 86).

Scheme 84



As a result of studying the reaction of 3,6-diaryl-1,2,4,5-tetrazines **316** with thioethanones under basic alcoholic conditions, Kurth and co-workers obtained fully substituted pyrazol-4-ols **317** at room temperature (Scheme 87).[136] Remarkably, all atoms of the thioethanone counterpart except for sulfur were incorporated into the products. A speculative mechanism involving a consecutive series of condensation−fragmentation−cyclization−extrusion reactions was proposed.

A Mukaiyama−Michael-type addition/heterocyclization of Danishefsky's diene **319** with 1,2-diaza-1,3-butadienes **318** was applied to the synthesis of functionalized 1,3-substituted pyrazoles **321** via 1,4-adducts **320**, bearing an amide group (Scheme 88).[137] The proposed mechanism involved the nucleophilic attack of a water molecule on the hydrazone group of **320** followed by intramolecular cyclization promoted by wet Amberlist 15(H). Subsequent ring-opening and internal transfer of the hydrazone moiety would afford the target pyrazoles **321**.

In the course of a study of the synthetic potential of β-oxo amide derivatives, Dong and co-workers[138] developed a one-pot synthesis of fully substituted pyrazoles **323** from cyclopropyl oximes **322** under Vilsmeier conditions ($POCl_3$/DMF) (Scheme 89). Starting substrates **322** were prepared in up to 95% yield by the reaction of 1-acyl,1-carbamoyl cyclopropanes with hydroxylamine in the presence of NaOAc in methanol at room temperature. The proposed mechanism involved ring-opening, chlorovinylation, and intramolecular aza-cyclization.

7. TRANSITION METAL-CATALYZED C−N AND C−C CROSS-COUPLING REACTIONS IN PYRAZOLES

All aforementioned methods lead to differently substituted pyrazoles through reaction sequences in which the substituents

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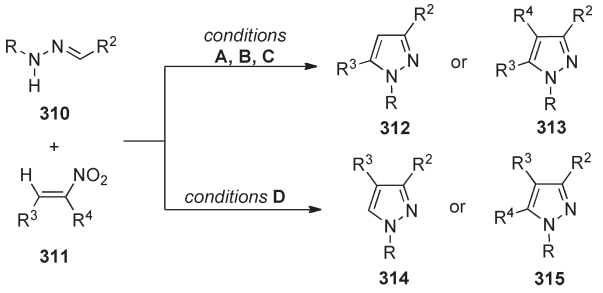
are introduced before cyclization. However, alkyl, aryl, and acyl substituents in both carbon and nitrogen atoms of the pyrazole ring can also be introduced after cyclization.[139] Among the methodologies developed to this end, transition metal-catalyzed cross-coupling reactions have emerged as a powerful tool for the construction of C−C and C−N bonds.

Scheme 85



R^1	R^2	R^3	R^4	Conditions, (% Yield)
Me	4-ClC_6H_4	3,4-$OCH_2OC_6H_3$	H	**A** (83)
Me	4-ClC_6H_4	Ph	Me	**A** (92)
Me	4-ClC_6H_4	$(CH_2)_4$		**A** (81)
Me	Bn	3,4-$OCH_2OC_6H_3$	H	**A** (82)
Me	*t*-Bu	3,4-$OCH_2OC_6H_3$	H	**A** (56)
Me	4-$MeOC_6H_4$	4-MeC_6H_4	H	**A** (72)
Me	4-$O_2NC_6H_4$	4-$O_2NC_6H_4$	H	**B** (58)
Me	4-$O_2NC_6H_4$	4-$O_2NC_6H_4$	H	**D** (41)
Ph	4-ClC_6H_4	3,4-$OCH_2OC_6H_3$	H	**A** (42), **D** (79)
Ph	Et	Ph	H	**A** (76)
Ph	4-ClC_6H_4	4-MeC_6H_4	H	**C** (70), **D**(82)
Ph	4-ClC_6H_4	Ph	Me	**C** (38)
Ph	4-ClC_6H_4	$(CH_2)_4$		**C** (52), **D** (63)
Ph	4-ClC_6H_4	3-$MeOC_6H_4$	H	**C** (56)
Ph	4-ClC_6H_4	2-Cl-6-FC_6H_3	H	**C** (56), **D** (88)
Ph	4-ClC_6H_4	4-BrC_6H_4	H	**C** (68), **D** (81)
Ph	4-ClC_6H_4	4-$O_2NC_6H_4$	H	**C** (31), **D** (52)
Ph	4-ClC_6H_4	3-$F_3CC_6H_4$	H	**C** (36), **D** (76)
Ph	4-ClC_6H_4	2-Thienyl	H	**C** (55), **D** (73)
Ph	4-$MeOC_6H_4$	4-MeC_6H_4	H	**B** (76), **D** (25)
Ph	4-$Me_2NC_6H_4$	4-MeC_6H_4	H	**B** (55), **D** (31)
Ph	3-HOC_6H_4	4-MeC_6H_4	H	**C** (81)
Ph	4-$MeO_2CC_6H_4$	4-MeC_6H_4	H	**B** (29), **D** (77)
4-$MeOC_6H_4$	4-ClC_6H_4	4-MeC_6H_4	H	**B** (63), **D** (83)
4-$O_2NC_6H_4$	4-ClC_6H_4	4-MeC_6H_4	H	**B** (19)
2,4-$F_2C_6H_3$	4-ClC_6H_4	4-MeC_6H_4	H	**C** (78)
4-NCC_6H_4	4-ClC_6H_4	4-MeC_6H_4	H	**C** (51), **D** (11)
4-$MeO_2SC_6H_4$	4-ClC_6H_4	4-MeC_6H_4	H	**B** (62)
Ph	4-ClC_6H_4	2-Furyl	H	**D** (51)
Ph	4-ClC_6H_4	3-Pyridyl	H	**D** (42)
Ph	4-$O_2NC_6H_4$	4-MeC_6H_4	H	**D** (80)
Ph	3-NCC_6H_4	4-MeC_6H_4	H	**D** (83)
1-Naphthyl	4-ClC_6H_4	4-MeC_6H_4	H	**D** (67)
2-Pyridyl	4-ClC_6H_4	4-MeC_6H_4	H	**D** (16)
2,4-$Cl_2C_6H_4$	COOEt	4-MeC_6H_4	H	**D** (78)
Bn	4-ClC_6H_4	4-MeC_6H_4	H	**A** (90)
i-Pr	4-ClC_6H_4	4-MeC_6H_4	H	**A** (26)
t-Bu	4-ClC_6H_4	4-MeC_6H_4	H	**A** (15)

Conditions: A = $MeOH/H_2O$, air, rt, 1-2 d. **B** = Ethylene glycol, air, 120-150 °C. **C** = CF_3CH_2OH, TFA (10 equiv.), rt, air, 2 d. **D** = 1. *t*-BuOK, THF, −78 °C, N_2; 2. TFA (2 equiv.), −78 °C-rt, N_2.

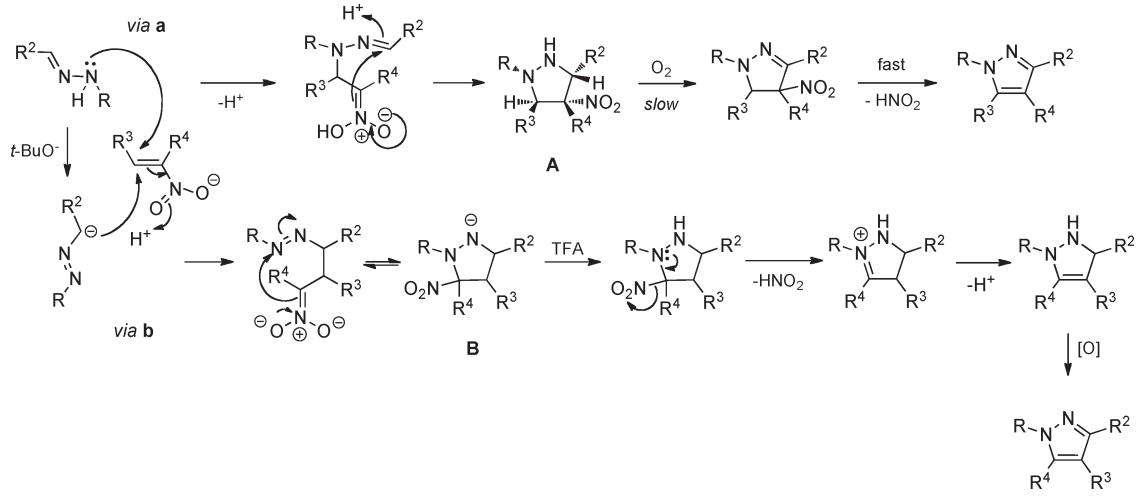
7.1. C−N Cross-coupling Reactions

An alternative method to the cyclocondensation of arylhydrazines and 1,3-dielectrophilic compounds for preparing *N*-arylpyrazoles involves transition metal-catalyzed *N*-arylation of 1*H*-pyrazoles with aryl halides and arylboronic acids as electrophiles (Scheme 90). This protocol has acquired a major role thanks to the versatility of the products, which are interesting building blocks for the synthesis of many natural products and medicinal agents.

7.1.1. Copper-Catalytic Systems. The copper-catalyzed *N*-arylation of azoles (Ullmann-type reaction) represents one of the most efficient methods to form C(aryl)−N bonds. The harsh reaction conditions employed in the traditional copper-catalyzed Ullmann condensation (temperatures as high as 210 °C, stoichiometric amounts of copper reagents) motivated the development of more efficient copper catalysts. In this context, consecutive studies have revealed a significant enhancement of the reaction rates when the arylations are conducted in the presence of an organic additive, probably due to the increased solubility and stability of the copper catalysts. In 2001, Taillefer's and Buchwald's research groups, respectively, discovered highly efficient copper/ligand systems that allowed the use of a catalytic amount of metal under mild conditions.[140] Since then, many research groups have developed new copper/ligand systems (Figure 1) to improve the efficiency of the cross-coupling reactions. Moreover, the low cost of copper-based catalytic systems makes them particularly attractive for large-scale industrial applications.

In general, copper-catalyzed cross-coupling reactions are not excessively sensitive to the copper source, but the choice of ligand, base, or solvent is often crucial.[141] Homogeneous and heterogeneous protocols have been developed. Cu(I) species such as CuI or Cu_2O are usually the main copper sources, but CuO and even Cu powder without any additional ligand[142] have also been employed. The most frequently used ligands are those containing nitrogen and/or oxygen atoms that may act as bi- and tetradentate ligands with copper. In general, reactions are performed in DMSO or DMF as solvents in the presence of either Cs_2CO_3 or K_2CO_3 as bases. Moreover, ligand-free and

Scheme 86



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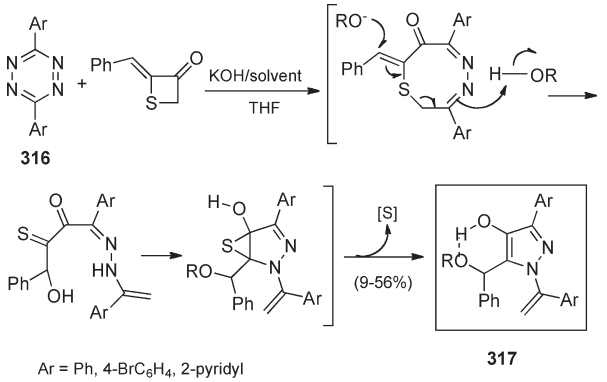
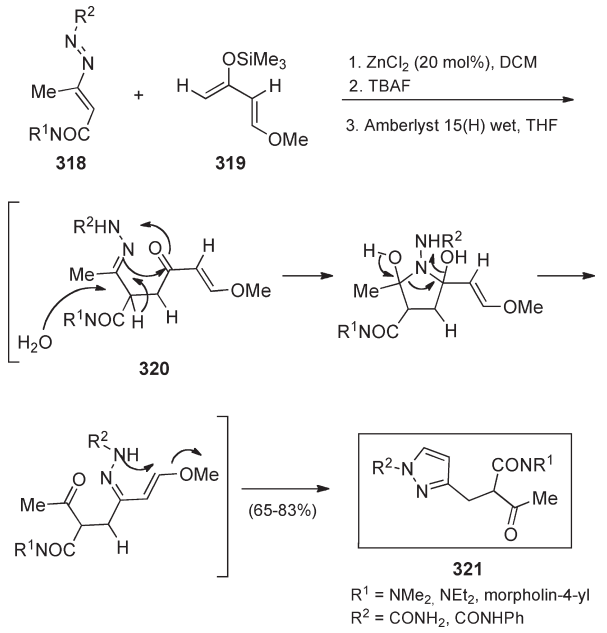
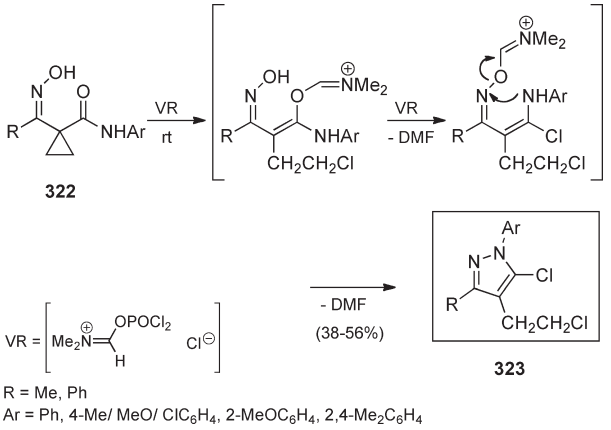
Scheme 87



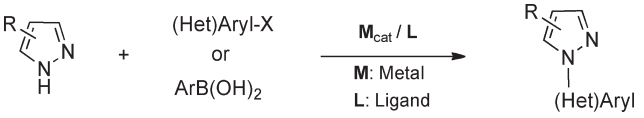
Scheme 88



Scheme 89



Scheme 90



solvent-free copper-catalyzed *N*-arylations have also been reported.

