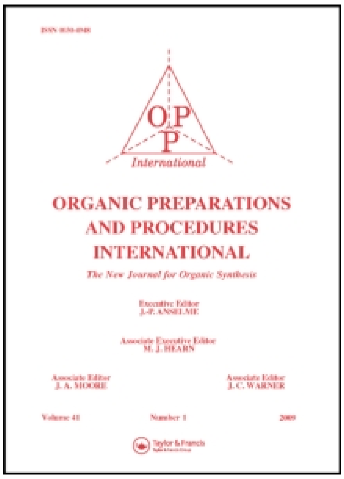

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

ORGANOMETALLIC CARBOXAMIDATION. A REVIEW

Constantinos G. Screttas[a]; Barry R. Steele[a]
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To cite this Article Screttas, Constantinos G. and Steele, Barry R.(1990) 'ORGANOMETALLIC CARBOXAMIDATION. A REVIEW', Organic Preparations and Procedures International, 22: 3, 269 — 314

To link to this Article: DOI: 10.1080/00304949009458205

URL: http://dx.doi.org/10.1080/00304949009458205

ORGANIC PREPARATIONS AND PROCEDURES INT. 22(3), 269-314 (1990)

ORGANOMETALLIC CARBOXAMIDATION. A REVIEW

Constantinos G. Screttas* and Barry R. Steele*

Institute of Organic Chemistry
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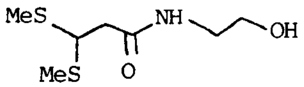
INTRODUCTION

Carboxylic acid amides occur widely in nature and while the most familiar examples are of peptides and proteins, simpler molecules have been isolated from various sources. Compounds **1-3** are examples from the recent literature.[1-3]



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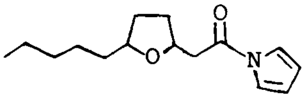

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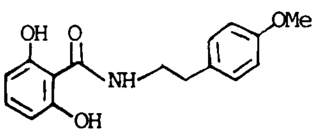
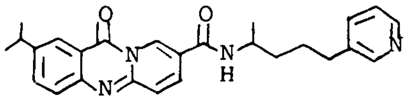


3

Many applications of carboxamides have been found. The amide group occurs in a number of biologically active compounds such as the dopamine antagonist **4**,[4] the platelet activating factor antagonist **5**,[5] the glucocorticoid antagonist **6**[6] and, of course, the β-lactam antibiotics.



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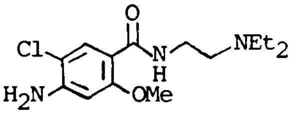

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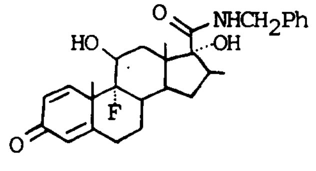
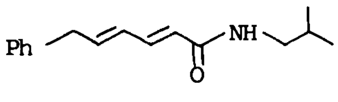
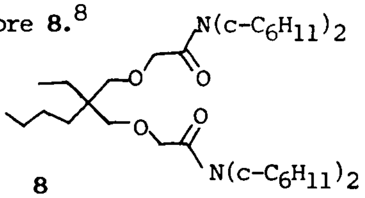


6

Other uses have also recently been noted for simple acid amides such as the insecticide, **7**,[7] and the lithium ionophore **8**.[8]

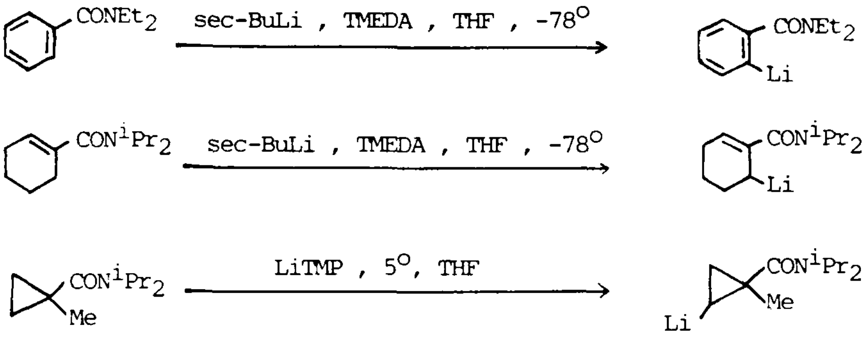


7



8

In organic synthesis the carboxamide group may be used as an intermediate functional group - as for example in heterocyclic synthesis - or as a means of promoting regioselective reactions. One of these of particular relevance to organometallic chemistry is the ability of secondary and tertiary carboxamides to direct metallation to specified positions in a molecule.[9]



Synthetic approaches to carboxamides may be classified according to the bond being formed. Whereas there are numerous ways of forming the carbonyl-nitrogen bond or of modifying the groups attached to nitrogen, there are relatively few methods of forming the carbon-carbon bond without recourse to organometallic reagents. These include the Friedel-Crafts reactions of aromatic molecules with hydroxamic acids, carbamoyl chlorides or isocyanates, free radical carbamoylation of heterocycles, the acid-catalysed aminocarbonylation of olefins, the Arndt-Eistert synthesis and the Willgerodt reaction.[13]

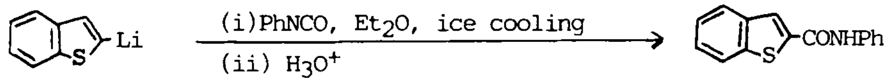
This review is concerned with routes to carboxylic amides in which carbon-carbon bond formation is induced by means of organometallic reagents. Reactions in which these reagents are used as starting materials or in which their intermediacy is well established will be considered. Both stoichiometric and catalytic reactions are included with emphasis being given to those which are synthetically the most useful.[14] The literature is covered up to the end of 1988, with some 1989 papers being included as well.

The review is divided into two main sections. The first deals with reactions involving Main Group organometallic reagents and the second with those of transition metal systems. Some reactions which deal with both main group and transition metals have been assigned to one of the sections according to their relationship to other similar procedures. Within each section further divisions are made according to the starting materials used.

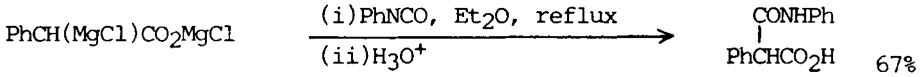
I. MAIN GROUP ORGANOMETALLIC REACTIONS

a. Reaction of Isocyanates

The reaction of organometallic reagents with isocyanates is the oldest example of an organometallic carboxamidation, having been reported in 1901 by Blaise for Grignard reagents[15] and, since that time, it has been applied extensively to other organometallic reagents.[16-76] Since the reaction with aryl isocyanates, in particular, gives solids which can readily be purified, it has often been employed for the characterisation of organometallics and the compounds from which they are derived. The reaction conditions are generally mild and the yields good (Table 1). Some examples are given below.



81%



$$PhCH(MgCl)CO_2MgCl \xrightarrow[(ii) H_3O^+]{(i) PhNCO,\ Et_2O,\ reflux} \underset{\displaystyle PhCHCO_2H}{\overset{CONHPh}{|}} \quad 67\%$$

$$BrZnCH_2CO_2Et \xrightarrow[(ii)\ H_3O^+]{(i)\ PhNCO,\ CH_2(OMe)_2,\ reflux} PhNHCOCH_2CO_2Et$$

65%

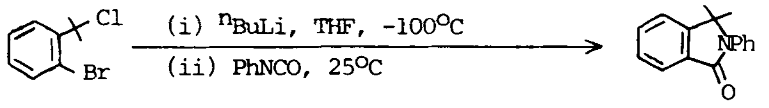
$$Me_3MnLi \xrightarrow[(ii)\ H_3O^+]{(i)\ PhNCO,\ THF,\ -50^\circ\ to\ +20^\circ C} MeCONHPh$$

98%

The reactions of the organomanganese reagents are included here since they behave in much the same way as the main-group metal reagents.[77,78]

N-PHENYL-o-(DIMETHYLAMINOMETHYL)BENZAMIDE.[35] Suspension of o-lithio-(dimethylaminomethyl)benzene in Et$_2$O/hexane added to PhNCO (14.3g, 0.12mol) in 250ml Et$_2$O. Reflux 4h, cool, hydrolyse (sat. NH$_4$Cl soln.), extract with Et$_2$O, dry, evaporate and distil. Yield 65%, bp. 190-200°/1mm.

When other functional groups are present further reactions to give cyclized products may occur.[52]



29%

Table 1. Reaction of Main Group Organometallics with Isocyanates.

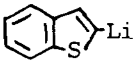
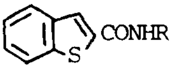
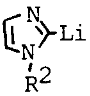
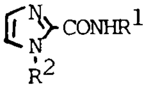
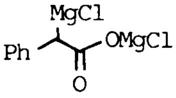
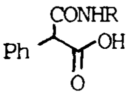
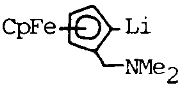
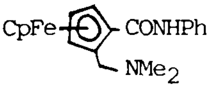
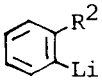
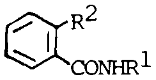
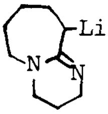
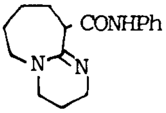
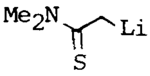
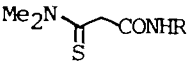
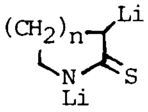
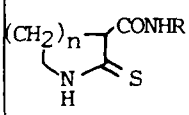
Organometallic	Conditions	Product		Yield	Ref
	i. $RNCO, Et_2O$ ii. H_3O^+		R = Ph	81	29
			R = o-tolyl	41	
			R = 2-pyridyl	54	
	i. R^1NCO, Et_2O ii. H_3O^+		R^1 = 2-naphthyl R^2 = Me;	66	31
			$R^1 = R^2$ = Ph	39	
	i. $RNCO, Et_2O$, C_6H_6 ii. H_3O^+		R = Me	29	32
			R = Et	57	
			R = Ph	67	
	i. $PhNCO, Et_2O$ hexane ii. H_3O^+			31	33
	i. R^1NCO, Et_2O hexane ii. H_3O^+		R^1 = Ph		
			R^2 = $-OCH_2OMe$	73	34
			R^2 = $-CH_2NMe_2$	65	35
			R^1 = ${}^tBu$ R^2 = 	81	68
	i. PhCNO, THF, 0^o ii. H_3O^+			41	37
 $Me_2NC(S)CH_2Li$	i. RNCO, THF, hexane ii. H_3O^+	 $Me_2NC(S)CH_2CONHR$	R = Ph	62	44
			R = $4\text{-}ClC_6H_4$	61	
	As above		n = 1		45
			R = Ph	53	
			R = $4\text{-}ClC_6H_4$	70	
			R = $3\text{-}MeC_6H_4$	41	
			n = 2		
			R = Ph	70	
			R = $4\text{-}ClC_6H_4$	96	
			R = $3\text{-}MeC_6H_4$	43	

Table 1 (continued)

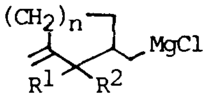
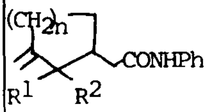
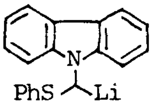
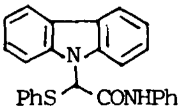
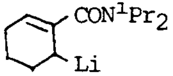
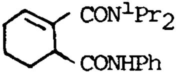
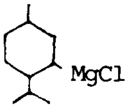
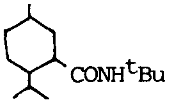
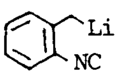
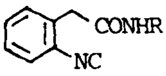
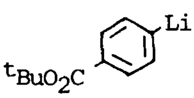
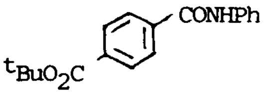
Organometallic	Conditions	Product	Yield	Ref
	As above (R = Ph)	 n = 1 $R^1 = R^2 = H$	71	
		n = 2 $R^1 = R^2 = H$	72	
		$R^1 = H, R^2 = Me$	86	49
		$R^1 = R^2 = Me$	80	
		n = 3 $R^1 = R^2 = H$	71	
	As above		66	50
	i. PhNCO,THF, TMEDA ii.H_3O^+		61	11
$R^2(C{:}C)_nLi$	i. R^1NCO, Et_2O, hexane ii.H_2O	$R^2(C{:}C)_nCONHR^1$ n = 2 $R^1 = R^2 = Ph$	77	51
		R^1 = t-Bu, R^2 = MePhN-	44	57, 64
		R^1 = t-Bu, $R^2 = Ph_2N$-	50	
		R^1 = t-Bu, R^2 = PhS-	72	65
		n = 3 R^1 = t-Bu, R^2= morpholino	48	58
	i. ^tBuNCO, THF or Et_2O ii.H_2O		77 74	53 54
	i. RNCO, diglyme ii.H_2O	 R = n-Bu	70	
		R = t-Bu	53	
		R = c-C_6H_{11}	55	56
		R = Ph	50	
	i. PhNCO,THF, hexane ii.H_2O		54	59

Table 1 (continued).

