Heterocyclic Chemistry

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Metal-Assisted Multicomponent Reactions Involving Carbon Monoxide—Towards Heterocycle Synthesis

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Multicomponent reactions have been refined in recent years into a powerful and useful tool in synthetic chemistry. Such processes enable the rapid elaboration of complex structures in a highly efficient and modular manner. In addition, the implementation of several transformations in a single manipulation is highly compatible with the goals of sustainable and "green" chemistry. The strategy is particularly attractive for the generation of compound libraries of small molecules for applications in medicinal chemistry. In combination with modern techniques in synthesis automation, this concept offers an appealing entry to a large diversity of drug candidate derivatives in a simple one-pot operation by reacting multiple simple building blocks.[1]

The application for this strategy to the preparation of heterocyclic compounds is a particularly attractive field in light of the paramount role of these targets in pharmaceutical chemistry. The number of drugs incorporating a heterocyclic structural motif is legion, and in the majority of cases this core system is critical for the desired biological activity. Several "classical" synthetic methods for heterocycles were successfully developed into multicomponent methods by taking advantage of the inherent difference in chemical reactivity of the reaction partners involved, such as the Hantzsch synthesis, the Biginelli reaction, or post-condensation modifications of the Passerini and Ugi reactions.[2,3]

Catalyzed versions of such transformations were developed to complement the reactivity and overcome some of the limitations of the intrinsic chemoselectivity of the reaction partners. From a mechanistic point of view, several subtypes of catalyzed multicomponent reactions can be distinguished depending on the action of the catalytic entity.[4] In this context, metal-assisted strategies have received increasing interest in heterocyclic chemistry in recent years.[5,6] In particular, in combination with multicomponent applications, this approach offers great potential and diversity in carbon–carbon and carbon–heteroatom bond-formation processes, together with outstanding functional group tolerance and high stereoselectivity.[7]

Some of the above concepts were further developed in recent years towards platform technologies for the modular construction of a variety of heteroaromatic systems. This Highlight focuses on some representative strategies utilizing CO as reaction partner or mediator in transition-metal-catalyzed tandem transformations for the multicomponent synthesis of heterocyclic cores (Figure 1).

The hydroformylation reaction has a history as a multireactant transformation for the introduction of a C_1 unit.[8,9] CO and H_2 are utilized in a Rh-catalyzed process to introduce a formyl group into olefins, which can further react in a multicomponent sequence. As the hydroformylation reaction represents an industrially applicable methodology, extension of this technique towards multistep one-pot transformations is particularly appealing.

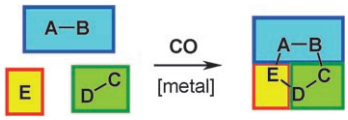

Figure 1. Multicomponent synthesis of heterocyclic systems involving CO either as reaction partner (e.g. as component E) or as mediator, which is not incorporated into the final product.

The group of Eilbracht has successfully developed such transformations towards various heterocyclic systems. In a tandem hydroformylation/Fischer synthesis sequence, they used catalytic amounts (1 mol%) of $[\{Rh(cod)Cl\}_2]$ or $[Rh(acac)(CO)_2]$ at elevated CO/H_2 pressures to prepare several substituted indoles **5** from hydrazines **3** and aminoolefin precursors **1** (Scheme 1, Table 1).[10] Both protected hydrazine derivatives (entries 2 and 3) and functionalized olefin reaction partners can be applied upon proper modification of the experimental protocol.

Under the standard reaction conditions, methallyl precursors exclusively react to give *n*-formylated intermediates. In the case of allyl substrates, this selectivity was decreased and led to the formation of isomeric products but could be improved by using the less reactive $[Rh(acac)(CO)_2]$ catalyst in combination with the biphosphane ligand xantphos[11] (Table 1, entries 6 and 7). In the case of chiral precursors, preexisting stereocenters are not affected under the reaction conditions (Ta-

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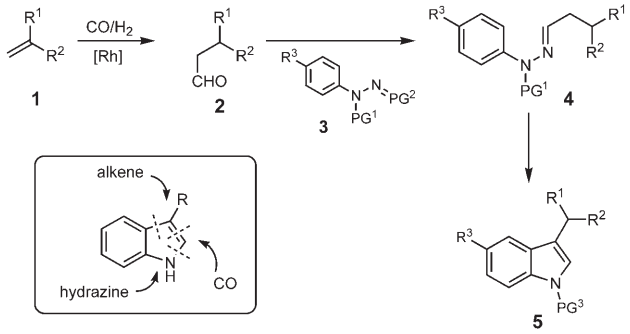
Table 1: Tandem hydroformylation/Fischer indole synthesis sequence (Scheme 1).[a]