Although imidazole has been the main *N*-heterocycle used as a model substrate for the study of Ullmann-type cross-coupling reaction with aryl halides, this methodology has also been applied to the C−N bond forming in pyrazole and pyrazole derivatives.

7.1.1.1. Aryl Halides As Electrophiles. Iodo- and bromo(het)aryl derivatives are the main electrophilic reagents used in copper-catalyzed C(aryl/heteroaryl)−N(pyrazole) bond formation. Since the C−I bond is weaker than the C−Br one, reactions with (het)aryl iodides occur under milder conditions and lead to higher yields than those with (het)aryl bromide analogues. Aryl chlorides have been employed to a lesser extent. However, the use of aromatic halides can be limited by their access, cost, and stability, in particular for iodides. To avoid these drawbacks, research has been done to develop the use of new leaving groups such as triflate derivatives. For cross-coupling reactions with organometallic reagents, aryl triflates are usually comparable with aryl bromides.

Results for the catalytic *N*-arylation of pyrazole and pyrazole derivatives by means of copper-catalyzed cross-coupling reactions with aryl halides are summarized in Table 4.

Buchwald and co-workers employed CuI (5 mol %) as precatalyst and the bidentate ligand *trans*-1,2-(*N*,*N*′-dimethylamino)cyclohexane **L1** in the catalytic *N*-arylation of pyrazole and pyrazole derivatives with aryl iodides and aryl bromides.[143] Reactions were carried out in toluene at 110 °C for 24 h with K_2CO_3 as base (Table 4, entry 1) and worked well with electron-neutral and even electron-deficient pyrazoles. Unsymmetrical pyrazoles led to products in which the less-hindered nitrogen was selectively arylated. Moreover, the reaction was efficient for very electron-rich aryl halides and compatible with functional groups such as primary amines, hydroxyl, carbonyl, or carboxylate moieties.

By changing the reaction conditions (copper precatalyst, ligand, and solvent), the *N*-arylation of pyrazole and substituted pyrazoles was performed at 82 °C in acetonitrile using Cs_2CO_3 as base.[144a,b] Reactions were completed in 24−96 h employing Cu_2O (5 mol %) as copper precatalyst and either the bidentate salicylaldoxime (salox) **L2** or the tetradentate *trans*-*N*,*N*′-bis(2-pyridyl)cyclohexane-1,2-diimine **L3** as ligands (Table 4, entry 2). Excellent reactivity was observed when reacting pyrazole with both electron-rich and electron-poor aryl bromides, as well as with heteroaryl bromides derived from pyridine, thiophene, or pyrazole. However, sterically hindered *o*-substituted aryl bromides required heating at 110 °C in DMF to complete the reactions. In agreement with Buchwald's observation, the steric hindrance in monosubstituted 1*H*-pyrazoles determined the selectivity of the reaction. Although this procedure tolerates a variety of functional groups such as amino, carbonyl, nitro, or cyano, the ester group was partially hydrolyzed by the base. In the

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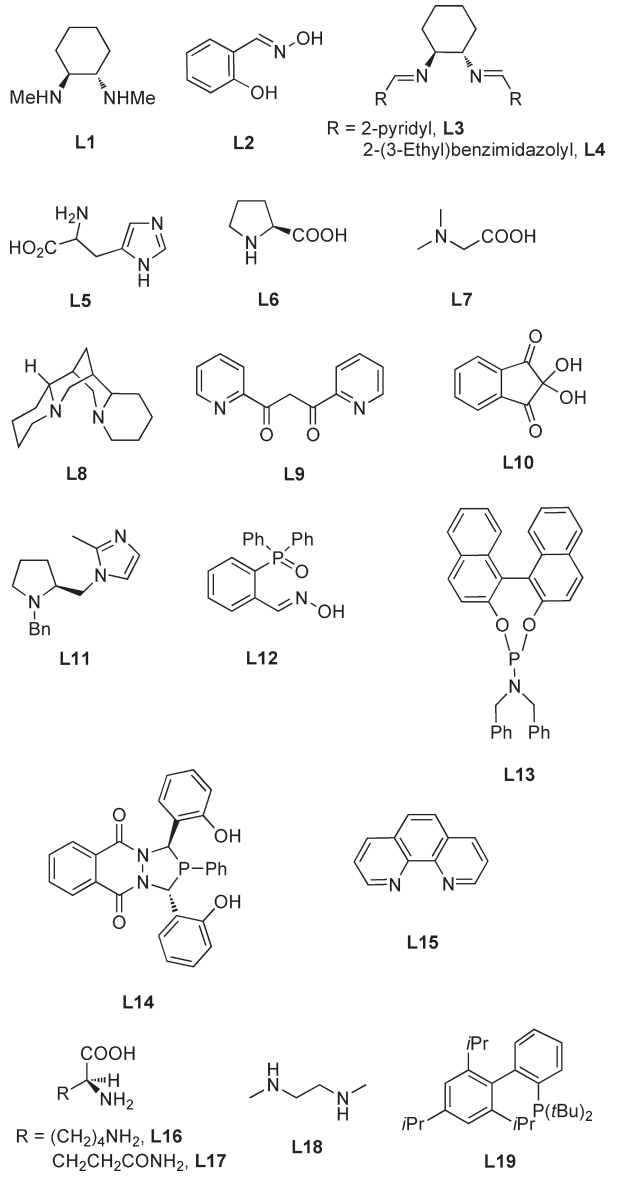


Figure 1

same reaction conditions (Cu_2O, **L3**, Cs_2CO_3, MeCN), 3-alkoxypyrazole derivatives **57** (Scheme 18) were *N*-arylated using 2-bromopyridine as electrophilic reagent.[144c] Reactions were carried out in a microwave reactor at 180 °C for 2 h in the presence of 4 Å molecular sieves. In general, variable mixtures of regioisomers were afforded (Table 4, entry 3).

Under the same conditions, pyrazole and 3/5-trifluoromethylpyrazole reacted with 2,4-difluoroiodobenzene, affording mixtures of monosubstituted products owing to the competing substitution at the C−I and C−F sites, with C−I substitution as the major product (Table 4, entry 4). Di- and trisubstituted pyrazolylbenzenes were also isolated. The results were compared with those obtained in the absence of the catalytic system.[145]

The CuI/*trans*-*N*,*N*′-bis(1-ethyl-2-benzimidazolylmethylene)-cyclohexane-1,2-diimine **L4** catalytic system was applied to the selective *N*-arylation of pyrazole in the presence of Cs_2CO_3 as base. Reactions were conducted in DMF at 100 °C for 24 h. High yields of 72−92% were obtained in the coupling with 2-pyridyl, 4-acetylphenyl, and 4-formylphenyl bromides (Table 4, entry 5). With 1,3- and 1,4-diiodobenzenes, the corresponding dicoupling products were obtained in excellent yields (92−93%).[146]

Amino acids such as L-histidine **L5**, L-proline **L6**, and *N*,*N*-dimethylglycine **L7** were also combined with CuI in the catalytic *N*-arylation of pyrazole (Table 4, entries 6 and 7). The best results were obtained with DMSO as solvent and K_2CO_3 as base.[147] Reactions with the activated 4-cyanophenyl and 2-pyridyl bromides proceeded at 75 °C in excellent yields (94−96%), whereas for phenyl and 4-methoxyphenyl bromides, the temperature had to be increased to 110 °C to achieve good yields (66−71%).

In the presence of 5 mol % of preformed bis(μ-iodo)bis((−)-sparteine, **L8**) dicopper(I) complex, pyrazole was *N*-arylated by coupling with 4-methoxyphenyl iodide(bromide) and 4-bromo(chloro)benzaldehyde (Table 4, entry 8).[148] With the aryl iodide and the electron-deficient aryl bromide, complete conversions (91 and 77% yield, respectively) were observed by heating the reaction mixtures at 115 °C in DMSO for 8 h in the presence of K_2CO_3. The electron-rich bromide required 12 h at the same temperature, whereas the activated aryl chloride took 18 h at 125 °C for its total transformation (65% yield).

Other compounds containing nitrogen and/or oxygen atoms as donors such as 1,3-di(pyridin-2-yl)propane-1,3-dione **L9** (Table 4, entry 9),[149] ninhydrin **L10** (Table 4, entry 10),[150] or (*S*)-pyrrolidinylmethyl−imidazole **L11** (Table 4, entry 11)[151] were found to be efficient ligands for the copper(I)-catalyzed C(phenyl)−N(pyrazole) bond formation.

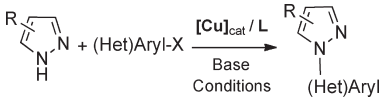
Phosphorus-containing derivatives such as phosphines have mainly been used as ligands in palladium-catalytic systems. Likewise, oxime-functionalized phosphine oxides **L12** (Table 4, entry 12),[152] phosphoramidites **L13** (Table 4, entry 13),[153] and diazophospholanes **L14** (Table 4, entry 14)[154] have proved to be effective chelating ligands for copper-catalyzed cross-coupling reactions of pyrazole and aryl iodides. Reactions were performed at 80−90 °C in DMSO or DMF in the presence of Cs_2CO_3, giving the corresponding *N*-arylated products in very good yields (76−95%).

Potassium fluoride supported on alumina (KF/Al_2O_3) has been employed as an alternative to other bases for the copper/1,10-phenantroline **L15**-catalyzed *N*-arylation of pyrazole with aryl iodides and bromides (Table 4, entry 15).[155] Reactions were completed in 13−18 h at 130−140 °C in xylene as solvent, affording the corresponding products in 81−95% yield.

To solve problems related to the low solubility of inorganic bases in some organic solvents, Fu, Liu, and co-workers proposed the use of organic ionic bases composed of organic cations and basic anions, which are soluble in organic solvents.[156] Thus, by using tetrabutylphosphonium acetate (TBPE) in DMSO, pyrazole reacted with electron-rich and electron-deficient aryl iodides at room temperature in the presence of CuI/ *N*,*N*-dimethylglycine **L7**, leading to C−N coupling products in 75−95% yield (Table 4, entry 16). The influence of the organic ionic base in terms of efficiency of the reaction was discussed in terms of its conductivity in polar and less polar organic solvents.

On the other hand, the *N*-arylation of pyrazole using heterogeneous catalytic systems was reported by Kantam et al.[157] In the absence of any ligand, several research groups