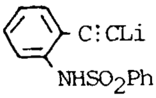
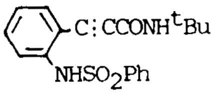
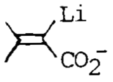
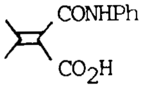
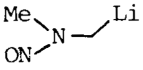
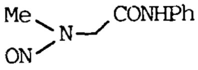
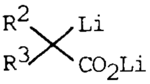
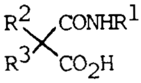
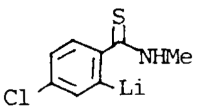
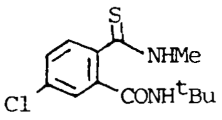
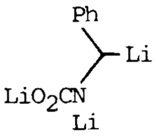
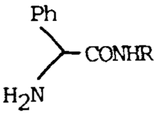
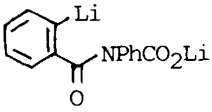
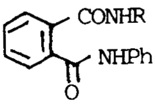
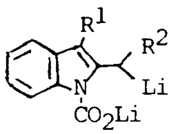
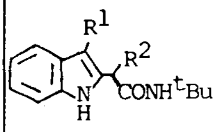
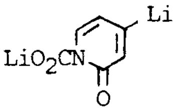
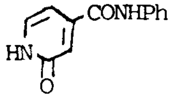
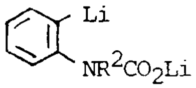
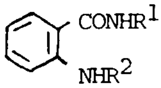
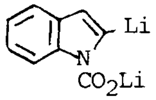
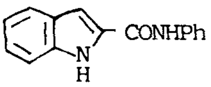
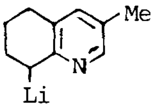
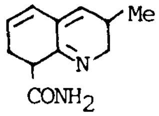
Organometallic	Conditions	Product	Yield	Ref
	i. ^{t}BuNCO, THF, hexane ii. H_2O		62	62
	i. PhNCO, THF, hexane ii. H_2O		58	60
	i. PhNCO, THF, hexane ii. AcOH		70	63
	i. R^1NCO, THF, TMEDA ii. H_2O	 R^1 R^2 R^3 Ph Me Me	65	66
		n-Pr Me Me	77	
		Ph Ph H	80	
		n-Pr Ph H	75	
		Ph Me H	65	
		n-Pr Me H	66	
		Ph $-(CH_2)_5-$	62	
		n-Pr $-(CH_2)_5-$	60	
	i. ^{t}BuNCO, THF, hexane ii. H_2O		61	67
$(EtO_2C)_2CHZnBr$	i. PhCNO, DME, reflux ii. aq. NH_4Cl soln.	$(EtO_2C)_2CHCONHPh$	65	61
	i. RNCO, THF/pentane -70^o to 25^o ii. H_3O^+	 R = Ph	45	40
		R = ^{t}Bu	57	
	As above	 R = Ph	80	41
		R = ^{t}Bu	76	

Table 1 (continued)

Organometallic	Conditions	Product	Yield	Ref
	As above	 R^1 R^2		42
		H H	61	
		H ^{n}Bu	60	
		H $^nC_6H_{13}$	47	
		Me H	77	
	As above			43
	i. R^1NCO, THF/ pentane -70° to 25° ii. H_3O^+	 R^1 R^2		46
		Ph Me	69	
		^{t}Bu Me	71	
		Ph Et	79	
		^{t}Bu Et	75	
	As above (R^1=Ph)		55	47
PhMgBr	i. Me_3SiNCO, 90° Dioxane + THF ii. aq. NH_4Cl	$PhCONH_2$	49	85
	i. Me_3SiNCO, hexane, -20° to rt ii. H_3O^+ iii. aq $NaHCO_3$		34	86
$PhCH{:}CHSiMe_3$	i. ClO_2SNCO, CCl_4, 0° ii. H_3O^+/Me_2CO, heat	$PhCH{:}CHCONH_2$	63	72
$RCH{:}C(OMe)SiMe_3$	i. ClO_2SNCO, $CHCl_3$, 0° ii. H_3O^+, heat	RCH_2CONH_2		73
		R = ^{n}Bu	48	
		$^nC_5H_{11}$	52	
$RC⋮CSiMe_3$	i. ClO_2SNCO, $CHCl_3$, 0° ii. H_3O^+, heat	$RC⋮CCONH_2$		73
		R = ^{n}Bu	69	
		$^nC_5H_{11}$	71	
		Ph	70	
		$Cl(CH_2)_3$	54	

Recently, Einhorn et al have shown that the sonochemical Barbier reaction may also be usefully applied in this reaction and that further reactions can be carried in situ (Table 2).[79]

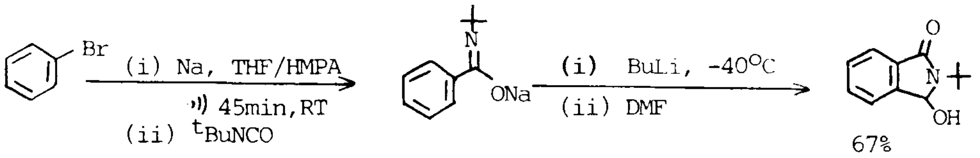
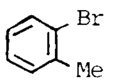
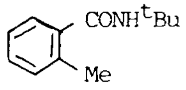
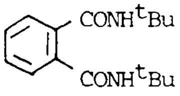
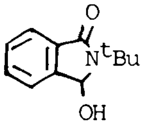
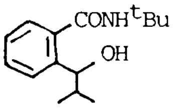
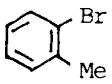
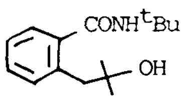
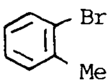
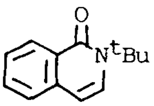
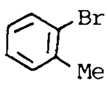
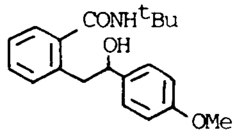


Table 2. Ultrasound Assisted Barbier Reactions with Isocyanates.[79]

ArBr	Conditions	Product	Yield
PhBr	Na/THF/HMPA/ᵗBuNCO, 45min US at RT	PhCONHᵗBu	51
	As above		74
PhBr	i. Na/THF/HMPA/ᵗBuNCO, 45min US/RT ii. ⁿBuLi iii. ᵗBuNCO iv. H_2O		75
PhBr	i. and ii. as above iii. DMF		67
PhBr	i. and ii. as above iii. ⁱPrCHO iv. H_2O		63
	i. and ii. as above iii. Me_2CO iv. H_2O		46
	i. and ii. as above iii. DMF		40
	i. and ii. as above iii. anisaldehyde iv. H_2O		63

Isocyanates are accessible via the Curtius rearrangement of acyl azides and this has been exploited in an amide synthesis which starts from acid chlorides. Isolation of pure intermediates is not necessary and the conversion of acyl azide to amide is essentially a one-pot reaction. Good yields have been reported for a variety of acid chlorides (Table 3).[80-83]

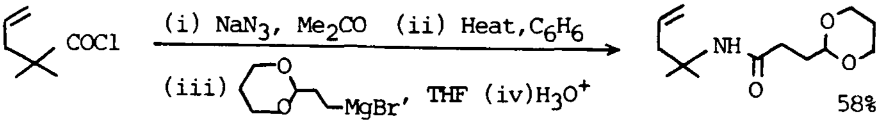
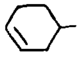


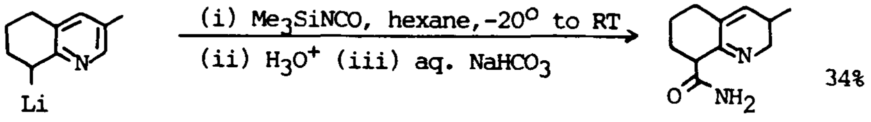
Table 3. Conversion of Acid Chlorides to Amides.[80]

$$R^1COCl \xrightarrow{i,ii} R^1NCO \xrightarrow{iii,iv} R^2CONHR^1$$

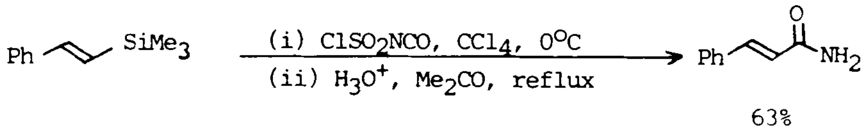
R^1	R^2	Yield
c-C_6H_{11}	Me	63
	Me	57
	Me	87
	Me	87
Ph	Me	73
$^nC_5H_{11}$	Me	57
$^nC_7H_{15}$	Me	77
$^nC_{15}H_{31}$	Me	97
c-C_6H_{11}	Ph	89
Ph	Ph	83
2-furyl	Ph	63
$^nC_5H_{11}$	Ph	83
Ph	^nBu	83
c-C_6H_{11}	^nBu	91

i. NaN_3, acetone, H_2O and isolation of crude azide.
ii. Heat in C_6H_6. iii. R^2Li/Et_2O. iv. H_3O^+.