Entry	Olefin	R^1	R^2	Hydrazine	PG^1	PG^2	R^3	Catalyst	Product	PG^3	Yield [%]
1	**1a**	Me	CH_2NPhth	**3a**	H	H,H	H	$[\{Rh(cod)Cl\}_2]$	**5a**	Ts	60
2	**1a**	Me	CH_2NPhth	**3b**	H	CPh_2	H	$[\{Rh(cod)Cl\}_2]$	**5b**	H	83
3	**1a**	Me	CH_2NPhth	**3c**	Boc	H,H	OMe	$[Rh(acac)(CO)_2]$	**5c**	H	95
4	**1b**	Me	$CH_2N(Et)Bz$	**3a**	H	H,H	H	$[Rh(acac)(CO)_2]$	**5d**	H	85
5	**1c**	Me	Ph	**3a**	H	H,H	H	$[\{Rh(cod)Cl\}_2]$	**5e**	H	67
6	**1d**	H	CH_2NPhth	**3a**	H	H,H	H	$[Rh(acac)(CO)_2]$[b]	**5f**	H	46
7	**1d**	H	CH_2CH_2COOMe	**3a**	H	H,H	H	$[Rh(acac)(CO)_2]$[b]	**5g**	H	91
8	**1e**	H	(+)/(−)-CH(Ph)Pip	**3a**	H	H,H	H	$[Rh(acac)(CO)_2]$[b]	(+)/(−)-**5h**	H	54[c]

[a] Abbreviations: acac = acetylacetonate, Boc = *tert*-butyloxycarbonyl, Bz = benzoyl, cod = 1,5-cyclooctadiene, Phth = phthaloyl, Pip = piperidinyl. [b] In the presence of xantphos bidentate ligand. [c] 95% *ee*.

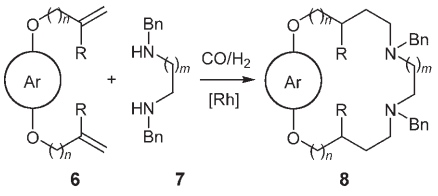


Scheme 1. Tandem hydroformylation/Fischer indole synthesis: a) 0.5–1 mol% [Rh] cat., 50 bar CO, 10 bar H_2, (eventually 1 equiv TsOH), 80–120°C, 1–3 days [eventually: b) TsCl, NaOH for PG^3 = Ts]. Ts: = *para*-toluenesulfonyl.

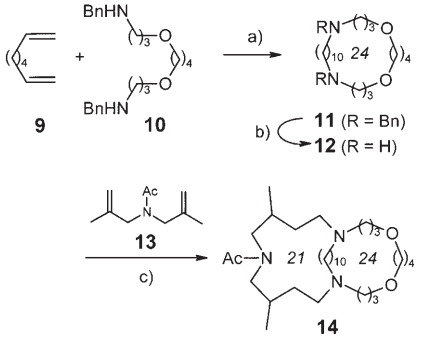
ble 1, entry 8). The methodology was successfully applied to the synthesis of various serotonin analogues, plant growth regulators, and intermediates in the synthesis of sertindole derivatives.

The concept could also be applied to the reaction of dienes **6** with (di)amines **7**. Although the conditions are only moderately successful for the synthesis of small-sized nitrogen heterocycles, the transformation is very powerful to access large ring systems **8** with several heteroatoms (Scheme 2, 59–78% yields).[12] Again, careful modification of the reactivity of the Rh catalyst by addition of biphephos or xantphos ligands improved the site-selectivity in the formylation of allyl precursors. However, in this case a two-step protocol turned out to be more efficient (29–71% yields).