Table 4. Copper-Catalyzed *N*-(Het)Arylation of Pyrazole Derivatives



entry	R	(het)aryl	X	[Cu]	L[a]	base	conditions	yield (%)	ref
1	H, 3-Me, 4-CO_2Et, 3,5-Me_2, 3-Ph-5-NH_2, 3-CF_3-4-CO_2Et	Ph, 2-Me/NH_2/$CH_2OHC_6H_4$, 3-$CH_2NH_2C_6H_4$, 4-OH/C(O)Et/$CO_2EtC_6H_4$, 3-CO_2Me-4-ClC_6H_3, 3-Pyridyl	I, Br	CuI	**L1**	K_2CO_3	toluene, 110 °C, 24 h	71−98	143
2	H, 3(5)Me, 3-CF_3, 3,5-Me_2	Ph, 2-MeC_6H_4, 3-NO_2/ $CO_2EtC_6H_4$, 4-Me/MeO/CF_3/ MeCO/Cl/Br/CN/ $NH_2C_6H_4$, 2,4-$(Cl)_2C_6H_3$, 2-Thiophenyl, 3-Pyridyl, 4-Pyrazolyl	I,Br	Cu_2O	**L2** **L3**	Cs_2CO_3	MeCN, or DMF 25−110 °C, 24−96 h	50−100	144a, 144b
3	3-OEt, 4-F/Ph/Bn/CO_2Et, 5-Me/Ph/Bn	2-Pyridyl	Br	Cu_2O	**L3**	Cs_2CO_3	MeCN, MW 180 °C, 2 h	67−83	144c
4	H, 3(5)-CF_3	2,4-$(F)_2C_6H_3$	I	Cu_2O	**L2**	Cs_2CO_3	MeCN, 80 °C, 12−24 h	48−55	145
5	H	Ph, 2-/3-IC_6H_4, 4-CHO/$COMeC_6H_4$, 2-Pyridyl	I,Br	CuI	**L4**	Cs_2CO_3	DMF, 100 °C, 24 h	72−92	146
6	H	Ph	Br	CuI	**L5**	K_2CO_3	DMSO, 110 °C, 48 h	66	147a
7	H	4-MeO/CNC_6H_4, 2-Pyridyl	Br	CuI	**L6** **L7**	K_2CO_3	DMSO, 75−110 °C, 45 h	71−96	147b
8	H	Ph, 4-MeO/$CHOC_6H_4$	I, Br, Cl	CuI	**L8**	K_2CO_3	DMSO, 115−125 °C, 8−18 h	65−91	148
9	3,5-$(Me)_2$	Ph	I	CuI	**L9**	K_2CO_3	DMF, 90 °C, 24 h	71	149
10	H	Ph	I	Cu_2O	**L10**	KOH	DMSO, 110 °C, 24 h	92	150
11	H	Ph	Br	CuI	**L11**	Cs_2CO_3	DMF, 110 °C, 24 h	87	151
12	H	Ph, 3-$CF_3C_6H_4$, 4-$MeOC_6H_4$	I	Cu_2O	**L12**	Cs_2CO_3	MeCN, 80 °C, 18 h	81−95	152
13	H	4-$MeOC_6H_4$	I	CuBr	**L13**	Cs_2CO_3	DMF, 90 °C, 24 h	76	153
14	H	Ph, 3-CN/$NO_2C_6H_4$	I	CuBr	**L14**	Cs_2CO_3	DMSO, 80 °C, 24 h	89−95	154
15	H	Ph, 2-MeC_6H_4, 4-$MeOC_6H_4$	I,Br	CuI	**L15**	KF/Al_2O_3	xylene, 130−140 °C, 13−18 h	81−95	155
16	H	Ph, 3-NO_2/ $CO_2MeC_6H_4$, 4-Cl/ $MeOC_6H_4$	I	CuI	**L7**	TBPE[b]	DMSO, rt, 24 h	75−95	156
17	H	Ph, 2-Me/$MeOC_6H_4$, 3-Me/$NO_2C_6H_4$, 4-CN/$CO_2EtC_6H_4$, 2-Thiophenyl	I,Br Cl	Cu_2O	-	Cs_2CO_3	DMF, 100−110 °C, 18 h	93−99	158c
18	H, 3-Me, 3,5-$(Me)_2$	Ph, 4-$MeOC_6H_4$	I,Br	CuI		Cs_2CO_3 K_3PO_4	DMF, 120 °C or 35−40 °C, 40 h	50−85	158d 158e
19	H	Ph, 4-MeO/CHO-C_6H_4	I,Br	CuTC[c]		K_2CO_3	DMSO, 135 °C, 24−48 h	75−82	158f
20	H	3-/4-MeC_6H_4, 3-/4-$MeOC_6H_4$, 3-/4-MeC(O)C_6H_4	Br	CuI	**L16** **L17**	K_3PO_4	solvent-free, 150 °C, μW 2−10 h	27−83	159

[a] For the structure of ligands, see Figure 1. [b] TBPE = tetrabutylphosphonium acetate. [c] CuTC = copper thiophene-2-carboxylate.

have carried out the catalytic *N*-arylation of pyrazole and pyrazole derivatives.[158] For example, Correa and Bolm[158c] reported the use of Cu_2O in DMF in the presence of Cs_2CO_3. Reactions with aryl iodides were performed at 100 °C (aryl bromides and 4-chlorocyanobenzene at 110 °C) for 18 h in an oven-dried tube under argon atmosphere (Table 4, entry 17). Both aryl iodides and aryl bromides, independently of the nature of their substituents, afforded the corresponding coupling products in excellent yields (93−99%). The more electrophilic 4-chlorocyanobenzene also led to the corresponding coupling product in 98% yield; however, chlorobenzene failed as aryl source. Ortho-substituents did not hamper the *N*-arylation reaction, and even 2-bromothiophene led to the coupling product in 95% yield.

Ligand-free CuI (20 mol %) also catalyzed the *N*-phenylation of pyrazole, 3-methylpyrazole, and 3,5-dimethylpyrazole with phenyl iodide and phenyl bromide in DMF at 120 °C in the presence of Cs_2CO_3 (Table 4, entry 18).[158d] With 3-methylpyrazole, a mixture of the two regioisomers was observed (3:1 ratio, 85% yield). Notably, in the presence of

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K_3PO_4 as base instead of Cs_2CO_3, the temperature was decreased below 40 °C in the coupling of 4-iodoanisole with both pyrazole (70% yield) and 3-methylpyrazole (5:1 ratio of regioisomers, 50% yield).[158e]

Pyrazole was efficiently *N*-arylated (75−82% yield) with 4-methoxyphenyl iodide and phenyl-, 4-methoxy-, and 4-formylphenyl bromides in the presence of CuTC (copper thiophene-2-carboxylate) (25 mol %) without any additional ligand (Table 4, entry 19).[158f] Reactions were carried out in DMSO at 135 °C for 24−48 h, using K_2CO_3 as base.

On the other hand, a microwave-assisted solvent-free *N*-arylation of pyrazole was reported by Chow and Chan (Table 4, entry 20).[159] Reactions were carried out in a sealed tube at 150 °C for 2−10 h. K_3PO_4 was employed as base and aryl bromides bearing methyl, methoxyl, and acetyl substituents were used as coupling counterparts. The catalytic system composed of CuI and L-lysine **L16** or L-glutamine **L17** as ligands allowed for the attainment of the products in moderate yields in general. The role of amino acids in the coupling reaction was also discussed.

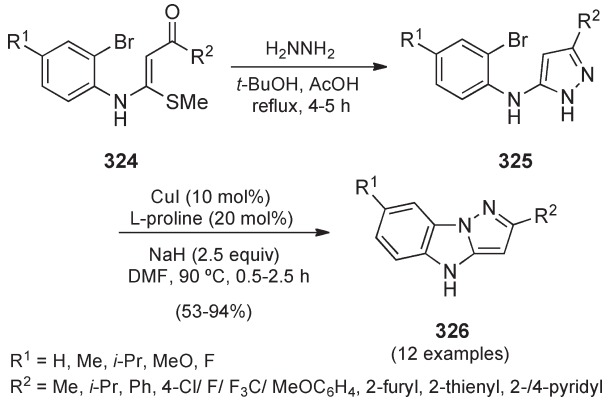
Copper-catalyzed C−N bond formation was applied for the first time by Ila and co-workers[160] to the intramolecular arylamination of 5-(2-bromoanilino)-1*H*-pyrazole **325** in the synthesis of pyrazolo[1,5-*a*]benzimidazoles **326**. Precursors **325** were prepared by cyclocondensation of hydrazine with appropriate *N*,*S*-ketene acetals **324** (Scheme 91). Coupling reactions were completed in 0.5−2.5 h at 90 °C in DMF using CuI as precatalyst, L-proline as ligand, and NaH as base. Pyrazoles bearing either electron-donating or electron-withdrawing substituents at the C-3 position furnished the desired tricyclic compounds in 53−84% yield, whereas heterocyclic substituents such as 2-thienyl, 2-furyl, and 2- and 4-pyridyl groups led to the corresponding products in higher yields (72−94%).

7.1.1.2. Aryl Boronic Acids As Electrophiles. Phenyl-, tolyl-, and 4-methoxyphenylboronic acids have been employed in the C−N cross-coupling reaction with pyrazole under heterogeneous catalysis conditions in the presence of Cu_2O (Scheme 92).[161] Reactions were carried out at room temperature in methanol for 12 h. All three *N*-arylpyrazole products were obtained in excellent yields (90−94%) without the need of any base.

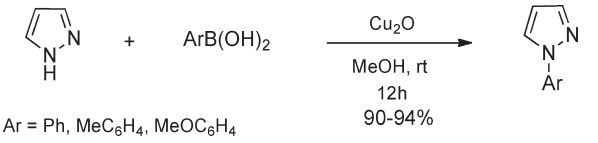
The *N*-arylation of 3-alkoxy-1*H*-pyrazoles **57** (see Scheme 18) through the cross-coupling reaction with arylboronic acids **327** has recently been reported by using stoichiometric amounts of $Cu(OAc)_2$ (Scheme 93). Reactions were conducted in open air in the presence of molecular sieves.[162] In general, mixtures of both *N*-aryl regioisomers **328** and **329** were obtained in variable yields starting from **57**. The reaction products are immediate precursors of 1-aryl-3/5-pyrazolones by deprotection of the alkoxy group. This approach could be a complementary alternative to the Knorr reaction in the preparation of one or another *N*-aryl regioisomer.

7.1.2. Other Transition Metal Catalyts. Apart from copper, other transition metals have shown to be effective catalysts in the *N*-arylation of pyrazoles. Thus, with a commercially available Fe/Cu bimetallic catalytic system ($[Fe(acac)_3]$/CuO as precatalysts), Taillefer et al.[163] obtained similar results to those previously achieved by using the Cu_2O-salox catalytic system[144] in the *N*-arylation of pyrazole. In general, reactions were performed in DMF at 90 °C for 30 h in the presence of Cs_2CO_3 (Table 5, entry 1). *N*-Aryl pyrazoles were obtained in very good yields (81−94%) from aryl iodides with both electron-withdrawing and electron−donor substituents, as well as from

Scheme 91



Scheme 92



bromobenzene or electron-poor aryl bromides. However, the reaction temperature had to be increased to 120 °C to attain the transformation of electron-rich aryl bromides and iodoaniline (57−86%), whereas the electron-poor 4-trifluoromethylphenyl chloride required 140 °C to react, although in moderate yield (40%).

With $FeCl_3$ as precatalyst, *N*,*N*′-dimethylethylenediamine (dmeda) **L18** as ligand, and K_3PO_4 as base, Correa and Bolm reported the cross-coupling reaction between pyrazole and aryl iodides and bromides in toluene at 135 °C for 24 h (Table 5, entry 2).[164] In general, aryl iodides gave the *N*-arylated products in higher yields (up to 87%) than aryl bromides (up to 64%), while the substitution of the chlorine atom was not observed. In agreement with the results obtained using copper catalysis, the steric hindrance in the aryl ring also exerted a significant influence in the yields.

More recently, Teo et al. described the *N*-arylation of pyrazole and 3-methylpyrazole with aryl iodides and bromides in water by using two catalytic systems, namely, $FeCl_3$/dmeda **L18** and $CoCl_2 \cdot 6H_2O$/dmeda **L18**, in the presence of $K_3PO_4 \cdot H_2O$ as base (Table 5, entries 3, 4).[165] Results were very similar in both cases. The reaction was highly chemoselective, reacting only the nitrogen atom and the iodine substituent even in the presence of other halogen substituents. Iodobenzene and monosubstituted *meta*-/*para*-iodobenzenes bearing either electron-donating or electron-withdrawing substituents led to the corresponding cross-coupling products in very good yields (up to 88%). However, lower yields (up to 45%) were obtained with both aryl iodides with ortho-substituents and aryl bromides. Yields for the *N*-arylation reaction in water were improved by using $FeCl_3 \cdot H_2O$/**L1** as the catalytic system (Table 5, entry 5).[166] In this case, reactions were performed under nitrogen atmosphere at 135 °C for 24 h in the presence of $K_3PO_4 \cdot H_2O$. A wide variety of functional groups on the

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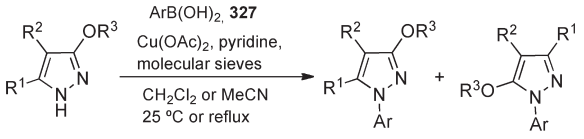
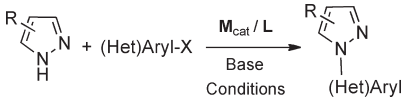
Scheme 93



57 328 329

R¹	R²	R³	Ar	328 (%)	329 (%)	R¹	R²	R³	Ar	328 (%)	329 (%)
i-Pr	H	Me	Ph	39	53	*i*-Pr	I	Me	4-ClC$_6$H$_5$	69	15
			4-ClC$_6$H$_5$	20	37				3-MeOC$_6$H$_5$	63	13
			3-MeOC$_6$H$_5$	37	40				2-MeOC$_6$H$_5$	25	n.d.
			2-MeOC$_6$H$_5$	15	11	Et	Bn	Me	Ph	75	traces
i-Pr	Br	Me	Ph	75	14				4-ClC$_6$H$_5$	66	<10%
			4-ClC$_6$H$_5$	70	17				3-MeOC$_6$H$_5$	74	traces
			2-MeOC$_6$H$_5$	21	n.d.	Et	H	Ph	4-ClC$_6$H$_5$	2	83
i-Pr	I	Me	Ph	70	11	Et	H	CF_3	Ph	---	94

Table 5. Metal-Catalyzed *N*-(Het)Arylation of Pyrazole Derivatives



entry	R	(het)aryl	X	M	L[a]	base	conditions	yield (%)	ref
1	H	Ph, 3-MeOC$_6$H$_4$, 4-Me/MeO/MeC(O)/ F_3C/NC/H_2N/$O_2NPhC_6H_4$	I, Br Cl	CuO/Fe^{3+}		Cs_2CO_3	DMF, 90−140 °C, 24−30 h	40−98	163
2	H	Ph, 2-MeO/ClC$_6$H$_4$, 3-Me/MeO/ClC$_6$H$_4$, 4-F/Cl/MeO/F_3C/$EtO_2CC_6H_4$	I, Br	$FeCl_3$	**L18**	K_3PO_4	toluene, 135 °C, 24 h	34−87	164
3	H, 3-Me	Ph, 2-MeO/ClC$_6$H$_4$, 3-Me/MeO/ClC$_6$H$_4$, 4-F/Cl/Br/MeOC$_6$H$_4$	I, Br	$FeCl_3$	**L18**	$K_3PO_4 \cdot H_2O$	water, 125 °C, 36 h	17−88	165a
4	H	Ph, 2-MeO/ClC$_6$H$_4$, 3-Me/MeO/ClC$_6$H$_4$, 4-F/Cl/MeOC$_6$H$_4$	I, Br	$CoCl_2$ 6H_2O	**L18**	$K_3PO_4 \cdot H_2O$	water, 120 °C, 36 h	16−85	165b
5	H	Ph, 2-MeC$_6$H$_4$, 3-MeOC$_6$H$_4$, 3-$HOCH_2C_6H_4$, 4-Me/MeO/F/ Cl/$H_2NC_6H_4$, 3,5-(Me)$_2$-C$_6$H$_3$, 2-/3-pyridyl, 2-thiophenyl, 2-pyrimidinyl	I	$FeCl_3 \cdot H_2O$	**L1**	$K_3PO_4 \cdot H_2O$	water, 135 °C, 24 h	53−92	166
6	H, 3-Me	3,5-(Me)$_2$C$_6$H$_3$, 3-pyridyl	Br Cl	Pd_2 (dba)$_3$	**L19**	NaO*t*-Bu	toluene, 80−105 °C, 2−24 h	76−88	167

[a] For the structure of ligands, see Figure 1.

electrophile were tolerated, including free amino and hydroxyl groups.