All the above methods give secondary amides after hydrolytic work-up. Primary amides may, however, be obtained using triorganosilyl isocyanates, the R_3Si group being cleaved during the work-up.[84-87]



Alternatively, primary amides may be obtained by reaction of vinyl-, alkynyl- or allylsilanes with chlorosulphonyl isocyanate and subsequent hydrolysis.[72-74]

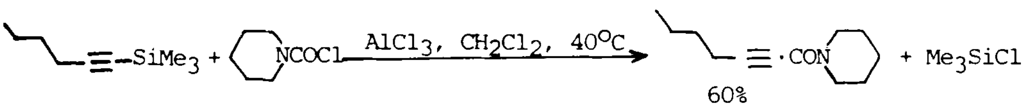


b. Reaction with Carbamic Acid Derivatives

Amides may be formed by the reaction of organometallic reagents with carbamoyl chlorides and carbamate esters, analogous to the reactions with carboxylic acid chlorides and esters (Table 4). They suffer, however, from the same disadvantage, namely that of the possibility of subsequent reaction with the amide formed. This may be overcome by the use of low temperatures.[88-97]

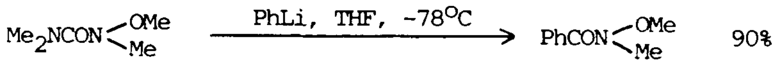
$$\mathrm{LiC{\equiv}CCH_2CH(OEt)_2} \xrightarrow[\text{hexane, } Et_2O]{\text{ClCONMe, } -40^\circ C} \mathrm{Me_2NCOC{\equiv}CCH_2CH(OEt)_2} \quad 40\%$$

$$\mathrm{EtMgBr} \xrightarrow[\text{(ii) } H_3O^+]{\text{(i) } PhNHCO_2Et} \mathrm{EtCONHPh} \quad 55\%$$



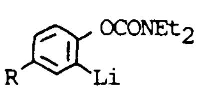
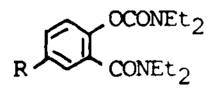
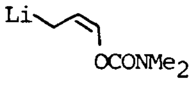
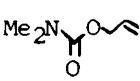
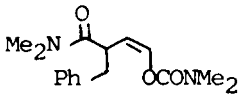
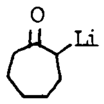
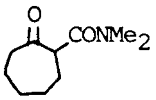
N,N-DIETHYL-4,4-DIETHOXYBUT-2-YNAMIDE. To 1-lithio-3,3-diethoxypropyne (0.04mol) in Et_2O/hexane at -50° add Et_2NCOCl (0.055mol). Warm to RT over 6-7h. Hydrolyse (sat. NH_4Cl soln.), extract, dry, distil. Yield 45%, bp. 103°/0.1mm.

A related reaction which has recently been reported uses N-methoxyurethanes and ureas. Although the reaction is used as a basis for the preparation of unsymmetrical ketones, the intermediate N-methoxyamides may be isolated.[93]

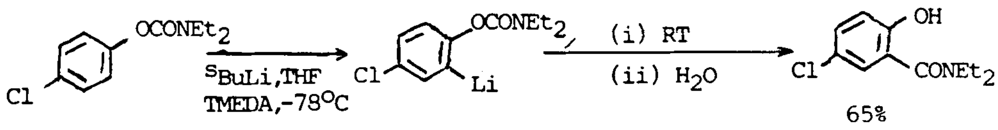


$$\mathrm{Me_2NCON}\begin{smallmatrix}\mathrm{OMe}\\ \mathrm{Me}\end{smallmatrix} \xrightarrow{\text{PhLi, THF, } -78^\circ C} \mathrm{PhCON}\begin{smallmatrix}\mathrm{OMe}\\ \mathrm{Me}\end{smallmatrix} \quad 90\%$$

Table 4. Reaction of Organometallics with Carbamic Acid Derivatives

Organometallic	Coreactant	Conditions	Product	Yield	Ref
	Et_2NCOCl	i. THF/TMEDA, -78° to rt ii.aq. NH_4Cl			95
			R = H	89	
			R = Cl	77	
		i. THF, $PhCH_2Br$ ii. H_2O		40	89
EtMgBr	Et_2NCO_2Et	Not given	$EtCONEt_2$	28	90
EtMgBr	$PhNHCO_2Et$	Not given	EtCONHPh	55	90
	Me_2NCOCl	THF, -100°		84	75
$(EtO)_2CHC:CLi$	Me_2NCOCl	Hexane/Et_2O -40°	$(EtO)_2CHC:CCONMe_2$	45	92
$(EtO)CH_2CHCH_2C:CLi$	Me_2NCOCl	As above	$(EtO)_2CHCH_2C:CCONMe_2$	40	92
$R^1C:CSiMe_3$	R^2NCOCl	$AlCl_3$, CH_2Cl_2 40°	$R^1C:CCONR^2_2$		97
			R^1 R^2		
			^nBu ½(-$(CH_2)_4$-)	55	
			$^nC_6H_{11}$ ½(-$(CH_2)_4$-)	60	
			^nBu ½(-$(CH_2)_5$-)	60	
			$^nC_5H_{11}$ ½(-$(CH_2)_5$-)	55	
			$^nC_5H_{11}$ Et	65	

One interesting reaction which seems to involve this type of reaction is the formal rearrangement of ortho-metallated O-aryl carbamates (Table 5).[92-96,98]

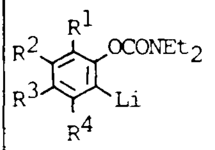
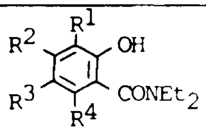
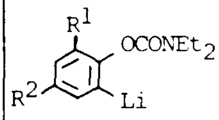
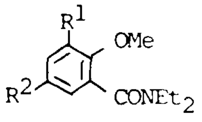
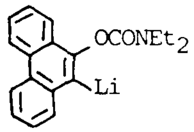
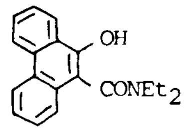


This is equivalent to the well-known Fries rearrangement of aryl esters.

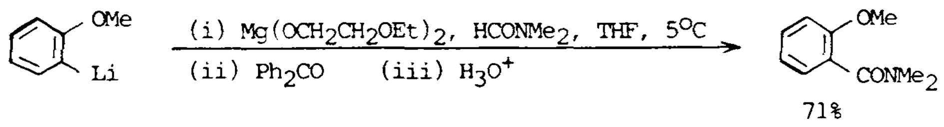
c. Reaction with Formamides

A recently reported route to amides involves the addition of organolithium or organomagnesium reagents to tertiary formamides followed by oxidation of the intermediate α-aminoalkoxide by an Oppenauer type pro-

Table 5. Rearrangement of Metalated Aryl Carbamates

Organometallic	Conditions	Product				Yield	Ref
	i. THF/TMEDA,hexane -78° to rt ii.H_3O^+						94
		R^1	R^2	R^3	R^4		
		H	H	H	H	75	
		Me	H	H	H	70	
		OMe	H	H	H	68	
		H	OMe	H	H	18	
		H	H	OMe	H	60	
		H	H	Cl	H	65	
		H	H	H	OMe	48	
	i. THF/TMEDA/hexane -78° to rt ii.H_3O^+ iii.K_2CO_3/MeI Me_2CO/reflux						
		R^1	R^2				
		CO_2H	H			37	95
		CO_2H	Cl			60	95
		$CONEt_2$	H			59	95
		$CONEt_2$	Cl			42	95
		$SO_2{}^tBu$	H			81	96
	i. and ii. as above					81	98

cedure.[99] A magnesium alkoxide was found to be required when organolithium reagents were employed whereas for Grignard reagents a lithium alkoxide was added (Table 6).



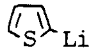
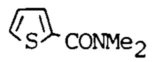
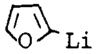
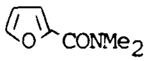
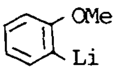
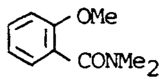
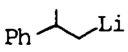
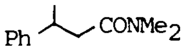
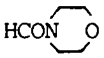
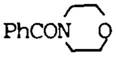
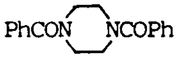
N,N-DIMETHYL-o-METHOXYBENZAMIDE. $Mg(OCH_2CH_2OEt)_2$ (10mmol) is added to o-$MeOC_6H_4Li$ (20mmol from 12ml 1.7N ^nBuLi in MCH, 20mmol anisole, 4ml THF) at 5°C. Stir RT 1h, cool in ice, add DMF (20mmol), stir 1h 5°C, 2h RT, add 30mmol Ph_2CO, stir overnight. Hydrolysis (dil. H_2SO_4), CH_2Cl_2 extraction, drying ($MgSO_4$), removal of solvent and chromatography (silica gel, 1:1 CH_2/EtOAc) gives 71% product.

It has now been found that, for certain organolithium reagents, mercuric chloride will also oxidize the intermediate α-aminoalkoxide and that no additional metal alkoxide is needed.[100]

$$ {}^{n}\text{BuLi} \xrightarrow[\text{(ii) HgCl}_2\text{, -78}^{\circ}\text{C to RT}]{\text{(i) HCONMe}_2\text{, MCH-THF, -78}^{\circ}\text{C}} {}^{n}\text{BuCONMe}_2 $$

90%

Table 6. Reaction of Organolithium and Organomagnesium Reagents with Formamides and Subsequent Oxidation.[99]

Organometallic	Formamide	Solvent*	Product	Yield
^{n}BuLi	$HCONMe_2$	MCH/CH	^{n}BuCONMe$_2$	65
Ph_2Mg	$HCONMe_2$	Toluene	$PhCONMe_2$	80
^{s}Bu$_2$Mg	$HCONMe_2$	MCH	^{s}BuCONMe$_2$	65
	$HCONMe_2$	CH/THF		61
	$HCONMe_2$	CH/THF		29
	$HCONMe_2$	CH/THF		71
	$HCONMe_2$	THF		34
^{n}BuLi	HCONPhEt	MCH/CH	^{n}BuCONPhEt	39
^{n}BuLi		MCH/CH		53
Ph_2Mg		Toluene		68
^{n}BuLi		MCH/CH		71
Ph_2Mg		Toluene		17

* Conditions: reaction in solvent indicated at 5°C to rt in presence of $Mg(OCH_2CH_2OEt)_2$ followed by oxidation with Ph_2CO (MCH = methylcyclohexane, CH = cyclohexane).

d. Reactions of Carbamoylmetallic Reagents

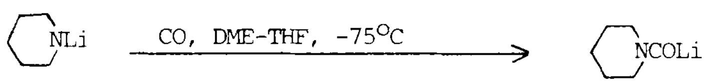
Carbamoylmetallic reagents are analogous to acylmetallic reagents and can be expected to give amides upon reaction with electrophiles.

$$ MCONR_2 \quad + \quad E^+ \longrightarrow ECONR_2 \quad + \quad M^+ $$

Three methods exist for the formation of these reagents. The first is by metalation of a tertiary formamide. This may be achieved using either a lithium amide or ^{t}butyllithium.[101-105]

$$\mathrm{HCON^{i}Pr_2} \xrightarrow[{}^{t}\mathrm{BuLi,\ THF\text{-}Et_2O\text{-}pentane,\ -95^{o}C}]{\mathrm{LiN^{i}Pr_2,\ THF,\ -78^{o}C\quad or}} \mathrm{LiCON^{i}Pr_2}$$

The second route involves insertion of carbon monoxide into the metal-nitrogen bond of a metal amide.[106-114]



$$\mathrm{LiCu(NEt_2)_2} \xrightarrow{\mathrm{CO,\ Et_2O,\ 0^{o}C}} \mathrm{LiCu(CONEt_2)_2}$$

Lastly, carbamoyllithium compounds have been obtained by transmetalation of a bis(carbamoyl)mercury with butyllithium.[115]

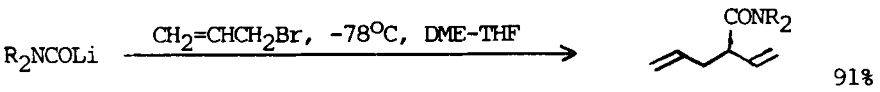
$$\mathrm{Hg(CONEt_2)_2} \xrightarrow{{}^{n}\mathrm{BuLi,\ THF,\ -75^{o}C}} \mathrm{LiCONEt_2}$$

This method has found only limited application however. Carbamoylmetallics are generally stable only at low temperatures and are thus used _in situ_. The lithium reagents react satisfactorily with carbonyl compounds but the reaction with alkyl halides tends to become uncontrollable (Table 7). The initial product in the latter case is a simple amide and presumably competes with the alkyl halide for the organolithium compound whereas with carbonyl compounds the product of addition is an α-alkoxidoamide which, perhaps because of chelation of the metal by the alkoxide and the carbonyl or simply because of the negative charge, is less reactive than the initial reactant.[101-107,109,110,115,116]

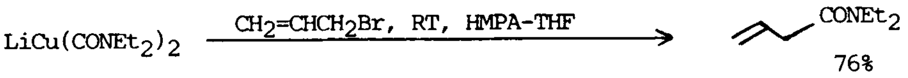
$$\mathrm{{}^{i}Pr_2NCOLi} \xrightarrow[\mathrm{(ii)\ H_2O}]{\mathrm{(i)\ Me_2CO,\ -78^{o}C\ to\ RT}} \underset{81\%}{\mathrm{{}^{i}Pr_2NCOC(OH)Me_2}}$$

<u>N,N-DI-ISOPROPYL-α-HYDROXY-DIPHENYLACETAMIDE</u>. MeLi (2.6mmol) added to $\mathrm{{}^{i}Pr_2NH}$ (2.6mmol) in 50ml THF at -78°. After 2min. is added $\mathrm{{}^{i}Pr_2NCHO}$ (2.6mmol). Stir 5min. Add $\mathrm{Ph_2CO}$ (2mmol). Stir 45min. Warm to RT, evaporate, dissolve in $\mathrm{CH_2Cl_2}$, wash with $\mathrm{H_2O}$, dry and evaporate. Chromatography (silica gel, $\mathrm{CHCl_3}$) gives 92% product, mp. 150.5-151°C.