This strategy of repeated sequential hydroformylation and reductive amination of terminal dialkenes and a diamine also enabled rapid access to the cryptand system **14** (Scheme 3).[12b]



Scheme 2. Synthesis of large-sized heterocycles by a hydroformylation/reductive amination strategy. [Rh]: $[Rh(acac)(CO)_2]$ (eventually with xantphos), 20–80 bar CO/H_2 (1:1), 70–80°C, 1–3 days; Ar = 1,4-phenyl, 1,1′-biphenyl, 1,1′-binaphthyl; R = Me, H; *m* = 3, 5; *n* = 1–4. Bn = benzyl.

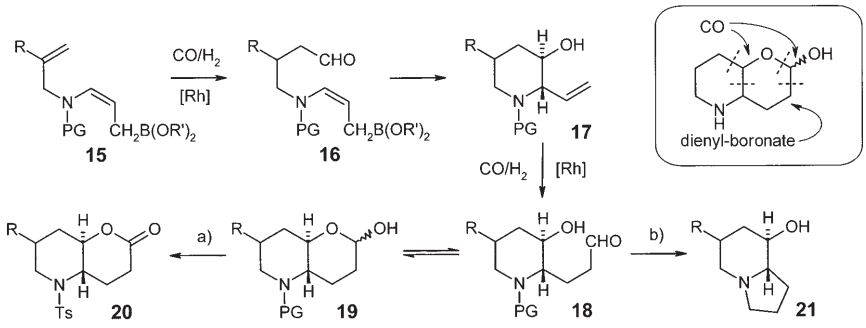


Scheme 3. Repeated hydroformylation/reductive amination in the synthesis of **14**: a) $[Rh(acac)(CO)_2]$, biphephos, 10 bar CO/H_2 (1:1); b) H_2/Pd(C); c) $[\{Rh(cod)Cl\}_2]$, 100 bar CO/H_2 (1:1).

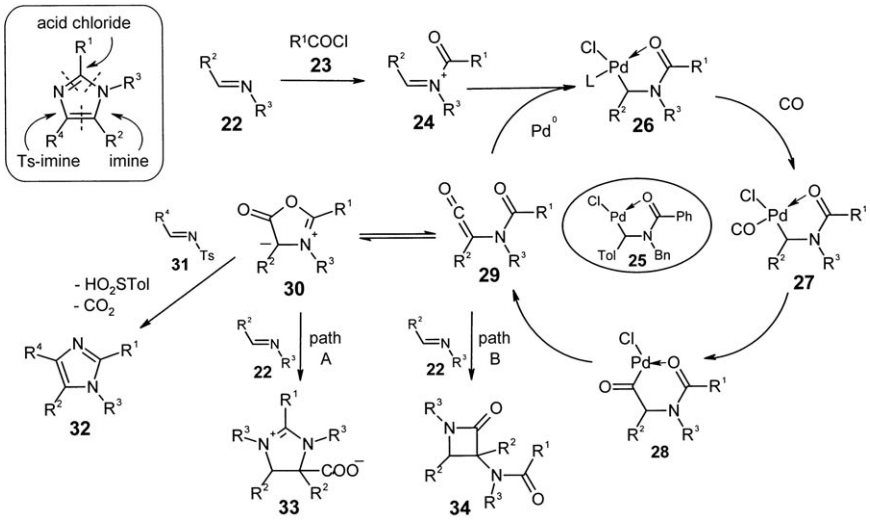
Double hydroformylation of terminal boronic esters of type **15** was utilized by Hoffmann et al. in a domino reaction involving an allylboration step.[13] Again, careful optimization of the ligand system was required to favor the formation of linear aldehydes, and the best results were obtained using $[Rh(acac)(CO)_2]$ and biphephos. The cascade reaction first gives rise to intermediate **16**, which undergoes cyclization and another hydroformylation (Scheme 4). Ultimately, aldehyde **18** was isolated, which is in equilibrium with lactol species **19**, and was oxidized to lactone **20** to obtain one product. When using an easily cleavable N-protecting group (Cbz), a further domino reaction leads to the indolizine ring system **21**.[13a]

A major obstacle in multicomponent hydroformylation strategies towards heterocyclic systems is the requirement for high-pressure transformations, which makes parallelization in library syntheses difficult. In a recent series of contributions, the group of Arndtsen reported the development of an elegant alternative to cascade transformations towards heterocyclic cores utilizing CO as mediator.