Finally, impressive results were obtained in the cross-coupling reaction of pyrazole and 3-methylpyrazole with 3,5-dimethylphenyl bromide (88% yield at 80 °C) and 3-pyridyl chloride (76% yield at 105 °C) by using a palladium complex and a monodentate phosphine **L19** as the catalytic system and sodium *tert*-butoxide as base (Table 5, entry 6).[167]

7.2. C−C Cross-coupling reactions

Suzuki, Stille, Sonogashira, Negishi, and Heck cross-coupling reactions are efficient methods for the introduction of alkenyl, alkynyl, acyl, and (het)aryl substituents at the carbon atoms of the pyrazole ring (Scheme 94).[168] The scope and applications of these reactions in the area of azole chemistry were reviewed up to the end of 2005.[169]

Suzuki coupling is probably the most versatile approach because a variety of both aryl- and heteroarylboronic acids and esters, as well as pyrazole halides, can be employed as reagents. In addition, a number of boronic acids are commercially available, stable to air and moisture, and also less toxic. Moreover, they can tolerate a wide range of functional groups, and the boron-containing side products of the reaction can be easily removed.[170]

In recent years, the application of the Suzuki cross-coupling reaction has undergone considerable progress mainly thanks to the discovery of more active catalysts such as the versatile palladium catalytic system $Pd_2(dba)_3/PCy_3/K_3PO_4$/dioxane−$H_2O$, which allows for cross-couplings of a vast array of nitrogen-containing boronic acids and aryl halides.[171]

In this context, several research groups have focused their investigations on synthesizing C-(het)aryl pyrazole derivatives by means of Suzuki cross-coupling reactions between (het)aryl halides and pyrazolylboronic esters, mainly derived from pinacol.

It is well established that the 4-position of pyrazole is the most nucleophilic one and readily undergoes electrophilic

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substitution, whereas the 5-position carries the most acidic C−H bond, which can be selectively deprotonated by strong bases. Consequently, functionalization at the C-4 position is possible through electrophilic substitution of the hydrogen by, e.g., bromine or iodine, followed by substitution of the electrophile. On the other hand, the deprotonated C-5 position can be functionalized by treatment with electrophiles. Alternatively, the C-5 position can be arylated by cross-coupling reaction of aryl reagents with previously prepared 5-halopyrazole derivatives. However, functionalization of the C-3 position is more problematic. In any case, functionalization at all three pyrazole positions can be achieved by means of cross-coupling reactions on previously prepared pyrazoles bearing heteroatoms in those positions such as ether, thioether, silyl ethers, or halogen-containing functionalities.

7.2.1. Functionalization at the C-4 Position. *7.2.1.1. From 4-(Pseudo)halopyrazoles.* Since the end of past decade, Vedsø and co-workers have been interested in developing efficient approaches to introduce a variety of substituents at the C-3, C-4, and C-5 positions of a preformed 1-hydroxy- and 1-benzyloxypyrazole ring in a regioselective manner.

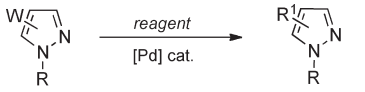
In this context, regioisomeric 4-substituted 1-(benzyloxy)-pyrazoles **331** were synthesized in good yields (72−99%) via highly regioselective monoiodination of 1-(benzyloxy)pyrazole **330** followed by iodine−magnesium exchange and reaction with different electrophiles (**E**) (Scheme 95).[172] The method was extended to the preparation of 4-aryl and 4-heteroaryl-substituted 1-benzyloxypyrazoles **332** by combining the iodine−magnesium exchange followed by transmetalation with zinc chloride and palladium-catalyzed cross-coupling reaction (Negishi-type conditions). However, Stille-type cross-coupling between 1-benzyloxy-5-(tributylstannyl)pyrazole and acid chlorides failed.

Despite the good results, this approach was not suitable for the preparation of 4-acyl-1-benzyloxypyrazoles **335** derived from aliphatic acid chlorides possessing acidic α-protons (Scheme 96). Neither pyrazol-4-ylmanganese nor pyrazol-4-ylzinc chlorides led to satisfactory results. However, moderate to excellent yields (57−93%) were obtained by means of the Stille cross-coupling between 1-benzyloxy-4-(tributylstannyl)-pyrazole **333** and acid chlorides **334** in the presence of 3 mol % of $Pd_2(dba)_3$, 6 mol % of the bulky electron-rich ligand 2-(di-*tert*-butylphosphino) biphenyl, and catalytic amounts of CuI.[172]

Stille coupling reaction was also employed as the key step in the synthesis of 1,4,5-substituted 3-trifluoromethylpyrazoles **338** from conveniently prepared 1,5-substituted 4-bromo-3-trifluoromethylpyrazoles **336** and allylstannane or arylstannanes **337** in the presence of $Pd(PPh_3)_4$ as catalyst (Scheme 97). Products were obtained in excellent yields in <3 h under microwave irradiation at 180 °C in acetonitrile.[173]

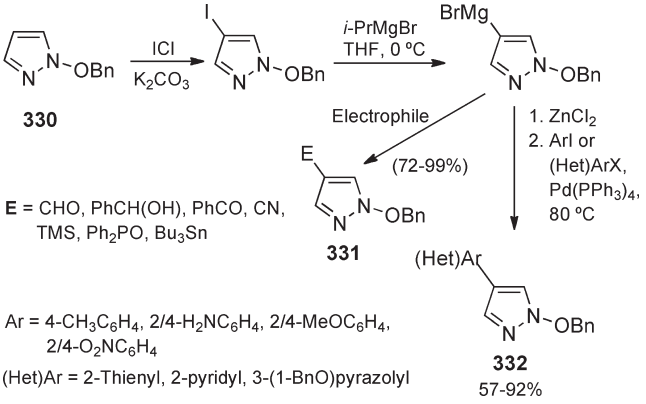
Despite the broad synthetic utility of $Pd(PPh_3)_4$ in the Suzuki cross-coupling reaction, its air- and light-sensitivity and the formation of a number of byproducts stimulated the development of more efficient ligands such as trialkylphosphines or 1,1-bis(diphenylphosphino)ferrocene (dppf). In the presence of $PdCl_2$/dppf, Suzuki cross-coupling between 3-alkoxy-4-halopyrazole derivatives **339** and arylboronic acids **340** allowed for the introduction of an aryl group at the C-4 position of the pyrazole ring (Scheme 98).[174] Reactions were performed in dioxane−water or propanol−water as solvent systems, with Cs_2CO_3 as base. With N*H* pyrazoles, addition of LiCl was required for the reproducibility of the results.

Scheme 94



Reaction	*reagent*	W
Suzuki	$R^1B(OH)_2$	X, OTf
Suzuki	R^1X	BPin
Stille	R^1SnBu_3	X, OTf
Sonogashira	R^2-C≡CH	X, OTf
Negishi	R^1ZnCl_2	X, OTf
Heck	R^2-CH=CH_2	X, OTf

Scheme 95

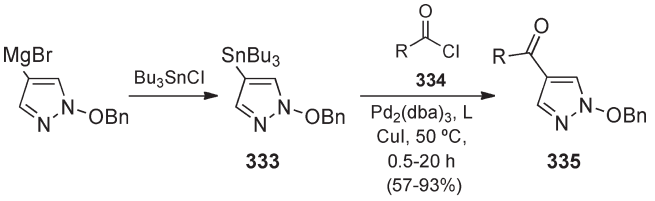


4-Halopyrazole-3-ols **342** (X = Br, I) have been used as coupling partners in Heck and Sonogashira cross-coupling reactions with *tert*-butyl acrylate and phenylacetylene, respectively.[175] The reactivity of these pyrazoles is influenced by both the nature of the halogen atom and the presence of the hydroxy group in the pyrazole ring. Thus, while the Heck reaction between 4-bromopyrazole **342a** and *tert*-butyl acrylate took place in a moderate 50% yield, the Sonogashira reaction between 4-iodopyrazole **342b** and phenylacetylene only afforded the target product **343** in 55% yield (Scheme 99). Neither **342a** nor **342b** could be coupled with boronic acids under standard Suzuki reaction conditions. However, acetyl-protected 4-bromopyrazole **346** reacted with phenyl-, 2-chlorophenyl-, and 3-thiophenylboronic acids, leading to the corresponding 4-aryl pyrazoles **347** in moderate yields. This approach allows one to prepare 3,4-substituted-1-phenylpyrazoles **345** in a highly regioselective manner with excellent yields from **343** through the formation of triflates **344**, followed by a Suzuki cross-coupling with phenylboronic acids (Scheme 99).[176]

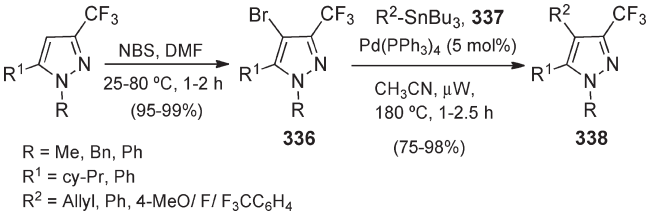
Ila and co-workers[160] have reported the first palladium-catalyzed intramolecular Heck heteroarylation of 1,3-disubstituted-5-(2-bromoanilino)pyrazole derivatives **348**. This cross-coupling reaction led to pyrazolo[3,4-*b*]indoles **349** in good yields (Scheme 100). The best results were obtained by using $Pd(OAc)_2$ as catalyst and K_2CO_3 as base in DMSO, with tetrabutylammonium bromide as additive. The cyclization was compatible with substrates bearing both electron-donating

dx.doi.org/10.1021/cr2000459 |*Chem. Rev.* 2011, 111, 6984–7034

Scheme 96



Scheme 97

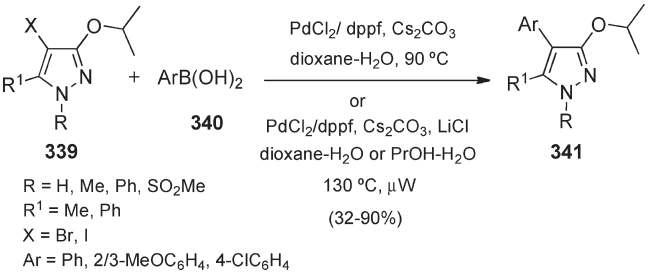


and electron-withdrawing substituents either on the pyrazole or aniline frameworks. However, no reaction was observed with 3-(2-pyridyl)- and 3-(4-pyridyl)-substituted pyrazoles (R^3 = 2-/4-pyridyl).