Exceptions to the reactions with organic halides are those with allyl and benzyl halides, although even here dialkylation occurs.[110]



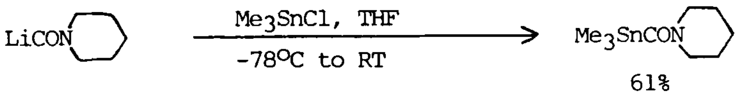
The lithium cuprate reagents, on the other hand, react cleanly with a number of halogen compounds in the expected manner.[113,114]

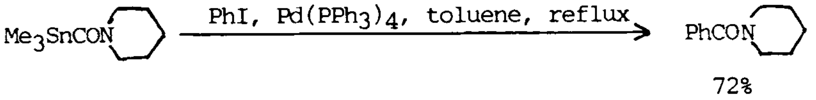


Primary and secondary amides can be prepared by the metalation route if the corresponding formamides are first protected with the methoxymethyl group which is easily removed by mild acid hydrolysis.[103]

$$HCONMe(CH_2OMe) \xrightarrow[\text{(ii) } H_3O^+]{\text{(i) LDA, PhCHO, THF, } -78^\circ C \text{ to RT}} PhCH(OH)CONHMe \quad 70\%$$

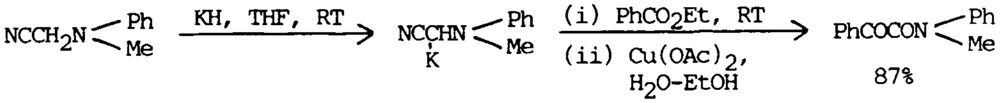
Reaction of carbamoyllithiums with triorganotin halides proceeds normally and the carbamoyltin compounds formed react with aryl, hetaryl, or alkenyl halides in the presence of a palladium(0) catalyst (Table 8).[110]





e. Reaction of Cyano(amino)methyl Carbanions with Esters

The carbanion produced by metalation of α-(N-methyl-N-phenylamino)-acetonitrile with NaH or KH reacts with esters at room temperature and subsequent hydrolysis in the presence of $Cu(OAc)_2$ gives α-ketoamides.[117]



$$NCCH_2N{<}^{Ph}_{Me} \xrightarrow{\text{KH, THF, RT}} NC\underset{K}{C}HN{<}^{Ph}_{Me} \xrightarrow[\text{(ii) } Cu(OAc)_2,\ H_2O\text{-}EtOH]{\text{(i) } PhCO_2Et, \text{ RT}} PhCOCON{<}^{Ph}_{Me} \quad 87\%$$

N-METHYL,N-PHENYL-PHENYLGLYOXYLAMIDE. To KH (0.59g,14.7mmol) and $PhCO_2Et$ (1.18g,7.9mmol) in 30ml THF add $MePhNCH_2CN$ (0.98g,6.7mmol) in 10ml THF at 0° . Stir at RT 3h, hydrolyse (sat. NH_4Cl soln), extract with $(^iPr)_2O$, dry, concentrate. Yield of E- and Z-Ph(OH)C=C(CN)NMePh 87%,mp 136-9°C. To 0.5g (2.0mmol) is added $Cu(OAc)_2$ (0.74g,4.1mmol) in 20ml 50% aq. EtOH. After 4h at 50° cool,filter,extract with CH_2Cl_2 , wash with H_2O, dry, filter. Purify by recrystallisation. Yield 79%, mp. 63°C.

Table 7. Reactions of Carbamoylmetallic Reagents.

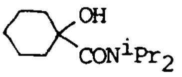
Organometallic	Prep.	Reaction/Conditions	Product			Yield	Ref
$LiCONMe_2$	A	i. R^1R^2CO,THF	$R^1R^2C(OH)CONMe_2$				101
		-78° to rt	R^1	R^2			
		ii.H_2O	Ph	H		45	
			Ph	Ph		85	
			PhCH:CH	H		48	
			^tBu	H		76	
			$-(CH_2)_5-$			62	
$LiCON^iPr_2$	A	As above	$R^1R^2C(OH)CON^iPr_2$				102
			R^1	R^2			
			Ph	H		51	
			Ph	Ph		92	
			Me	Me		30	
			Et	H		41	
$LiCONR(CH_2OMe)$	A	As above	$R^1R^2C(OH)CONR(CH_2OMe)$				103
			R^1	R^2	R		
			Ph	H	CH_2OMe	74	
			Ph	Ph	CH_2OMe	88	
			$-(CH_2)_5-$		CH_2OMe	44	
			Ph	H	Me	76	
			Ph	Ph	Me	85	
			$-(CH_2)_5-$		Me	39	
			PhCH:CH	H	Me	40	
$LiCON^iPr_2$	B	i. R^1R^2CO,Et_2O/	$R^1R^2C(OH)CO^iPr_2$				105
		THF/pentane	R^1	R^2			
		-95° to rt	Ph	Ph		85	
		ii.H_2O	Ph	H		80	
			Me	Me		81	
			Et	H		62	
			$-(CH_2)_5-$			83	
			PhCH:CH	H		68	
$LiCON^iPr_2$	B	As above with $PhCO_2Et$	$PhCOCON^iPr_2$			70	105
$LiCON^iPr_2$	B	As above with $PhCH_2Br$	$PhCH_2CHPhCO^iPr_2$			68	105
$LiCON^iPr_2$	C	i. Cyclohexanone, DME/THF,-75 to+5° ii. H_2O				50	107

Table 7 (Continued).

Organometallic	Prep.	Reaction/Conditions	Product	Yield	Ref
LiCONR$^1_2$	C	R$^2_3$SnCl,THF -78° to rt	R$^2_3$SnCONR$^1_2$		110
			R^1 R^2		
			½(-(CH$_2$)$_4$-) Me	58	
			½(-(CH$_2$)$_5$-) Me	61	
			^{i}Pr Me	40	
			½(-(CH$_2$)$_4$-) ^{n}Bu	90	
			½(-(CH$_2$)$_5$-) ^{n}Bu	87	
			^{i}Pr ^{n}Bu	78	
			½(-(CH$_2$)$_4$-) Ph	57	
			½(-(CH$_2$)$_5$-) Ph	53	
Li^{11}	C	THF,RI,-78°	R^{11}		109
			R = Me	12	
			R = Et	15	
CuLi(CONEt$_2$)$_2$	D	THF/HMPA,RX	RCONEt$_2$		114
			RX = MeI	10	
			PhI	49	
			CH$_2$:CHCH$_2$Br	76	
			PhCH:CHBr	51*	
			MeCOBr	70	
			PhCOBr	74	
			PhCOCl	61	
			EtOCOCl	36	
CuLi()$_2$	D	As above RX = CH$_2$:CHCH$_2$Br		93	114
CuLi(CONMePh)$_2$	D	MeI/Et$_2$O	MeCONMePh	72	113
CuLi(CONR^{1}R^2)$_2$	D	RX,Pd(0) catalyst C$_6$H$_6$/DME 35-40°	RCONR^{1}R^2		113
			R R^1 R^2		
			Ph Me Ph	71	
			PhCH:CH Me Ph	65	
			Ph Et p-ClC$_6$H$_4$	67	
			Ph ^{i}Pr ^{i}Pr	49	
			Ph Et Et	58	

* In the presence of 10mol% Ni(OAc)$_2$.

Method of preparation: A. LiNR$_2$ in THF,-78°. B. ^{t}BuLi in Et$_2$O/THF/pentane,-95°. C. R$_2$NLi + CO,DME/THF,-78°. D. LiCu(NR$_2$)$_2$ + CO,Et$_2$O,0°.

Table 8. Amide Synthesis via Carbamoylstannanes[110]

$$Me_3SnCONR^1_2 \quad + \quad R^2X \xrightarrow{i} R^2CONR^1_2$$

R^1	R^2X	Yield
^iPr	Ph	78
^iPr	p-$MeOC_6H_4I$	83
^iPr	$^nC_5H_{11}CH{:}CHI$	71
$\frac{1}{2}(-(CH_2)_4-)$	p-$MeOC_6H_4I$	80
$\frac{1}{2}(-(CH_2)_4-)$	$^nC_5H_{11}CH{:}CHI$	79
$\frac{1}{2}(-(CH_2)_4-)$	PhCH:CHI	82
$\frac{1}{2}(-(CH_2)_4-)$	1-iodocyclohexene	62
$\frac{1}{2}(-(CH_2)_5-)$	Ph	72
$\frac{1}{2}(-(CH_2)_5-)$	p-$MeOC_6H_4I$	72
$\frac{1}{2}(-(CH_2)_5-)$	$^nC_5H_{11}CH{:}CHI$	64
$\frac{1}{2}(-(CH_2)_5-)$	PhCH:CHBr	49
$\frac{1}{2}(-(CH_2)_5-)$	PhCH:CHI	77
$\frac{1}{2}(-(CH_2)_5-)$	1-iodocyclohexene	58
$\frac{1}{2}(-(CH_2)_5-)$	2-iodofuran	84
$\frac{1}{2}(-(CH_2)_5-)$	2-bromothiophene	57
$\frac{1}{2}(-(CH_2)_5-)$	2-iodothiophene	24
$\frac{1}{2}(-(CH_2)_5-)$	3-bromopyridine	63

i. RX, $Pd(PPh_3)_4$,THF,65°.