On the basis of their initial findings of a metal-assisted formation of Münchnones upon reaction of imines and acid chlorides in the presence of a Pd catalyst and CO,[14] Arndtsen and co-workers immediately recognized the potential of this transformation for accessing diverse heterocyclic systems. The tentative mechanism of this type of reaction is outlined by the synthesis of imidazoles from two imine species and an acid chloride (Scheme 5). Reaction of imine **22** and acyl chloride **23** in situ generates iminium species **24**.[15] This intermediate



Scheme 4. Double hydroformylation/allylboration towards perhydropyranopyridines: [Rh(acac)(CO)$_2$], biphephos, 5 bar CO/H$_2$ (1:1); R = H, Me; R′ = pinacolyl, PG = Ac, Ts, Cbz; 66–86% yield; a) Pr_4NRuO_4 (PG = Ts); b) H$_2$/Pd(C), 60% (PG = Cbz). Cbz = carbobenzyloxy.



Scheme 5. Mechanism of CO-mediated synthesis of imidazoles **32** and modification of the reaction pathway towards imidazolines and β-lactams. Tol = *p*-tolyl.

enters the catalytic cycle of the Pd-assisted reaction within an oxidative addition. A moderate pressure of CO (1–4 atm) leads to ligand exchange at the metal center. It is critical at this stage that sterically encumbered phosphines such as P(*o*-tolyl)$_3$ are used to allow subsequent catalytic steps. The presence of base leads to formation of Münchnone species **30** as reactive intermediates for subsequent transformations. In the case of imidazole synthesis, possible side reactions could be suppressed by the addition of LiCl.

Münchnone **30** can then undergo in situ 1,3-dipolar cycloaddition with *N*-tosylimines **31** in high yields to provide imidazoles **32** upon elimination of CO_2 and $TolSO_2H$ (Table 2). Although the best results were obtained with the Pd catalyst **25**, commercially available [Pd$_2$(dba)$_3$]·CHCl$_3$ (dba = *trans*,*trans*-dibenzylideneacetone) gave comparable (or slightly lower) yields. The methodology offers access to imidazoles with four possible positions for introduction of molecular diversity and was successfully applied in the modular synthesis of the p38 MAP kinase inhibitor **32 f** (Table 2, entry 6).[15]

Table 2: Synthesis of imidazoles **32** with CO (Scheme 5).[a]

Entry	R^1	R^2	R^3	R^4	Product	Yield [%]
1	Ph	Tol	Et	Ph	**32 a**	76
2	Tol	Tol	4-MeOC$_6$H$_4$	Furyl	**32 b**	71
3	Furyl	4-MeSC$_6$H$_4$	Et	3-Pyridyl	**32 c**	70
4	Ph	Tol	Et	PhCH=CH-	**32 d**	74
5	Tol	Tol	Et	*c*Hex	**32 e**	68
6	4-MeOC$_6$H$_4$	4-FC$_6$H$_4$	Allyl	4-Pyridyl	**32 f**	65[b]

[a] Tol = *p*-tolyl. [b] Yield after deprotection of the allyl group with $PhSiH_3$, [Pd(PPh$_3$)$_4$], HBr.

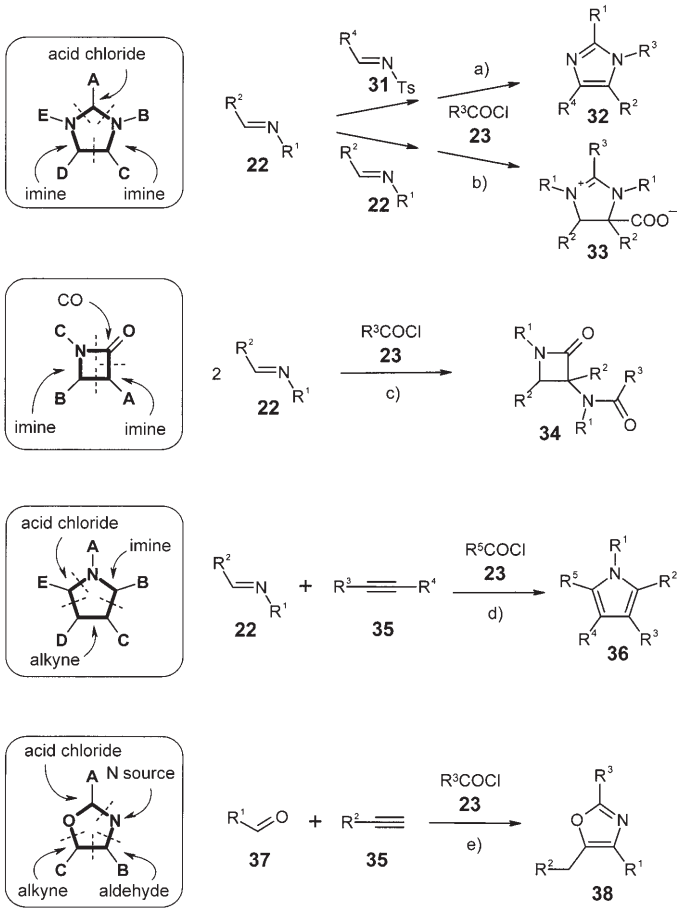
If the elimination of CO_2 and $TolSO_2H$ is not possible to generate a heteroaromatic core, the reaction stops at the imidazoline stage (**33**) through path A (Scheme 5 and Scheme 6). This process is synthetically useful also, and several compounds of type **33** were obtained upon reaction of imines and acid chlorides in the presence of CO under Pd catalysis with 2,2′-bipyridine (bipy) ligands.[14a]