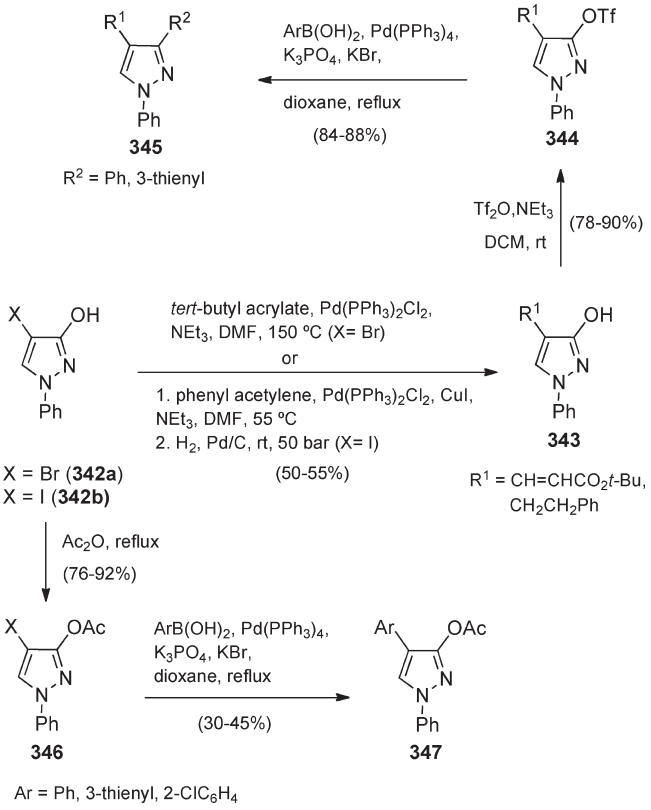
7.2.1.2. Suzuki Cross-Coupling Reactions with Pyrazol-4-ylboronates. Pyrazol-4-ylboronates can be prepared from 4-halopyrazoles by lithium−halogen exchange followed by treatment with borates. Thus, 1-methyl-1*H*-pyrazole-4-boronic acid pinacol ester **350** was prepared in 30% yield from 4-bromo-1-methyl-1*H*-pyrazole in a two-step process involving the reaction of the unstable intermediate 1-methyl-1*H*-pyrazole-4-boronic acid with pinacol (Scheme 101).[177] Yield was improved up to 70% through addition of 5 equiv of water to the crude reaction mixture. Under these conditions, lithium hydroxyl−ate complex **353** was formed as a stable solid in 88% yield. Neutralization of **353** provided pyrazolylboronate **350** in 80% yield. Both **350** and **353** were successfully coupled with aryl chlorides **351**, leading to 4-(het)arylpyrazole derivatives **352**.[178] In general, reactions proceeded in high yields without the presence of any base in the case of **353**. These results were compared with those obtained from ester **350** under the same reaction conditions and using KF as base. In all cases, a 10-fold time increase in the reaction rate was observed using complex **353**. The more electron-poor aryl chlorides achieved complete conversion in 1 h or less (<10 min for 2-$O_2NC_6H_4Cl$), whereas the electron-rich ones required 2 h; however, using ester **350** and KF, 80−90% conversion was observed in 24 h (90 min for 2-$O_2NC_6H_4Cl$ at 100% conversion). On the other hand, when KF was replaced by LiOH in the Suzuki reaction with **350**, the reaction rate was comparable to when complex **353** was used.

Functionalized pyrazole-4-boronic esters **354** were prepared for the first time by Harrity and co-workers through the cycloaddition reaction of alkynylboronates with sydnones (see Scheme 64). Subsequent Suzuki coupling reactions of **354** with 1-bromo-4-chlorobenzene provided 1,3,4-triaryl substituted pyrazoles **355** in high yields (Scheme 102).[111a]

Scheme 98



Scheme 99



7.2.2. Functionalization at the C-5 Position. *7.2.2.1. Metalation/Cross-coupling Reactions.* 5-Acyl- and 5-(het)aryl substituted 1-(benzyloxy)pyrazoles **356**, **357**, and **358** have been prepared in high yields from **330** by means of a one-pot procedure combining a directed *ortho*-lithiation/transmetalation and a Pd(0) catalyzed cross-coupling reaction with acyl chlorides or (het)aryl halides (Scheme 103).[179] Subsequent debenzylation gave rise to the corresponding 5-substituted 1-hydroxypyrazoles.

The introduction of an aryl substituent at C-5 of ethyl 3-methoxy-1-methyl-1*H*-pyrazole-4-carboxylate **359** has been performed by combining a transmetalation and a palladium-catalyzed cross-coupling reaction.[180] Treatment of **359** with butyllithium in THF led to quantitative lithiation at C-5, and the resulting intermediates reacted with a variety of reagents, thus affording 1,3,4,5-substituted pyrazoles **360** (Scheme 104).

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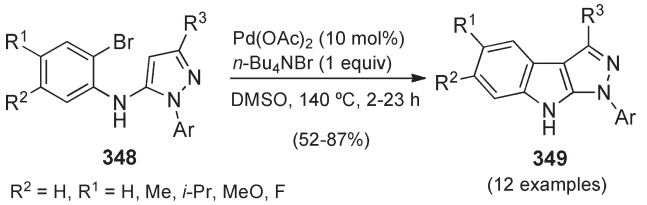
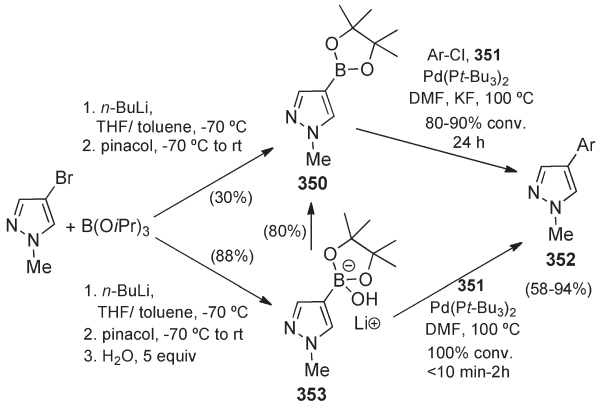
Scheme 100



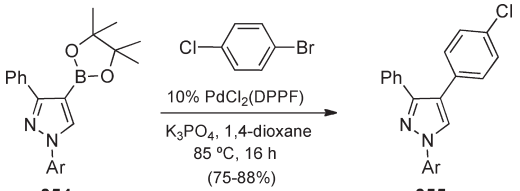
R^2 = H, R^1 = H, Me, *i*-Pr, MeO, F
R^2 = R^1 = MeO
R^3 = Me, *i*-Pr, Ph, 4-Cl/ MeO/ F/ $F_3CC_6H_4$, 2-furyl, 2-thienyl
Ar = Ph, 4-F/ Cl/ MeO

Scheme 101



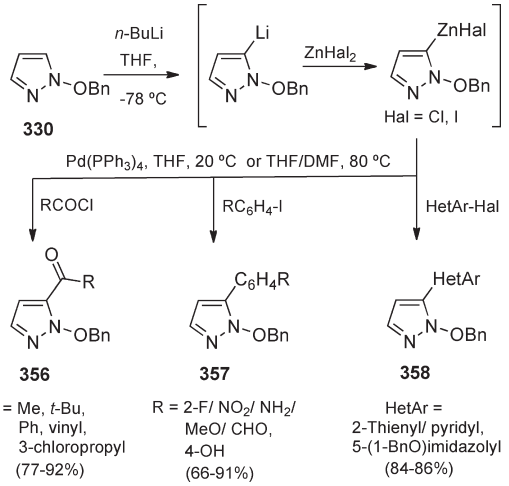
Ar = Ph, 4-F/ Me/ $MeOC_6H_4$, 2-$O_2NC_6H_4$, 2,6-$(Me)_2C_6H_3$, 2,4-$(MeO)_2C_6H_3$, 3-pyridyl

Scheme 102



Ar = Ph, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$

Scheme 103



R = Me, *t*-Bu, Ph, vinyl, 3-chloropropyl (77-92%)

R = 2-F/ NO_2/ NH_2/ MeO/ CHO, 4-OH (66-91%)

HetAr = 2-Thienyl/ pyridyl, 5-(1-BnO)imidazolyl (84-86%)

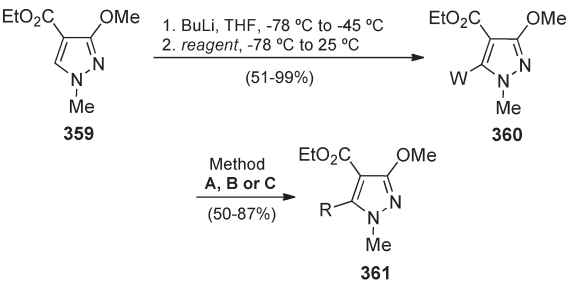
Two of them (W = I, ZnCl) were then coupled either with arylboronic acids under Suzuki conditions or with aryl bromides using palladium(0) as catalyst (Scheme 104, methods A and B, respectively). In this manner, substituted 5-arylpyrazoles **361** were obtained in good yields. The reaction of 5-iodopyrazole derivative **360** (W = I) with olefins under Heck conditions (Scheme 104, method C) afforded 5-vinylpyrazole derivatives **361** as a mixture of diastereoisomers (ratio *E*/*Z* = 5/5−1/0), whereas the bromopyrazole analogue (W = Br) remained unreactive. Using the most efficient $PdCl_2$/dppf catalyst (reaction conditions in Scheme 98), both iodo- and bromopyrazole analogues to **360** coupled well with phenylboronic acid, leading to 5-phenylpyrazole derivatives in good yield (62−74%).[36b]

The cross-coupling reaction of 4-trifluoromethyl-3(5)-tributylstannylpyrazole **175** (see Scheme 53) with 4-iodoacetophenone or 1-iodo-4-nitrobenzene led to the corresponding 4-trifluoromethyl-3(5)-substituted pyrazoles **362** in 71 and 81% yield, respectively (Scheme 105).[94a] Treatment of the lithium salt of **175** with iodomethane afforded 5-tributylstannyl-4-trifluoromethyl-1-methylpyrazole **363** in excellent yield and total regioselectivity. This derivative was then reacted with a series of aldehydes and ketones **364**, leading to pyrazole derivatives **365**. Other electrophiles such as *S*-phenyl benzenethiosulfate and phenyl isocyanate afforded their respective 1-methyl-5-functionalized-4-trifluoromethylpyrazoles in good yields.[94b]

On the other hand, the 4-fluoro analogue **178** (see Scheme 54) was reacted with aryl iodides **366** in the presence of 5 mol % $Pd(PPh_3)_4$ in DMSO to afford 5-aryl-4-fluoropyrazoles **367** in good to excellent yields (Scheme 106). In addition, carbonylative cross-coupling reaction of **178** with (het)aryl iodides **368** led to 5-acyl-4-fluoropyrazoles **369** in variable yields depending on the aryl iodide employed.[95]

Pyrazolyl-5-boronic acid pinacol esters have also been used in the Suzuki cross-coupling reaction with (het)aryl halides. A general

Scheme 104



reagent = Br_2, I_2, $ZnCl_2$, $B(O\text{-}i\text{-}Pr)_3$, $Sn(Bu)_3Cl$, $Me_2C{=}CHCH_2Br$, $Me_2NC_6H_4CHO$, 2,2,4-$(MeO)_3C_6H_2CHO$, DMF, CO_2

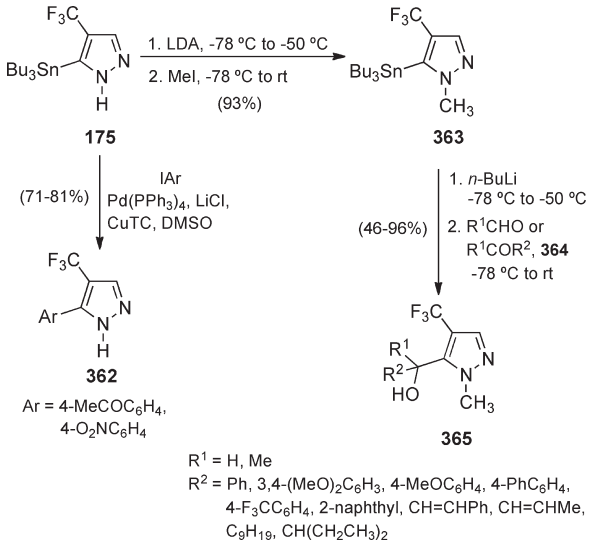
Method **A** (W = I): $ArB(OH)_2$, $Pd(PPh_3)_4$, 2M Na_2CO_3, toluene-MeOH
R = Ph, 4-$MeOC_6H_4$, 3-$O_2NC_6H_4$

Method **B** (W = ZnCl): ArBr, $Pd(PPh_3)_4$, THF, reflux
R = 4-MeC_6H_4, 2-Br-C_5H_4N

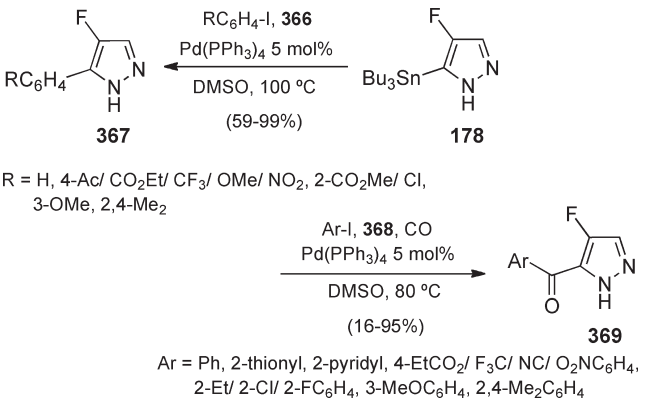
Method **C** (W = I): $CH_2{=}CHR'$, $Pd(OAc)_2$, PPh_3, K_2CO_3, CuI, DMF, 140 °C
R' = CO_2Me, CN, C_6H_5, O-*n*-Bu
E/*Z* = 7/3, 5/5, 1/0

dx.doi.org/10.1021/cr2000459 |*Chem. Rev.* 2011, 111, 6984–7034

Scheme 105



Scheme 106

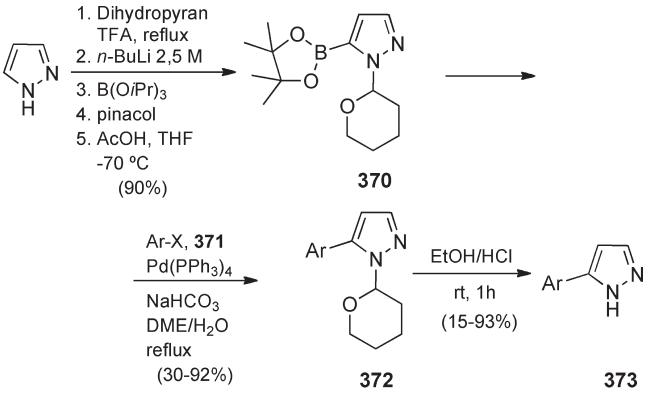


procedure for the synthesis of these boronic esters involved the reaction of *N*-substituted 5-pyrazolyl lithium salts with appropriate borates.