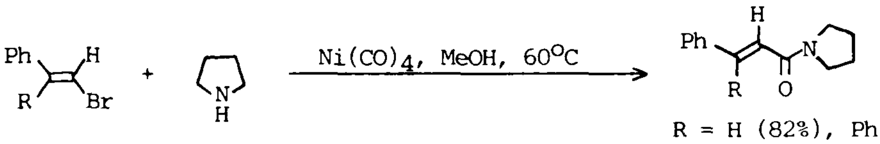
II. TRANSITION METAL SYSTEMS

a. Aminocarbonylation Reactions

The carbonyl and amino fragments may be introduced in a variety of ways using transition metal reagents in either stoichiometric or catalytic reactions.

i. Metal Carbonyls and Amines (Table 9)

The reaction of 2-bromostyrene or 2-bromo-1,1-diphenylethene with excess pyrrolidine and $Ni(CO)_4$ gives good yields of the corresponding α,β-unsaturated amides.[118]



R = H (82%), Ph (85%)

while sodium tetracarbonylferrate reacts with alkyl halides to give an intermediate acyliron complex from which the carboxamide can be obtained by reaction with iodine and a tertiary amine.[119]

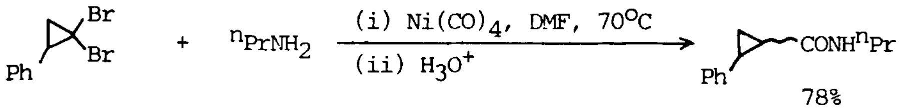
$$ {}^{n}C_5H_{11}Br \xrightarrow[\text{(ii) } Et_2NH,\ I_2]{\text{(i) } Na_2Fe(CO)_4,\ THF,\ -15 \text{ to } +25^{o}C} \underset{80\%}{{}^{n}C_5H_{11}CONEt_2} $$

A related reaction uses nitro-compounds instead of amines. The iron carbonylate species are strong reducing agents and the required amine is formed in situ.The acyliron complex may be formed in a number of ways and for simple substituents the yields are quite good. Lower yields are obtained when benzyl halides or α-haloacetophenones are used.[120,121]

$$ MeCOCl \xrightarrow[\text{(ii) } PhNO_2]{\text{(i) } Na_2Fe(CO)_4,\ THF,\ RT} \underset{86\%}{MeCONHPh} $$

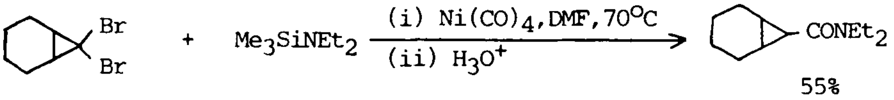
$$ PhCOCH_2Cl \xrightarrow[\text{(ii) } PhNO_2]{\text{(i) } Na_2Fe(CO)_4,\ THF,\ RT} \underset{44\%}{PhCOCH_2CONHPh} $$

More extensive studies have been made on the reactions of dibromocyclopropanes with amines and $Ni(CO)_4$. With unsubstituted 1,1-dibromocyclopropanes reaction with a primary or secondary amine and $Ni(CO)_4$ gives the corresponding cyclopropanecarboxamide.[122,123]



GENERAL PROCEDURE. The gem-dibromocyclopropane (1mmol),amine (2.5mmol), DMF (2.4ml) and $Ni(CO)_4$ are heated at 70° for 3h. Evaporate, add 30ml 5%HCl, extract with Et_2 O,dry, concentrate and isolate by chromatography (silica gel).

Silylamines may also be used in this reaction, the silyl group being removed.[124]



and if an electrophile is also present α-substituted products can be obtained.[124]

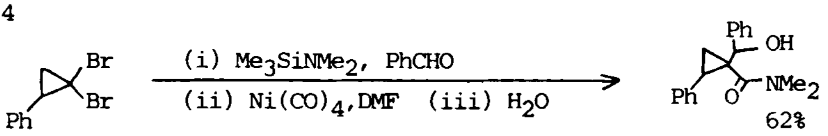


Table 9. Aminocarbonylation via Nickel Tetracarbonyl and Amines

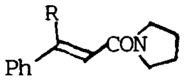
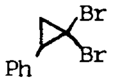
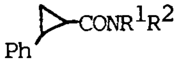
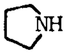
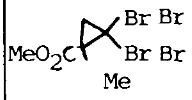
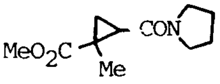
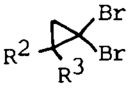
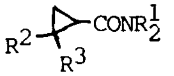
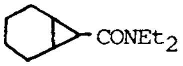
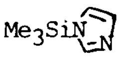
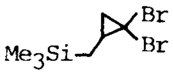
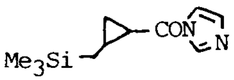
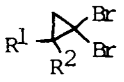
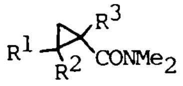
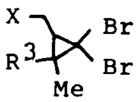
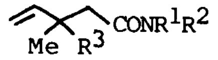
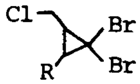
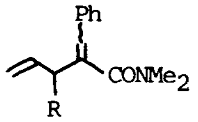
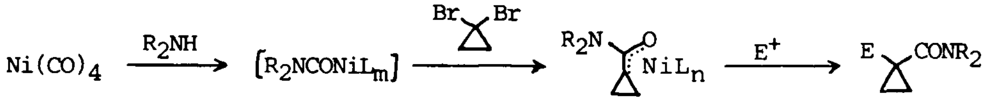
Amine	Coreactant	Conditions	Product	Yield	Ref
	Ph(R)C:CHBr	CH_3OH, 55-60°			118
			R = H	82	
			R = Ph	85	
R^1R^2NH		i. DMF, 70° ii.aq HCl			122 123
			R^1 R^2		
			^{n}Pr H	78	
			Ph H	63	
			CH_2:CH.CH_2 H	56	
			-$(CH_2)_4$-	66	
		As above		44	122
$Me_3SiNR^1_2$		As above			124
			R^1 R^2 R^3		
			Me Ph H	39	
			Et Ph H	85	
			Et MeO_2C Me	73	
			Et $^{n}C_6H_{13}$ H	73	
			-$(CH_2)_4$- Ph H	80	
Me_3SiNEt_2		As above		55	124
		As above		65	124
Me_3SiNMe_2	 + PhCHO or CH_2:$CHCO_2Et$	As above			124
			R^1 R^2 R^3		
			Ph H PhCH(OH)-	62	
			MeO_2CEt Me PhCH(OH)-	40	
			Ph H $EtO_2CCH_2CH_2$	35	
			MeO_2CEt Me $EtO_2CCH_2CH_2$	40	

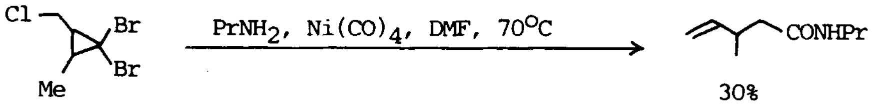
Table 9 (continued).

Amine	Coreactant	Conditions	Product	Yield	Ref
RNR^1R^2		As above			125
			X=Cl,R^1=^{n}Pr,R=R^2=R^3=H	30	
			X=OMes,R^1=^{n}Pr,R=R^2=H,R^3=Me	34	
			X=OMes,R^1=R^2=Et,R=H,R^3=Me	15	
			X=OMes,R^1=R^2=R^3=Me,R=Me_3Si	46	
Me_3SiNMe_2		As above			125
			R = Me	28	
	+ PhCHO		R = Ph	30	

The mechanism proposed for this reaction involves initial formation of a carbamoyl-nickel complex which reacts with the dibromocyclopropane to give a nickel-enolate species. Treatment with the electrophile then gives the product.



If the cyclopropane also contains a 2-chloromethyl or 2-mesylmethyl substituent a ring-opened product is obtained.[125] Yields are rather low although the reaction could be useful for otherwise inaccessible amides.



A stoichiometric reaction of aroylcobalt complexes with lithium amides may also be mentioned here.[126] The main products are α-ketoamides.

$$PhCOCo(CO)_3PMe_3 \xrightarrow[\text{(ii) } Br_2]{\text{(i) } LiNMe_2,\ THF,\ RT} \underset{87\%}{PhCOCONMe_2} + \underset{13\%}{PhCONMe_2}$$

ii. Carbon Monoxide and Amines (Table 10).

The above reactions all use stoichiometric or greater quantities of metal carbonyls. Catalytic reactions are, however, known for a number of transition metal systems. The majority of these use complexes of cobalt, nickel or palladium with those of the latter being the most widely studied. An early example of this type of reaction is the amidation of aryl, hetaryl or vinylic halides in the presence of $PdX_2(PPh_3)_2$ as catalyst.[127,128]

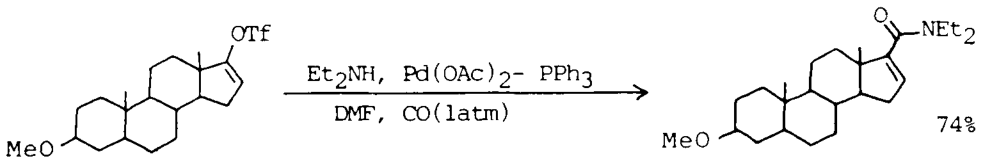
$$\text{PhBr} + \text{PhCH}_2\text{NH}_2 \xrightarrow{\text{CO(1atm), PdBr}_2(\text{PPh}_3)_2,\ 100^\circ\text{C}} \underset{79\%}{\text{PhCONHCH}_2\text{Ph}}$$

CINNAMOYLPYRROLIDINE. Pyrrolidine (3.56g,50mmol) and trans-β-bromostyrene (3.12g,17.2mmol) heated to 60° under CO (1atm). $PdBr_2(PPh_3)_2$ (0.198g) added. When calculated amount of CO has been absorbed, cool extract with ether, evaporate, extract with hot heptane, decolorise and cool. Yield 91%, mp 100.0-100.5°C.

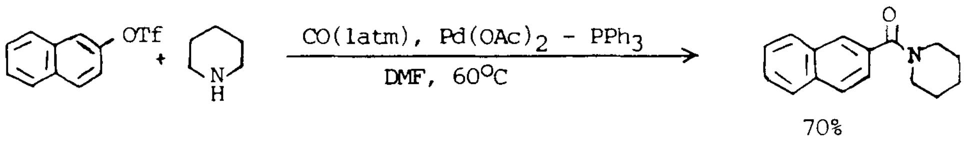
Both primary and secondary amines may be used. If the amine is too weak a base to remove the HX formed in the reaction, a tertiary amine is also required. The conditions are relatively mild (1atm. of CO and 100°C) and the yields are satisfactory.