As the corresponding Münchnone **30** is in equilibrium with its ketene isomer **29** (Scheme 5), formal [2+2] cycloaddition with another imine moiety is likely to form β-lactams **34** by path B. Such reactions have been reported previously. Hence, the direction of the transformation can be determined by proper choice of reaction conditions: whereas imidazolines **33** are exclusively obtained under acidic conditions (no trapping of the HCl formed during the conversion), lactams are generated in the presence of base (Scheme 6). Bidentate chelating ligands further promote the formation of lactam products.[16] In the formation of imidazolines **33**, CO is ultimately incorporated into the product as a substituent (-COO$^-$) whereas the CO carbon atom becomes part of the heterocyclic core in β-lactams **34**.

When the transformation is carried out in the presence of alkynes **35** instead of imines, pyrroles **36** incorporating five centers of possible diversity are obtained in equally good yields (Scheme 6).[17]

Although it is not technically a CO-mediated one-pot reaction, the strategy of multicomponent transformations involving imines and acid chlorides as exploited by Arndtsen and co-workers can also be applied to the synthesis of another five-membered heterocyclic system, underscoring its high modularity: The Cu^I/BF$_3$-assisted conversion of aldehydes and a nitrogen source with terminal alkynes gives oxazoles in high yields.[18]

The methods presented herein are an indication of the potential of metal-mediated cascade transformations in



Scheme 6. Access to various heterocyclic systems using metal-assisted CO-mediated imine cyclization and a further extension of the general strategy towards oxazole formation: a) CO (4 atm), 5 mol% **25**, 15 mol% P(*o*-tolyl)$_3$, EtN*i*Pr$_2$/LiCl, 45 °C (10 examples, see Table 2); b) CO (1 atm), 5% [Pd$_2$(dba)$_3$], 10% bipy ligand, 55 °C (six examples, 62–92% yield); c) CO (1 atm), 1.4% [Pd$_2$(dba)$_3$], bidentate ligand, 55 °C (11 examples, 27–66% yield); d) CO (4 atm), 5 mol% **25**, 15 mol% P(*o*-tolyl)$_3$, EtN*i*Pr$_2$, 65–75 °C (14 examples, 56–95% yield); e) 1. LiN(TMS)$_2$, 0 °C, then **23**, RT; 2. **35**, 10% CuI, 20% $BF_3{\cdot}Et_2O$, EtN*i*Pr$_2$, 65 °C, then NaH (four examples, 76–85% yield). TMS = trimethylsilyl.

general. Carbon monoxide assisted multicomponent transformations towards heterocyclic systems in particular have received increasing attention in recent years and led to several new strategies. Versatile platform technologies for a variety of ring systems are emerging, and we hope to see further activity in this exciting area as a result of this Highlight.

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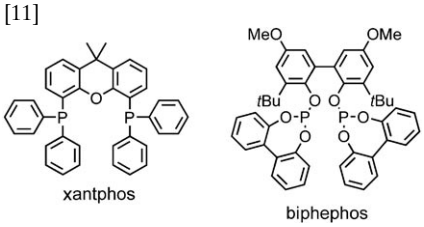

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