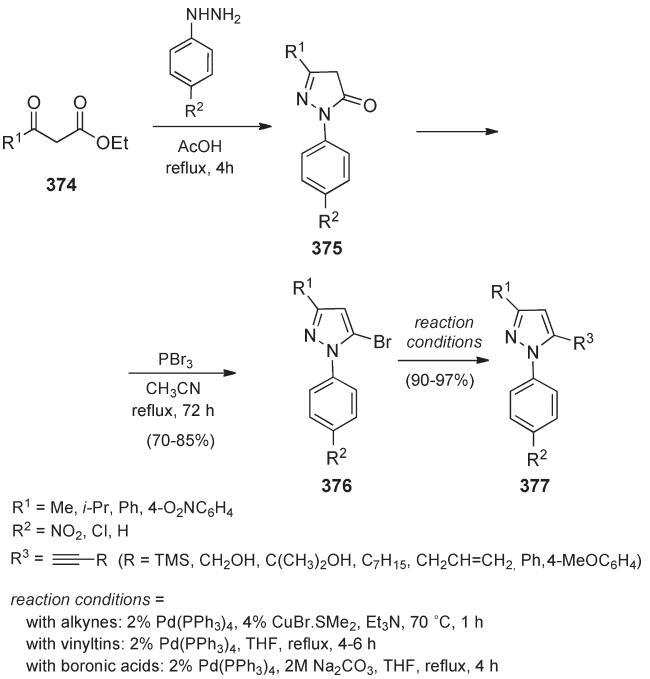
1*H*-Pyrazol-3(5)-yl-boronic acid was synthesized for the first time by Young et al.[181] starting from pyrazole through a sequence of reactions involving protection of the N*H* by treatment with 2,3-dihydro-2*H*-pyran, lithiation at C-5, reaction with triisopropyl borate, and subsequent deprotection. This reagent was coupled with aryl bromides under Suzuki conditions.

Rault and co-workers[182] generalized this approach for the synthesis of 3(5)-(het)arylpyrazoles **373** by means of the cross-coupling reaction of 1-(2-tetrahydropyranyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole **370** with (het)aryl iodides and bromides **371** (Scheme 107). Compound **370** was previously prepared in excellent yield from pyrazole through a five-step sequence. The cross-coupling products, 1-THP-5-(het)arylpyrazoles **372**, were obtained in variable yields and, upon treatment with ethanolic HCl at room temperature, afforded the target 5-arylpyrazoles **373**. When [2-(trimethylsilyl)ethoxy]methyl (SEM) was used as a protecting group of the nitrogen, the analogue 5-pyrazolylboronate

Scheme 107



Scheme 108



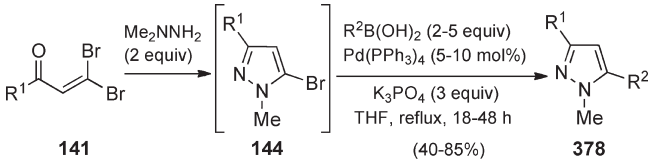
derivative could be coupled with **371**, but removing the SEM group proved to be more difficult.

7.2.2.2. C-5 Heterosubstituted Pyrazoles. Cross-coupling reactions at the C-3 and C-5 positions of the pyrazole ring represent an attractive and usually efficient alternative to the conventional condensation of 1,3-dielectrophilic synthons with hydrazines in the synthesis of 3,5-disubstituted pyrazoles.

Thus, Sonogashira, Stille, and Suzuki reaction conditions have been successfully applied to the regioselective synthesis of 1-aryl-3-alkyl(aryl)-5-substituted pyrazoles **377** through the cross-coupling of 1-aryl-3-alkyl(aryl)-5-bromopyrazoles **376** and alkynes, vinyltins, and arylboronic acids, respectively, promoted by $Pd(PPh_3)_4$ (Scheme 108).[183] 5-Bromopyrazole derivatives **376** were in turn prepared starting from β-ketoesters **374** via formation of 1-arylpyrazolones **375** and subsequent treatment with PBr_3.

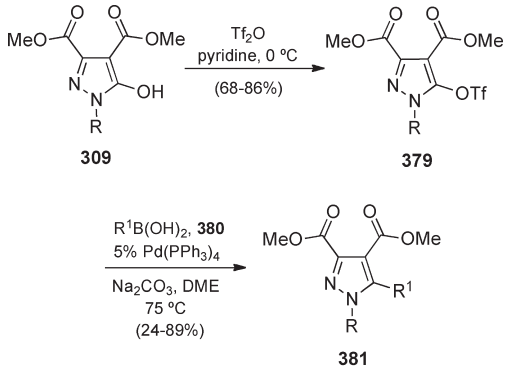
dx.doi.org/10.1021/cr2000459 |*Chem. Rev.* 2011, 111, 6984–7034

Scheme 109



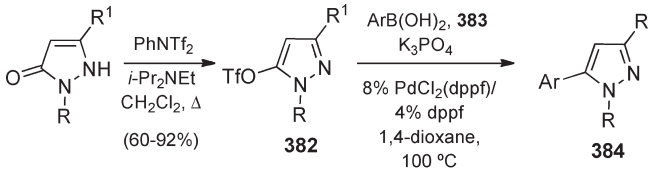
R^1 = Ph, 4-MeO/ $O_2NC_6H_4$, 2-naphtyl, 2-thiophenyl, 2-α-pinenyl, 17-androstanyl
R^2 = Me, Ph, 4-Me/ Cl/ $MeOC_6H_4$, CH=CHMe

Scheme 110



R = $(CH_2)_2CH(CH_3)_2$; R^1 = Allyl, 1-cyclopentenyl, 4-Me_2N/ MeO/ F_3C/ ClC_6H_4, 4-Me-3-thiophenyl, 5-Cl-2-thiophenyl, 1-Me-4-pyrazolyl, 2-/3-MeC_6H_4, 4-pyridyl,
R = $CH_2C_6H_{11}$; R^1 = 4-FC_6H_4, 3-NCC_6H_4
R = Ph; R^1 = 4-NC/ $O_2NC_6H_4$

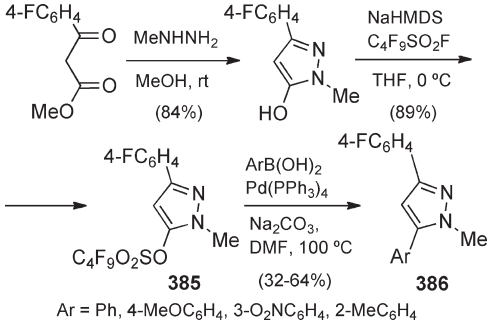
Scheme 111



R = H, Me, Ph
R^1 = Me, CF_3
Ar = Ph, 4-F/ MeO/ $MeCOC_6H_4$, 2-MeC_6H_4

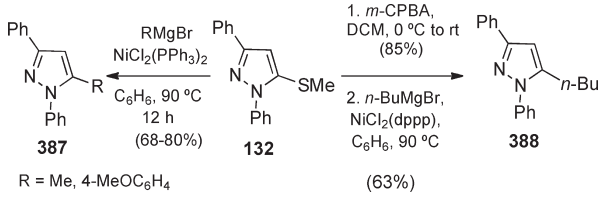
This methodology was applied to the preparation of a series of diaryl-substituted pyrazoles as potent CCR2 receptor antagonists.[184] Taylor and co-workers[81] regioselectively prepared 5-alkyl/aryl-3-aryl-1-methylpyrazoles **378** through a one-pot, tandem condensation/Suzuki cross-coupling process starting from β,β-dibromoenones **141** via in situ formed 3-alkyl/aryl-5-bromo-1-methylpyrazoles **144** (see Scheme 43). The process was equally successful with arylboronic acids, (*E*)-prop-1-enylboronic acid and methylboronic acid (Scheme 109). This methodology allows for the regioselective synthesis of 1,3-dimethyl-5-phenyl and 1,5-dimethyl-3-phenylpyrazoles as the only products in 73 and 85% yield, respectively. The traditional condensation of 1-phenyl-1,3-butanedione with methylhydrazine leads to a mixture of both regioisomers in a 60:40 ratio.

Scheme 112



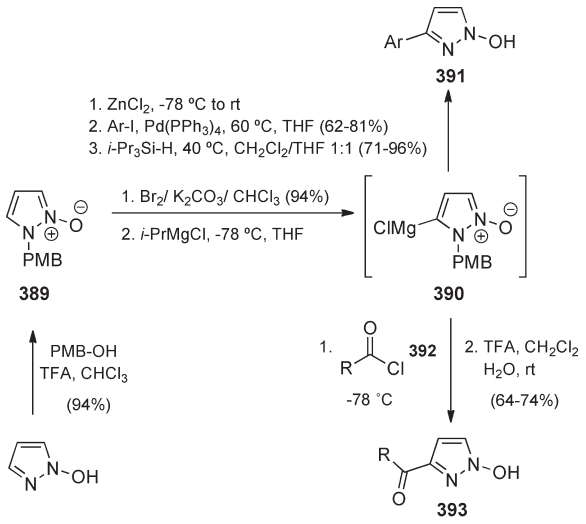
Ar = Ph, 4-$MeOC_6H_4$, 3-$O_2NC_6H_4$, 2-MeC_6H_4

Scheme 113



R = Me, 4-$MeOC_6H_4$

Scheme 114

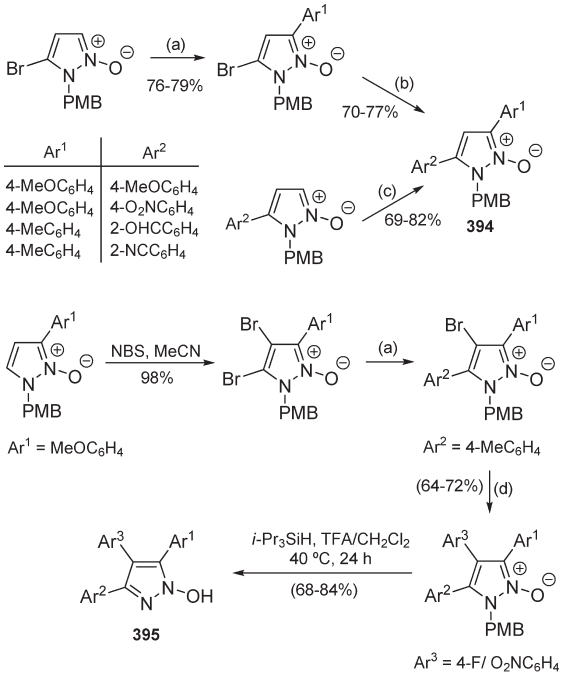


Ar = 4-Me/ $MeOC_6H_4$, 2/4-$O_2NC_6H_4$, 2-FC_6H_4, 2-pyridyl, 2-thienyl
R = Me, *t*-Bu, $Cl(CH_2)_3$, $Br(CH_2)_3$, $CO_2Me(CH_2)_2$, Ph

The hydroxyl group at the C-5 position of the pyrazole ring can be easily transformed into triflate or nonaflate groups, which can be further substituted through palladium-catalyzed cross-coupling reactions with aryl and alkenyl boronic acids. Thus, the treatment of 5-hydroxy-3,4-pyrazole dicarboxylates **309** (see Scheme 84) with triflic anhydride led to the corresponding pyrazole triflates **379**, which underwent palladium-mediated Suzuki coupling under anhydrous conditions with a variety of boronic acids **380**, affording fully substituted pyrazoles **381** in moderate to excellent yields (Scheme 110).[134] The best results (56−89%) were obtained with monosubstituted phenyl boronic acids, whereas the

dx.doi.org/10.1021/cr2000459 |*Chem. Rev.* 2011, 111, 6984–7034

Scheme 115

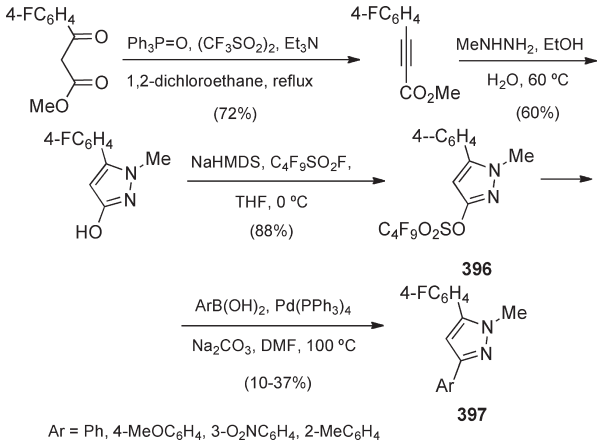


Ar^1	Ar^2
4-$MeOC_6H_4$	4-$MeOC_6H_4$
4-$MeOC_6H_4$	4-$O_2NC_6H_4$
4-MeC_6H_4	2-$OHCC_6H_4$
4-MeC_6H_4	2-NCC_6H_4

PMB: 4-Methoxybenzyl

(a): 1. LDA, -100ºC; 2. $ZnCl_2$, -100 ºC to rt; 3. Ar^1-I, Pdº, 60 ºC.
(b): 1. *i*-PrMgCl, -78 ºC; 2. $ZnCl_2$, -78 ºC to rt; 3. A^2-Hal, Pdº, 60 ºC
(c): 1. *i*-PrMgCl, rt; 2. $ZnCl_2$, rt; 3. Ar^1-Hal, Pdº, 60 ºC
(d): 1. *i*-PrMgCl, 0 ºC, $ZnCl_2$, to rt; 2. Ar^3-I, Pdº, 60 ºC