Nickel complexes give similar reactions with aryl iodides using more strenuous conditions[129] whereas cobalt catalysts have been used to effect carboxamidation with benzylic[134] and olefinic[135] substrates. Olefinic carboxamidation is also catalysed by $Ru_3(CO)_{12}$[136] while acetylenes undergo a similar reaction in the presence of a nickel catalyst.[133]

One variation which has found particular application in steroid chemistry starts from enol triflates which in turn are readily obtained from ketones.[137,138]



A similar reaction also provides a route to aryl carboxamides starting from hydroxyaromatics.[139]



In certain cases tertiary amines may be used. Somewhat more vigorous conditions are required (20atm. CO) and the reaction is most successful for low molecular weight amines. When mixed tertiary amines are used, more

Table 10. Catalytic Aminocarbonylation Reactions

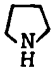
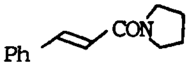
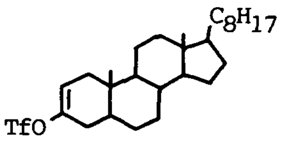
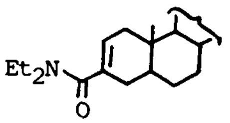
Catalyst	Amine	Coreactant/Conditions	Product	Yield	Ref
$PdPhBr(PPh_3)_2$	$PhNH_2$	$PhBr, {}^nBu_3N$, 1atm.CO, 100°.	PhCONHPh	94	127
$PdBr_2(PPh_3)_2$	$PhCH_2NH2$	PhBr, 1atm.CO, 100°	$PhCONHCH_2Ph$	79	127
$PdBr_2(PPh_3)_2$		PhCH:CHBr, 1atm.CO, 60°.		91	127
$PdBr_2(PPh_3)_2$	$PhNH_2$	$RBr, {}^nBu_3N$, 1atm.CO, 100°.	RCONHPh		127
			R = $p\text{-}MeO_2CC_6H_4$	86	
			$p\text{-}MeOC_6H_4$	76	
			$p\text{-}O_2NC_6H_4$	57	
			3-pyridyl	65	
			2-thienyl	63	
			E-PhCH:CH-	81[a]	
			Z-PhCH:CH-	80[a]	
			Z-PhC(Me):CH-	87	
			E-PhC(Me):CH-	88	
			$E\text{-}MeO_2CC(Me)\text{:}CH\text{-}$	80	
$PdI_2(PPh_3)_2$	$PhNH_2$	$RX, {}^nBu_3N$, 1atm.CO,	RCONHPh		127
			RX = E-EtCH:C(I)Et	71	
			Z-EtCH:C(I)Et	70	
			$CH_2\text{:}C(Cl)Me$	74	
$Pd(PPh_3)_4$	Et_2NH	$R(Me)C\text{:}C\text{:}CHBr, C_6H_6$, 20atm.CO, 45°.	$R(Me)C\text{:}C\text{:}CHCONEt_2$		130
			R = Me	96	
			${}^tBu$	85	
$Pd(OAc)_2$ + PPh_3	Et_2NH	1atm.CO, DMF + 		76	137

Table 10 (continued).

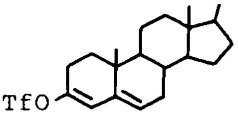
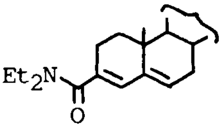
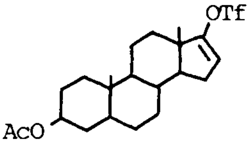
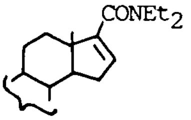
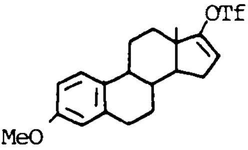
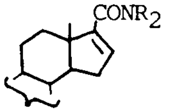
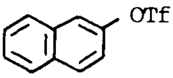
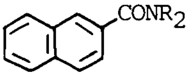
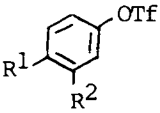
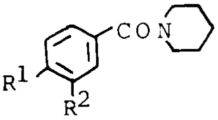
Catalyst	Amine	Coreactant/Conditions	Product	Yield	Ref
$Pd(OAc)_2$ + PPh_3	Et_2NH	1atm.CO,DMF + 		69	137
				91	
	R_2NH	As above 	 R = Et R_2 = $-(CH_2)_5-$	74 98	137
$Pd(OAc)_2$ + PPh_3 or dppf[b]	R_2NH	1atm.CO,DMF, Et_3N,60° + 	 R = Et R_2 = $-(CH_2)_5-$	78 70	139
			 R^1 = H,R^2 = MeO R^1 = MeO,R^2 = H	68 59	
$PdPhI(PPh_3)_2$	Et_3N	PhI,20atm.CO,120°	$PhCONEt_2$	74	140
	$^nPr_3N$	As above	$PhCON^nPr_2$	24	
	$^nBu_3N$	As above	$PhCON^nBu_2$	11	
	Et_2NPh	As above	PhCONEtPh +EtCONEtPh	42 9	
	Et_2NPh	EtI,20atm.CO,120°	EtCONEtPh	75	
$PdCl_2(dppf)$[b]	Et_3N	PhCH:CHBr,20atm.CO, 120°	$PhCH:CHCONEt_2$	44	
$Co_2(CO)_8$	Et_2NH	CH_2Br_2,4atm.CO, THF,Zn	$MeCONEt_2$	31	172

Table 10 (continued).

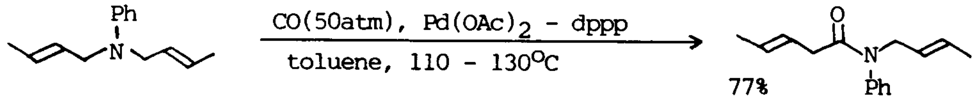
Catalyst	Amine	Coreactant/Conditions	Product		Yield	Ref
$Co_2(CO)_8$	R^1NH_2	R^2CH_2OH, 1atm.CO, PPE^c, NaI	$R^2CH_2CONHR^1$			134
			R^1	R^2		
			^iPr	Ph	71	
			$c\text{-}C_6H_{11}$	Ph	49	
			Et	Ph	20	
			^iPr	$p\text{-}MeOC_6H_4$	47	
			^iPr	$p\text{-}ClC_6H_4$	62	
			^iPr	$o\text{-}ClC_6H_4$	78	
			^iPr	$p\text{-}BrC_6H_4$	82	
			^iPr	$p\text{-}NO_2C_6H_4$	40	
$Ni(CO)_2(PPh_3)_2$	R^1R^2NH	PhI, 40atm.CO, 180°, C_6H_6	$PhCONR^1R^2$			129
			R^1	R^2		
			Ph	H	90	
			$p\text{-}ClC_6H_4$	H	80	
			$p\text{-}MeC_6H_4$	H	81	
			Ph	Me	80	
			Ph	Et	65	
$Ru_3(CO)_{12}$	R^1NH_2	$R^2CH{:}CH_2$, 120°, 4atm. CO	$R^2CH_2CH_2CONHR^1$			136
			R^1	R^2		
			$PhCH_2$	$^nC_6H_{13}$	88	
			$^nC_8H_{17}$	$^nC_6H_{13}$	43	
			^nBu	$^nC_6H_{13}$	86	
			PhEtCH	$^nC_6H_{13}$	62	
			$PhCH_2$	H	51	
			$^nC_8H_{17}$	H	62	

[a] At 60°. [b] dppf = $Fe(C_5H_4PPh_2)_2$. [c] PPE = ethyl polyphosphate

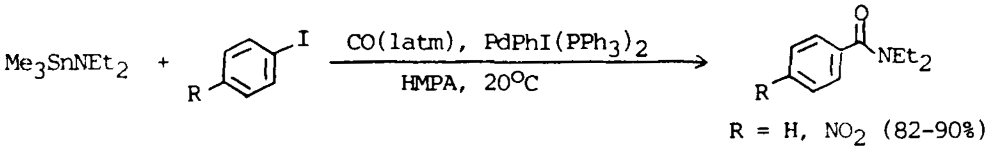
than one product can be obtained. These factors thus limit its synthetic utility.[140]

$$PhI + Et_2N \xrightarrow{CO(20atm),\ PdPhI(PPh_3)_2,\ 120^oC} \underset{74\%}{PhCONEt_2}$$

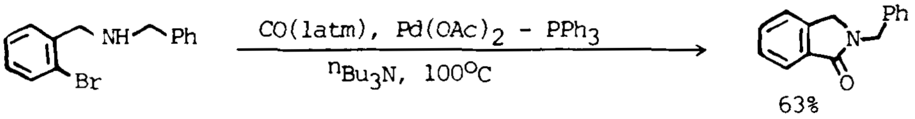
An exception, however, is the recently reported carbonylation of allylamines, which gives useful yields of β,γ-unsaturated amides.[141]

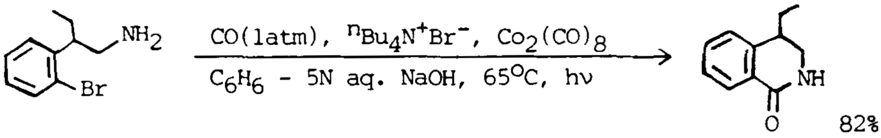


Tertiary trialkylstannylamines also give this reaction under very mild conditions using $PdPhI(PPh_3)_2$ as catalyst and in yields that can be superior to those obtained using the analogous secondary amine.[142,143]

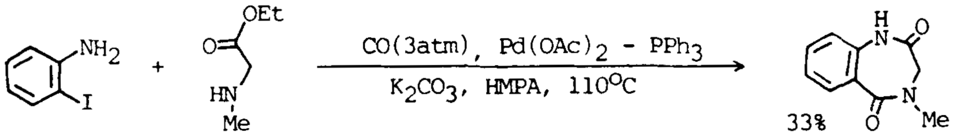


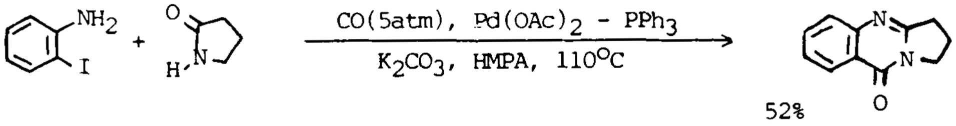
When the aryl halide and the amine are part of the same molecule, cyclized products may be obtained (Table 11). Benzolactams, for example, have been prepared using either a palladium or cobalt catalyst.[144-146] The latter may be of the type $XCH_2Co(CO)_4$ or it may be generated by irradiation of $Co_2(CO)_8$ under phase-transfer conditions.



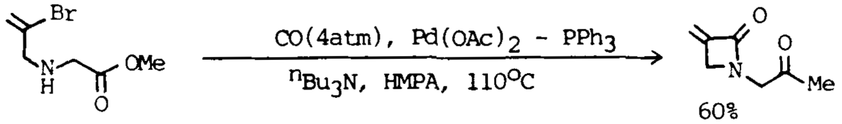


If suitable coreactants are employed, benzodiazepines or quinazolines can be prepared.[147,148]





The important β-lactam ring can also be constructed in this way, the yields being moderate.[149-151]



Alternatively, it may be obtained by insertion of CO into an aziridine. In this case a rhodium catalyst is used.[152]

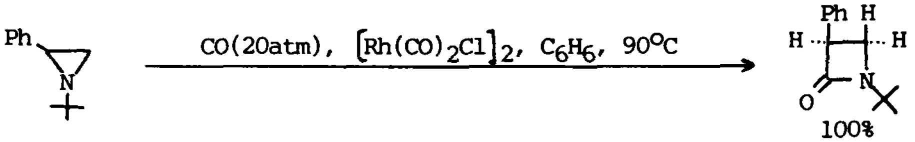


Table 11. Aminocarbonylation-Cyclization Reactions.

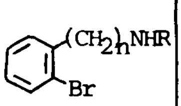
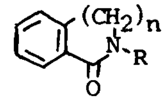
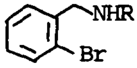
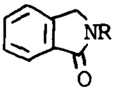
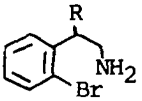
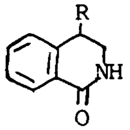
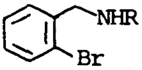
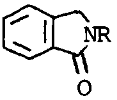
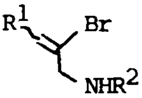
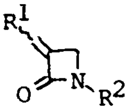
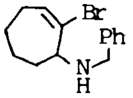
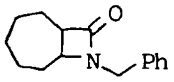
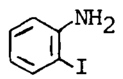
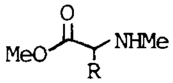
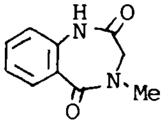
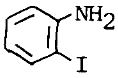
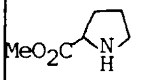
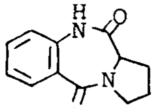
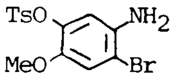
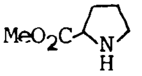
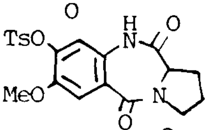
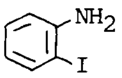
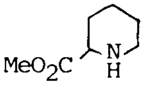
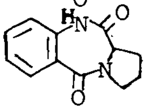
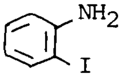
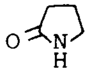
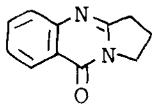
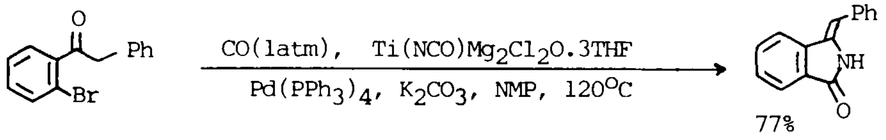
Catalyst	Coreactant	Conditions	Product	Yield	Ref
Pd(OAc)$_2$ + PPh$_3$		1atm.CO,^{n}Bu$_3$N, 100°			144
			n = 1,R = CH$_2$Ph	63	
			n = 2,R = H	38	
			n = 2,R = CH$_2$Ph	65	
			n = 3,R = H	41	
			n = 3,R = CH$_2$Ph	63	
Co$_2$(CO)$_8$		1atm.CO,hv, C$_6$H$_6$/5N NaOH/ ^{n}Bu$_4$N$^+$Br$^-$,65°			145
			 R=H	60	
			CH$_2$Ph	78	
Co$_2$(CO)$_8$		As above	 R=H	72	145
			Et	82	
EtO$_2$CCH$_2$Co(CO)$_4$		1atm.CO,MeOH, NaOMe	R=H	47	146
			 Et	55	
			CH$_2$Ph	62	
			Ph	71	
			Ph	84^c	
Pd(OAc)$_2$ + PPh$_3$		1atm.CO,HMPA, ^{n}Bu$_3$N,100°			149
			R^1 R^2		
			H PhCH$_2$	67	
			H PhCH$_2$CH$_2$	62	
			H THPO(CH$_2$)$_3$	63^b	
			H MeO$_2$C(CH$_2$)$_2$	38	
			H p-MeOC$_6$H$_4$	15	
			H PhCH$_2$O$_2$CCHMe	20	
			H PhCH$_2$O$_2$CCHMe	45^c	
			H MeO$_2$CCHMe	41^c	
			H MeO$_2$CCH$_2$	60^c	
			Z-Ph PhCH$_2$	76^c	
			E-Ph PhCH$_2$	90^c	
			E,Z-^{n}Bu PhCH$_2$	48^c	

Table 11 (continued).

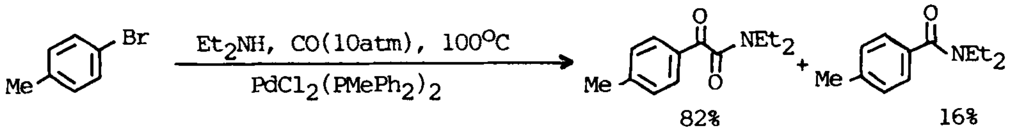
Catalyst	Coreactant	Conditions	Product	Yield	Ref
$Pd(OAc)_2$ + PPh_3		As above		86	149
$Pd(OAc)_2$ + PPh_3		3atm.CO,HMPA, K_2CO_3,110° + 	 R = H		147
			$PhCH_2$	33 16	
				79	
				41	
				18	
		5atm.CO,HMPA, K_2CO_3,110° + 		52	148

[a] NaOEt in EtOH used. [b] THP = 2-tetrahydropyranyl. [c] 4atm.CO

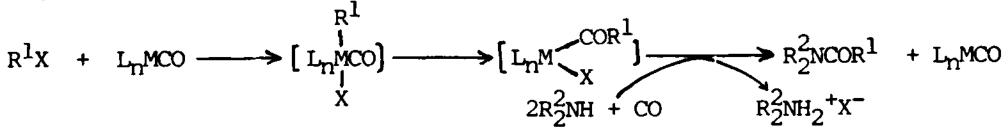
Although not involving an amine it is convenient to mention here a palladium(0) catalysed synthesis of benzolactams by the carbonylation of ortho-bromophenylketones using a titanium isocyanate complex as the source of nitrogen.[153]



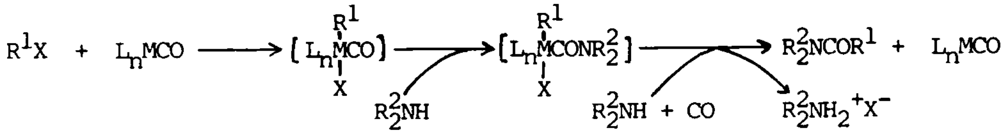
As mentioned above, the palladium catalysed aminocarbonylation of aryl halides proceeds under relatively mild conditions. If, however, the pressure of CO is increased to 20-40atm., and if a basic non-bulky amine is employed, then two molecules of CO may be incorporated to give synthetically useful α-ketoamides.[154-161] This reaction is most successful for aryl bromides but suffers from the drawback that some simple amide is almost invariably formed as a side-product.



The mechanism of the aminocarbonylation reaction has been extensively studied and two main pathways have been considered. The first involves oxidative-addition of RX to a carbonyl complex which rearranges to an acyl-metal species. This then reacts with either free or coordinated amine to give the amide.



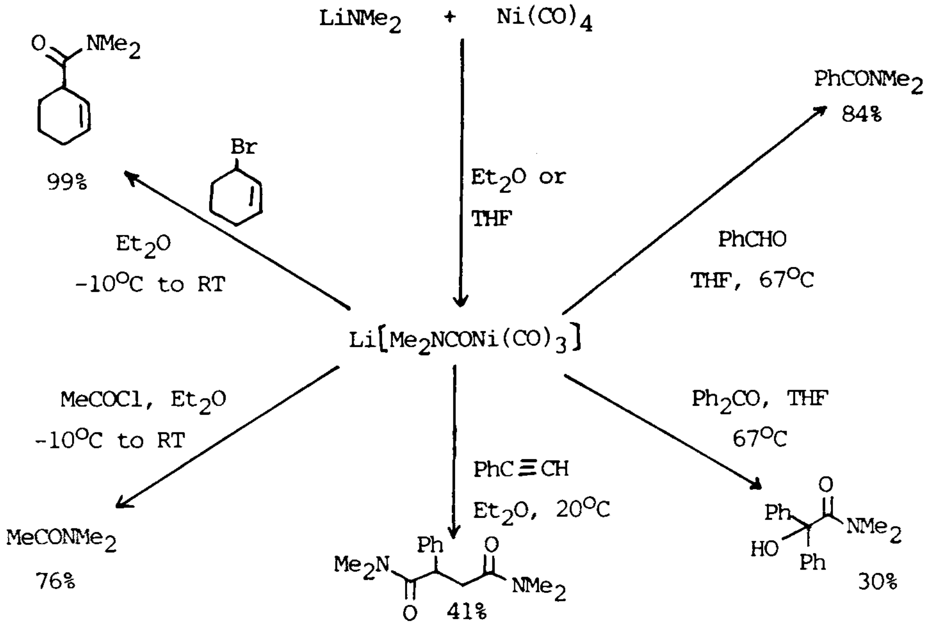
In the second mechanism a carbamoyl-metal species is formed by attack of amine, again either free or coordinated, on a carbonyl complex. Reductive elimination of the carbamoyl and organic fragments then gives the amide.



Evidence for both pathways has been presented and the existence of both acyl- and carbamoylmetal complexes is well-established. In the case of the Pd-catalysed double-carbonylation the second mechanism is strongly indicated. For other systems, however, the first has been proposed.

b. Reactions of Carbamoylmetal Species

Reaction of lithium dimethylamide with $Ni(CO)_4$ gives the compound $Li[Me_2NCONi(CO)_3]$. Like the main-group carbamoylmetallics, this complex reacts with a range of electrophiles although there are some notable differences in behaviour.[162,163] Thus whereas coupling products with organic halides and the normal addition product with benzophenone are obtained, acyl halides give simple amides rather than α-ketoamides, benzaldehyde gives dimethylbenzamide and phenylacetylene gives a diamide. Acetophenone gives self-condensation products rather than an amide.



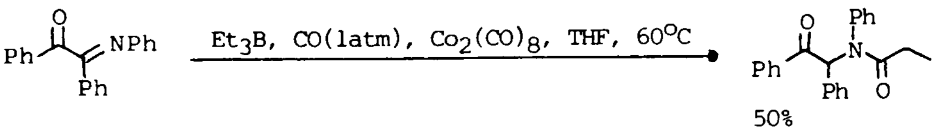
α-PHENYL-N,N-DIMETHYLMANDELAMIDE. To Li $Me_2NCONi(CO)_3$ (from 37mmol $Ni(CO)_4$ and 25mmol $LiNMe_2$) in 60ml THF is added Ph_2CO (4.55g,25mmol) in 20ml THF. Stir 20h at 67°C,hydrolyse (30ml 3N HCl) at RT, concentrate, extract with Et_2O, wash with brine,dry and distil. Product obtained by recrystallisation. Yield 30%, mp. 103°C.

Another reaction which may well proceed via a carbamoylmetal species is the carboxamidation of terminal alkynes catalysed by $CuI\text{-}PdCl_2(PPh_3)_2$ in triethylamine.[164]

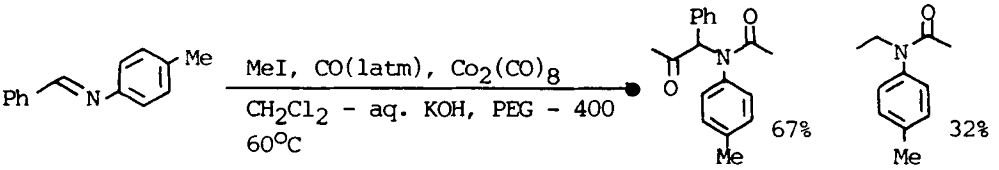
$$PhC\equiv CH \; + \; Me_2NCOCl \xrightarrow{CuI,\ PdCl_2(PPh_3)_2,\ Et_3N,\ RT} PhC\equiv CCONMe_2 \quad 92\%$$

c. Reactions of Schiff Bases (Table 12).

In the presence of $Co_2(CO)_8$, Schiff bases react with CO and triorganoboranes to give carboxamides.[165]



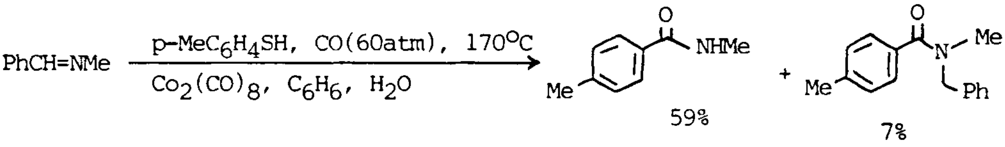
The β-ketoamides which are accessible via this reaction are potentially useful for the synthesis of 1,3-triazoles. A related reaction, which is carried out under phase-transfer conditions using MeI in place of the borane, provides a route to β'-ketoamides by double insertion of CO although some normal amide is usually found as a by-product.[166]



1-(N-ACETYL-N-PHENYLAMINO)-1-PHENYLPROPANONE. To 40ml CH_2Cl_2 add 20ml 0.33N KOH soln. and 0.5mmol PEG-400 under 1atm. CO. After 2-3min. add 0.2mmol $Co_2(CO)_8$ and 2.0ml MeI. Stir 5min. Add 1.5mmol PhCH=NPh, heat to 60°C for 3min.,cool, separate and concentrate organic phase. Chromatography (silica gel,Et_2O/hexane) gives product, yield 76%.