Scheme 116

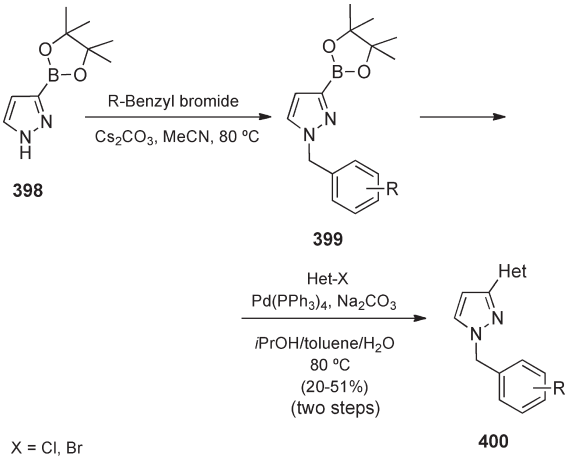


lowest yields (24−40%) were reached with heteroaryl and alkenyl ones.

By changing the reaction conditions, pyrazolyl triflates **382** were coupled with aryl boronic acids **383** to afford 5-arylpyrazole derivatives **384** in high yields (Scheme 111).[185] The coupling conditions were tolerant to a broad range of electronic and steric variations in the components of either boronic acid or pyrazolyl triflate.

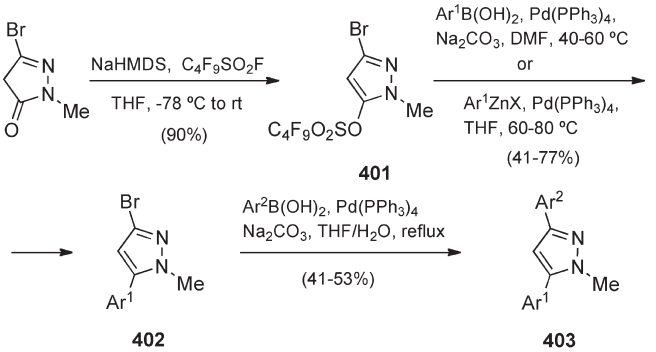
5-Aryl-3-(4-fluorophenyl)-1-methylpyrazoles **386** were obtained in poor to moderate yield by Suzuki coupling of pseudohalopyrazole 3-(4-fluorophenyl)-1-methyl-5-nonaflate **385** with aryl

Scheme 117



X = Cl, Br
R = CF_3, 2-/3-/4-Cl, H
Het = Ph, 4-FC_6H_4, 2-pyrimidinyl, 2-(4-F)pyrimidinyl, 2-(3-MeO)pyrimidinyl, 2-thiazolyl, 2-furyl, 2-(3-Me)pyridinyl, 2-pyridazolyl, 2-benzothiazolyl, 2-benzoxazolyl

Scheme 118



Ar^1 = 4-MeO/ $F_3CC_6H_4$, 3-$O_2NC_6H_4$, 2-MeC_6H_4, 5-Me-2-pyridyl, 3-Cl-4-FC_6H_3
Ar^2 = 3,5-$F_2C_6H_3$, 4-$MeOC_6H_4$, 3-thienyl

boronic acids under nonaqueous conditions in the presence of a weak base (Scheme 112).[186] 3-Aryl regioisomers were also obtained from the corresponding pyrazole-3-yl nonaflate (see below).

The substitution of the methylthio group in 1,3-diphenyl-5-methylthiopyrazole **132** (see Scheme 41) by means of a nickel-catalyzed cross-coupling reaction with methyl- and 4-methoxyphenyl Grignard reagents afforded 5-methyl/arylpyrazole derivatives **387** in good yields (Scheme 113).[77] In addition, 5-(*n*-butyl)pyrazole analogue **388** was prepared in 63% yield by nickel-catalyzed cross-coupling of the corresponding *n*-butyl Grignard reagent with 5-(methylsulfonyl)pyrazole, previously obtained by *m*-CPBA oxidation of **132**.

7.2.3. Functionalization at the C-3 Position. Vedsø and co-workers carried out a regioselective arylation at the C-3 position of 1-hydroxypyrazole by means of selective bromination of 2-(4-methoxybenzyl)pyrazole 1-oxide **389** and subsequent bromine−magnesium exchange, transmetalation with $ZnCl_2$, Negishi-type cross-coupling, and final acid-induced *N*-deprotection (Scheme 114).[187] 3-Acylated analogues **393** were prepared in good yields through the addition of acid chlorides **392** to pyrazol-3-ylmagnesium chloride **390** at −78 °C.[179]

dx.doi.org/10.1021/cr2000459 |*Chem. Rev.* 2011, 111, 6984–7034

Vedsø approaches[172,179,187] were adequately combined for the regioselective synthesis of 3,5-diarylpyrazole 1-oxides **394** and 3,4,5-triarylated 1-hydroxypyrazoles **395** (Scheme 115).[188] Other substituents could also be introduced at the C-3, C-4, and C-5 positions of the pyrazole ring. Thus, 5-methyl-3-(4-methoxyphenyl), 4-(1-hydroxybenzyl)-3-(4-methylphenyl)-5-(4-methoxyphenyl), and 3-thiomethyl-(4-methoxyphenyl)-2-(4-methoxybenzyl)pyrazole 1-oxides were obtained in 87, 35, and 79% yield, respectively, through metalation followed by reaction with the appropriate electrophile.[188]

3-Aryl-5-(4-fluorophenyl)-1-methyl pyrazoles **397** were prepared although in poor yield by palladium-catalyzed coupling of the pyrazol-3-yl nonaflate **396** with arylboronic acids (Scheme 116).[186]

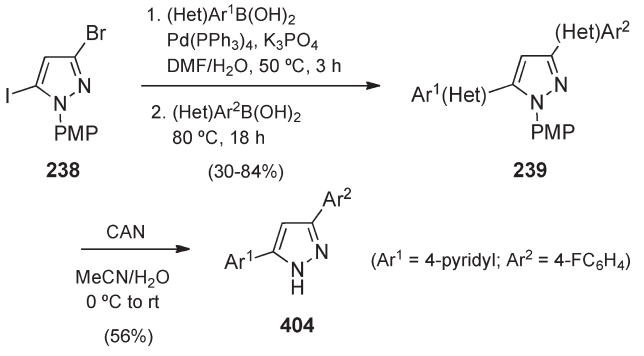
Nowadays, some pyrazolylboronic acid esters are commercially available. For example, starting from pyrazole-3-boronate **398**, an array of 1-benzyl-3-heteroarylpyrazoles **400** was prepared in 20−51% yield by means of a one-pot, two-step sequence involving benzylation/Suzuki cross-coupling (Scheme 117).[189] As *N*-benzylated intermediate products **399** decomposed during the work-up, they were used directly in the second step.

7.2.4. Functionalization at C-3 and C-5 Positions. Pyrazoles bearing different heteroatoms at the C-3 and C-5 positions can be sequentially synthesized. For example, palladium-catalyzed cross-coupling of difunctionalized 3-bromo-1-methylpyrazol-5-yl nonaflate **401** with arylboronic acids or arylzinc halides led to 5-arylpyrazole derivatives **402** through a highly regioselective nonaflate group substitution. Subsequent Suzuki couplings over bromides **402** afforded 3,5-diaryl-1-methylpyrazoles **403** in moderate yields (Scheme 118).[186]

The one-pot sequential double Suzuki cross-coupling reaction of *N*-PMP-3-bromo-4-iodopyrazole **238** (see Scheme 67) with (het)arylboronic acids led to unsymmetrical *N*-PMP-3,5-bis(het)arylpyrazoles **239**.[115] The first cross-coupling was highly site-selective at the C-5 position; thus, the second one allowed for the introduction of a different (het)aryl group at the C-3 position (Scheme 119). The PMP protecting group could subsequently be removed, thus giving 3,5-substituted pyrazole **404** in moderate yield.

7.2.5. Application to the Sequential Synthesis of Fully Substituted Pyrazoles. McLaughlin et al.[190] developed an efficient and modular strategy for the regiocontrolled synthesis of 3,4,5-triarylsubstituted pyrazoles **408** (Scheme 120). The use of the easily switchable 3,4-dihydro-2*H*-pyran (THP) metal-directing group turned out to be central for this approach because it enabled the sequential direct lithiation of the pyrazole 5- and 3-positions. Pyrazole boronic esters **405** and **406** derived from these lithiated intermediates underwent Suzuki cross-coupling under nonaqueous conditions to minimize undesirable protolytic deboronation. Finally, halogenation

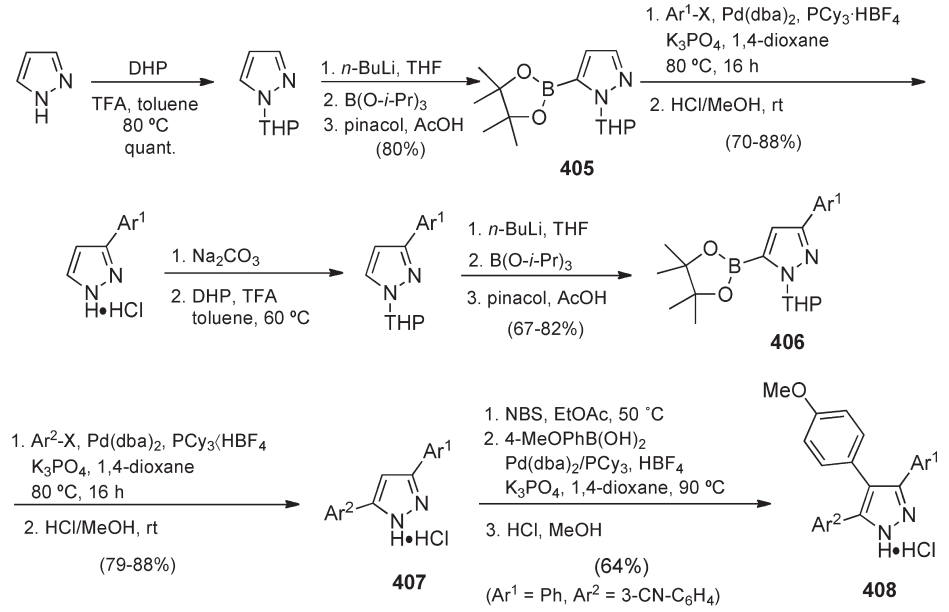
Scheme 119



(Het)Ar^1 = 2-thiophenyl, 2-furyl, 3-$F_3CC_6H_4$, 4-ClC_6H_4, 4-pyridyl, 4-$MeO_2CC_6H_4$, 3-pyridyl

(Het)Ar^2 = 3-pyridyl, 4-FC_6H_4, 2-tiophenyl, 4-$MeC(O)C_6H_4$I, 2-furyl, 3/4-$OCH_2OC_6H_3$

Scheme 120



406: Ar^1 = Ph, 2-MeC_6H_4, 3-NCC_6H_4, 4-F/ $EtO_2CC_6H_4$, 3-pyridyl

407: Ar^1 = Ph, Ar^2 = 2-MeC_6H_4, 3-NCC_6H_4, 4-F/ NCC_6H_4, 3-pyridyl

Ar^1 = 4-$EtO_2CC_6H_4$, Ar^2 = 3-NCC_6H_4

X = Cl, Br, I

THP = Tetrahydropyranyl

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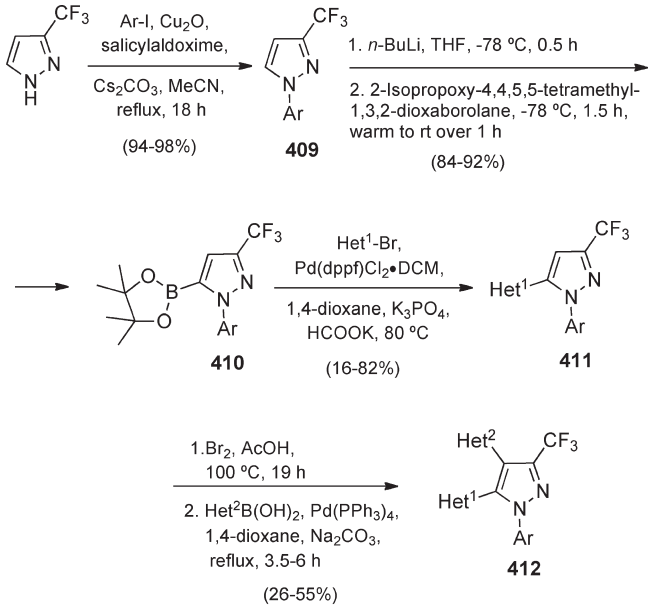
on the 4-position of pyrazoles **407** allowed for the introduction of an aryl substituent at the remaining carbon of the ring.

This methodology was applied to the synthesis of fully substituted 1-aryl/heteroaryl-3-trifluoromethyl-4,5-bis(heteroaryl)-pyrazoles **412** starting from commercially available 3-trifluoromethylpyrazole.[191] Suzuki cross-coupling reactions with **410** (Ar = Ph, 4-$MeOC_6H_4$) proceeded in 16−82% yield with a variety of heteroaryl bromides, thus affording 5-heteroarylpyrazoles **411**. However, with N-(2-pyridinyl) derivative **410**, the major product was the proto-deboronated precursor **409** (Scheme 121).

Sames and co-workers have recently reported a general approach to access fully substituted pyrazoles in a totally regioselective manner via a sequential catalytic *C*-arylation/*N*-arylation facilitated by a 2-(trimethylsilyl)ethoxymethyl (SEM)-group transposition.[192] The major strength of this methodology is the possibility of starting the synthesis from either the parent pyrazole or any pyrazole intermediate. Thus, starting from free (N*H*)-pyrazole, bromination at the 4-position, followed by silylation with SEM-Cl and subsequent Suzuki reaction with an aryl boronic acid, led to 4-aryl-*N*-protected pyrazoles **413** (Scheme 122). Selective arylation of **413** at the 5-position was achieved by means of palladium-catalyzed coupling with aryl bromides, thus affording 4,5-diarylpyrazoles **414** in moderate to good yields. Next, the transposition of the SEM-protecting group from one nitrogen to the other ("SEM switch") converted the unreactive C-3 position to a reactive C-5 position in **415**. At this point, the second palladium-catalyzed C−H arylation took place affording (SEM)-3,4,5-triaryl substituted pyrazoles **416**. The SEM group could be efficiently removed by treatment with HCl in ethanol. Furthermore, the nitrogen atom could be regioselectively methylated by reaction of SEM-protected 4,5-diarylpyrazoles **414** with $Me_3O{-}BF_4$, and the resulting 3,4-diaryl-1-methylpyrazoles **418** could be arylated again at the 5-position.

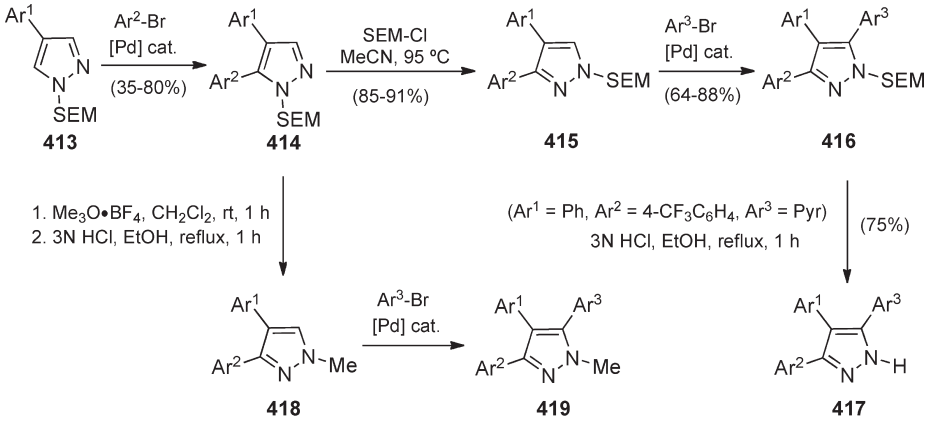
Finally, Knochel and co-workers[193] recently reported a regio- and chemoselective synthesis of fully substituted pyrazoles through successive metalations on *N*-SEM and *N*-methylpyrazoles **420a,b**

Scheme 121



409: Ar = Ph, 4-$MeOC_6H_4$, 2-pyridyl
411: Ar = Ph or 4-$MeOC_6H_4$, Het^1 = 2-Pyridyl, 3-(6-NH_2-5-NO_2)pyridyl, 5-pyrimidyl, 3-(5-MeO)pyridyl, 5-(2-NH_2)pyrimidyl, 2-thiophenyl
Ar = 2-pyridinyl, Het^1 = 2-Pyridyl, 5-pyrimidyl
412: Ar = Ph, Het^1 = 2-Pyridyl, Het^2 = 3-(4-MeO)pyridyl
Het^1 = 3-(6-NH_2-5-NO_2)pyridyl, Het^2 = 3-(4-MeO)pyridyl

Scheme 122



[Pd] cat. = $Pd(OAc)_2$, $PBuAd_2$, K_2CO_3, HOPiv, DMA, 140 °C, 12 h
413: Ar^1 = Ph, 2-MeC_6H_4, 4-$F_3CC_6H_4$, CO_2Et
414: Ar^1 = Ph, Ar^2 = Ph, 4-CF_3/ MeC(O)/ $O_2NC_6H_4$, 3/4-$MeOC_6H_4$, 3-Me_2N/ $EtO_2CC_6H_4$, 3-pyridyl
Ar^1 = 2-MeC_6H_4, Ar^2 = 3-pyridyl
Ar^1 = 4-$F_3CC_6H_4$ or CO_2Et, Ar^2 = Ph
416: Ar^1 = Ph, Ar^2 = Ph, Ar^3 = 3-$EtO_2CC_6H_4$
Ar^2 = 3-pyridyl, Ar^3 = 3-$EtO_2CC_6H_4$
419: Ar^1 = Ph, Ar^2 = 3-$MeOC_6H_4$, Ar^3 = 3-pyridyl
Ar^2 = Ph, Ar^3 = 3-pyridyl
Ar^2 = 3-/4-$EtO_2CC_6H_4$, Ar^3 = 3-pyridyl
Ar^2 = 4-$F_3CC_6H_4$, Ar^3 = 4-$O_2NC_6H_4$

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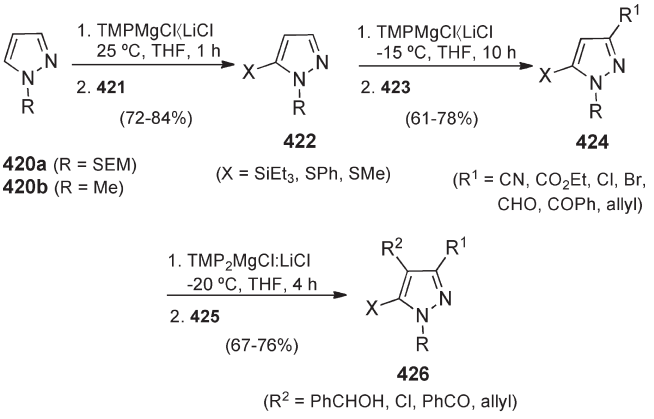
Scheme 123



(Scheme 123). Treatment with TMPMgCl·LiCl, followed by reaction with electrophiles **421** gave the corresponding 5-substituted pyrazoles **422a,b** in high yields. Subsequent deprotonation at the C-3 position, followed by quenching with a variety of reagents **423,** afforded the corresponding 3,5-substituted pyrazoles **424a,b** in good yields. The remaining free 4-position of pyrazoles **424a,b** was metalated once again by using a stronger base, $TMP_2Mg \cdot 2LiCl$, and the deprotonated intermediates were then coupled with reagents **425**, leading to fully substituted pyrazoles **426a,b**. This methodology was applied to the synthesis of the acaricide Tebufenpyrad[194] in an eight-step sequence starting from 1-methyl-1*H*-pyrazole.

8. CONCLUSIONS

Although pyrazoles are rarely found in natural products, numerous pyrazole derivatives display a broad spectrum of pharmaceutical and agrochemical activities, and they have also been successfully applied in other fields. For these reasons, the search for new and efficient procedures for the synthesis of pyrazole derivatives has experienced an unprecedented growth. Tuning multicomponent one-pot procedures and the use of new reaction conditions (polar aprotic solvents, fluorinated solvents, microwave irradiation, etc.) have made it possible to overcome some limitations, such as the preparation of the starting materials or the lack of regioselectivity in the synthesis of 1,3,5- and 1,3,4,5-substituted pyrazoles, by means of the condensation of hydrazine derivatives and 1,3-dielectrophilyc compounds. On the other hand, the introduction of new Lewis acids and new dipolarophiles has led to notable advances in the 1,3-dipolar cycloaddition.

In the past few years, an alternative strategy to traditional methods has been developed. This methodology is based upon the 5-exo/endo-dig cyclization of metal-activated alkynes by nucleophilic addition of nitrogen derivatives. Following this strategy, a variety of 1,3,5-, 3,4,5-, and 1,3,4,5-substituted pyrazoles have been obtained by catalytic intramolecular cyclization. In addition, the introduction of new multicomponent methods has permitted access to very interesting alkoxycarbonyl and phosphonylpyrazoles, in a single step, or the difficult-to-prepare 1,4,5-substituted pyrazoles, respectively. The Michael-type addition of *N*-monosubstituted hydrazones to nitroolefins, reported for the first time in 2006, has emerged as a versatile method for the regioselective synthesis of a plethora of alkyl-, aryl-, and heteroaryl-substituted pyrazoles.

Finally, the functionalization of previously prepared pyrazoles by C−N and C−C cross-coupling reactions has undergone spectacular progress in this decade. Transition metal-catalyzed *N*-(het)arylation of 1*H*-pyrazoles with (het)aryl halides and arylboronic acids constitutes a convenient, alternative method to the cyclocondensation of (het)arylhydrazines and 1,3-dielectrophilic compounds in many cases. The progress in this field has been achieved thanks to the discovery of highly efficient copper/ligand systems allowing for the use of a catalytic amount of metal under mild conditions. Moreover, the Suzuki, Stille, Sonogashira, Negishi, and Heck C−C cross-coupling reactions have been efficiently applied to the regioselective introduction of alkenyl, alkynyl, acyl, and (het)aryl substituents at the C-3, C-4, and C-5 positions of previously prepared pyrazoles bearing adequate heteroatoms containing functionalities. In particular, the application of the Suzuki reaction has undergone considerable progress in recent years mainly owing to the discovery of more active catalysts and the introduction of pyrazolylboronic esters as intermediates.

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BIOGRAPHIES

Santos Fustero was born in Aínsa, Spain, in 1949. He studied Chemistry at the University of Zaragoza, where he obtained his Licenciatura (equivalent to a B.Sc. degree) in Chemistry in 1972. He received his Ph.D. in Organic Chemistry in 1975 from the same University, working in the field of heterocyclic chemistry under the supervision of Prof J. Barluenga and Prof V. Gotor. He spent two years as a post-doctoral research associate at Prof H. Lehmkuhl's laboratory at Max-Planck-Institut für Kohlenforschung in Mülheim an der Ruhr, Germany, researching organometallic chemistry. In 1983, he became Associate Professor at University of Oviedo, Spain, and in 1990, he was promoted to Full Professor in Organic Chemistry at University of Valencia. In 2005, he also became research group leader at Centro de Investigación "Príncipe Felipe" (CIPF) in Valencia. His research interests include

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María Sánchez was born in Valencia, Spain, in 1977. She studied Pharmacy and received her Ph.D. in 2005 from the University of Valencia under the supervision of Professor Santos Fustero, working in the field of organofluorine chemistry and focusing on the synthesis of α- and β-amino acids through the olefin metathesis reaction. She spent two years as a postdoctoral researcher in the laboratories of Professor Scott J. Miller at Boston College and Yale University, U.S.A., working on peptide-based asymmetric catalysis. She then joined Professor Fustero's group, where she currently holds a Juan de la Cierva research contract. Her scientific interests include asymmetric organocatalysis and organofluorine chemistry.

Pablo Barrio was born in La Coruña (Spain) in 1979. He studied Chemistry at the University of Oviedo. In 2001 he obtained his Bs.C. in Chemistry. In 2007 he got his Ph.D., from the same University, under the supervision of Prof. Barluenga working on the transmetallation reaction between Cr(0) Fischer carbene complexes and Ni(0). A few months later, he joined the group of Prof. Carreira at ETH Zurich. During his 2 years post-doctoral stay he worked on several projects related with asymmetric catalysis as well as in the total synthesis of a natural product. In November 2009 he joined the group of Prof. Fustero as a Juan de la Cierva fellow. He is currently studying tandem addition/intramolecular aza- Michael reactions involving fluorinated nucleophiles.

Antonio Simón-Fuentes was born in Requena (Valencia, Spain). He studied Chemistry at the University of Valencia (1970−1975). He obtained his Ph.D. in the Instituto de Agroquímica y Tecnología de Alimentos (Valencia, CSIC). Since 1986 he is an Associate Professor in Organic Chemistry at the University of Valencia. His preferential research interest is the synthesis of organofluorinated compounds and the chemistry of pyrazoles.

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DEDICATION

Dedicated to Professor José Elguero.

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