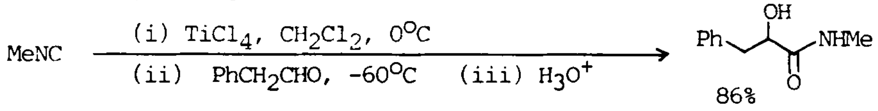
This reaction can also be carried out stoichiometrically.[167]

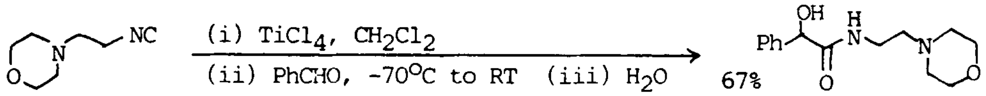
Using the same catalyst under somewhat more severe conditions, aryl- and benzylmercaptans react with Schiff bases in the presence of CO to give primary amides of the corresponding benzoic or phenylacetic acid and a symmetrically substituted olefin. Some secondary amide is also obtained as a side-product.[168]



d. Addition of Isocyanides to Carbonyl Compounds.

Isocyanides react with $TiCl_4$ to give $Cl_3TiC(=NR)Cl$ which with carbonyl compounds give α-hydroxyamides after hydrolysis.[169,170]





GENERAL PROCEDURE. To isocyanide (5.0mmol) in 20-30ml CH_2Cl_2 at 0°C under argon add 2.75ml (5.5mmol) 2M $TiCl_4$ in CH_2Cl_2. After 60min. add 5.0mmol carbonyl compound. Stir until TLC shows absence of staring material. Hydrolyse. After 20min. separate and extract with CH_2Cl_2. Wash with sat. $NaHCO_3$ soln.,H_2O,brine and H_2O. Dry and concentrate. Product obtained by flash chromatography or recrystallisation.

Table 12. Amides from Schiff Bases.

$$R^1C(R^2)=NR^3 \longrightarrow \underset{\textbf{A}}{R^4CONR^3CHR^1R^2} + \underset{\textbf{B}}{R^4CONHR^3}$$

Coreactant	Conditions	Product*				Yield	Ref
		R^1	R^2	R^3	R^4		
R^4_3B	THF, 60°, 1atm.CO, $Co_2(CO)_8$, (catalyst)	PhCO	Ph	Ph	Et	50	165
		PhCO	Ph	Ph	^nBu	82	
		PhCO	Ph	Ph	$^nC_7H_{15}$	55	
		PhCO	Ph	Ph	$PhCH_2CH_2$	50	
		PhCO	Ph	Ph	$PhCHMeCH_2$	80	
		PhCO	Ph	Ph	Ph	67	
		$p\text{-}MeC_6H_4CO$	$p\text{-}MeC_6H_4$	Ph	^nBu	87	
		$p\text{-}MeOC_6H_4CO$	$p\text{-}MeOC_6H_4$	Ph	Et	74	
		PhCO	Ph	$p\text{-}C_6H_4$	Et	33	
		$p\text{-}MeOC_6H_4$	H	Ph	Et	62	
MeI	KOH, H_2O, PEG-400, CH_2Cl_2, 60°, 1atm. CO, $Co_2(CO)_8$ (catalyst)	Ph	H	Ph	Me	76	166
		Ph	H	$p\text{-}MeC_6H_4$	Me	67	
		$p\text{-}MeC_6H_4$	H	Ph	Me	67	
		Ph	H	$p\text{-}MeOC_6H_4$	Me	68	
		$o\text{-}MeOC_6H_4$	H	Ph	Me	29	
		$o\text{-}MeC_6H_4$	H	Ph	Me	43	
		Ph	H	$o\text{-}MeOC_6H_4$	Me	34	
		Ph	H	Me	Me	40	
R^4SH	$C_6H_6\text{-}H_2O$, 60atm. CO, 170-180°, $Co_2(CO)_8$ (catalyst)	Ph	H	Me	$p\text{-}MeC_6H_4$	59	168
		Ph	H	CH_2Ph	$p\text{-}MeC_6H_4$	56	
		^nPr	H	CHMePh	$p\text{-}MeC_6H_4$	65	
		^iPr	H	^tBu	$p\text{-}MeC_6H_4$	38	
		^iPr	H	^nBu	$p\text{-}MeC_6H_4$	40	
		Ph	H	Me	$p\text{-}MeOC_6H_4$	62	
		Ph	H	Me	$p\text{-}BrC_6H_4$	43	
		2-furylCH:CH	H	$p\text{-}MeC_6H_4$	Ph	33	
		Ph	H	Me	2-naphthyl	52	
		Ph	H	Me	$p\text{-}MeC_6H_4CH_2$	34	

* Yields refer to product A for the reactions with R^4_3B and with MeI and to product B for the reactions with R^4SH.

Table 13. Reaction of $TiCl_4$ with Isocyanides and Carbonyl Compounds.

$$R^1NC \xrightarrow[\text{(ii) } R^2R^3CO \quad \text{(iii) } H_2O]{\text{(i) } TiCl_4, \quad CH_2Cl_2} R^2R^3C(OH)CONHR^1$$

R^1	R^2	R^3	Yield	Ref
Me	$^nC_5H_{11}$	H	96	169
Me	$^nC_6H_{13}$	H	82	
Me	^tBu	H	65	
Me	$PhCH_2$	H	86	
Me	PhMeCH	H	96	
Me	PhCH:CH	H	36	
Me	Ph	H	90	
Me	$p\text{-}MeOC_6H_4$	H	73	
Me	$p\text{-}BrC_6H_4$	H	95	
Me	Me	Me	84	
Me	Ph	Me	82	
Me	^tBu	Me	17	
Ph	Ph	H	98	170
Ph	$p\text{-}BrC_6H_4$	H	98	
Ph	$PhCH_2$	H	98	
Ph	Me	Me	88	
Ph	$-(CH_2)_5-$		59	
$3,4\text{-}(MeO)_2C_6H_4CH_2CH_2$	Ph	H	23	
$N\text{-}MorpholylCH_2CH_2$	Ph	H	67	
$N\text{-}MorpholylCH_2CH_2$	$Ph^{C}H_2CH_2$	H	57	
EtO_2CCH_2	Ph	H	44	
EtO_2CCH_2	$p\text{-}MeOC_6H_4$	H	70	
EtO_2CCH_2	$p\text{-}BrC_6H_4$	H	90	
EtO_2CCH_2	^nPr	H	96	
EtO_2CCH_2	^tBu	H	76	
EtO_2CCH_2	Ph	Me	81	
$(EtO)_2P(O)CH_2$	Ph	H	95	
PhMeCH	Ph	H	15	
$PhCH_2CHMe$	Ph	H	47	
$MeCH(O_2CH)CH_2$	Ph	H	55	
PhCH(OAc)CHMe	Ph	H	33	
$PhCH_2CH(CO_2Me)$	Ph	H	35	
$PhCH_2CH(CO_2Me)$	$p\text{-}BrC_6H_4$	H	38	
$PhCH_2CH(CO_2Me)$	^nPr	H	34	
$PhCH_2CH(CO_2Me)$	PhMeCH	H	35	
$PhMeC(CO_2Me)$	Ph	H	34	
$PhMeCHNHCOCH_2$	Ph	H	53	
$PhMeCHNHCOCH_2$	^nPr	H	52	
$PhMeCHNHCOCH(CH_2Ph)$	Ph	H	31	
$PhMeCHNHCOCH(CH_2Ph)$	^nPr	H	16	

Chirality in the isocyanide is preserved and the reaction was observed to fail only for those isocyanides which were capable of giving rise to a relatively stable carbocation, e.g. tert-butyl isocyanide or benzyl isocyanide.

The above titanium complex is also presumably involved in the reaction of isocyanides with acetals and ketals in the presence of $TiCl_4$ to give α-alkoxycarboxamide derivatives.[171]

e. Miscellaneous Reactions.

Certain reactions which are of limited usefulness as synthetic methods may also briefly be mentioned.[172-183] The catalytic carbonyl ion of geminal dibromoalkanes in the presence of diethylamine and zinc metal gives low yields of amides. A carbene is proposed to be an intermediate.[172]

$$\mathrm{MeCHBr_2} \xrightarrow{\mathrm{CO(20atm),\ Et_2NH,\ Zn,\ Co_2(CO)_8,\ C_6H_6,\ 50^oC}} \underset{31\%}{\mathrm{MeCONEt_2}}$$

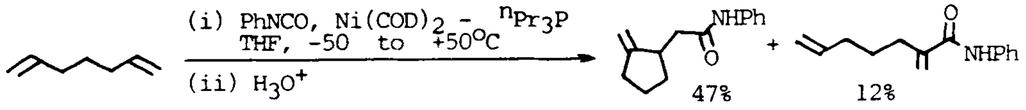
The titanium complex $TiNMg_2Cl_2(THF)$ reacts with CO and then MeI to give dimethylacetamide.[173]

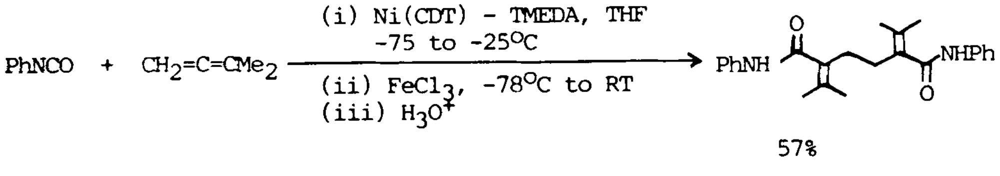
$$\mathrm{TiNMg_2Cl_2(THF)} \xrightarrow{\mathrm{(i)\ CO(1atm)\quad (ii)\ MeI,\ 100^oC}} \underset{73\%}{\mathrm{MeCONMe_2}}$$

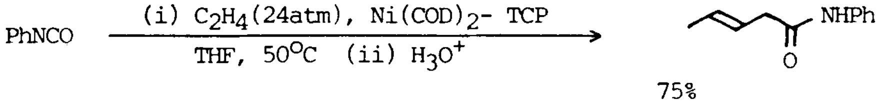
Osmium cluster complexes containing methylene bridging groups insert CO to give ketene complexes which react with primary or secondary amines to give amides.[174,175]

$$\mathrm{Os_3(CO)_{11}(\mu\text{-}CH_2)} \xrightarrow{\mathrm{CO(1atm),\ {}^nBuNH_2}} \underset{73\%}{\mathrm{MeCONH^nBu}}$$

Finally a variety of products may be obtained from olefins and isocyanates in the presence of nickel complexes or from preformed nickelocycles.[176-183]







CONCLUDING REMARKS

The decision as to which method to use to synthesise a carboxamide will depend on a number of factors. The usual procedure of condensing a carboxylic acid derivative with an amine will often be the first choice. However, as with all reactions, there will be instances where the simple method either refuses to work or is incompatible with other functionality in the reactant or product molecules. While protecting groups can provide a way round this problem, a direct procedure is generally more appealing. The methods described in this review are, in this respect, complementary to the traditional procedures, not only because of the reaction conditions involved, but also because they involve carbon-carbon bond forming reactions which often allow the construction of elaborate molecules in a small number of steps.

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Received June 14, 1989; in revised form February 2, 1990