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FULL PAPER

[Co(MeTAA)] Metalloradical Catalytic Route to Ketenes via Carbonylation of Carbene Radicals

Andrei Chirila,[a] Kaj M. van Vliet,[a] Nanda D. Paul,[a,b] and Bas de Bruin[a]*

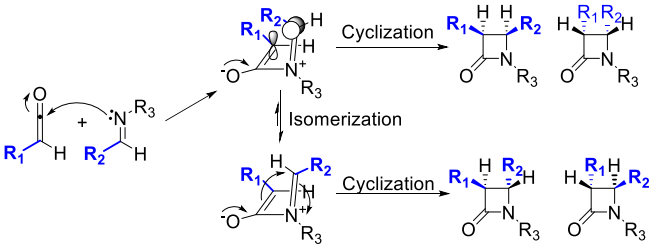
Abstract: An efficient synthetic strategy towards beta-lactams, amides and esters involving "in situ" generation of ketenes and subsequent trapping with nucleophiles is presented. Carbonylation of carbene radical intermediates using the cheap and highly active cobalt(II) tetramethyltetraaza[14]annulene catalyst [Co(MeTAA)] provides a convenient one-pot synthetic protocol towards substituted ketenes. *N*-tosylhydrazones are used as carbene precursors, thereby bridging the gap between aldehydes and ketenes. Activation of these carbene precursors by the metalloradical cobalt(II) catalyst affords Co(III)-carbene radicals, which subsequently react with carbon monoxide to form ketenes. In the presence of a nucleophile (imine, alcohol or amine) in the reaction medium the ketene is immediately trapped, resulting in the desired products in a one-pot synthetic protocol. The β-lactams formed upon reaction with imines are produced in a highly *trans*-selective manner.

Introduction

Ketenes are synthetically useful compounds with intriguing electronic structures, a versatile reactivity and interesting physical and chemical properties.[1] Ketenes are usually prepared in stoichiometric reactions such as base promoted elimination of acyl chlorides (first shown by Wedekind in 1901),[2] by metal halide abstraction (exemplified by Staudinger in 1905),[3] via a Wolff rearrangement from α-diazoketones,[4] or by (poorly controlled) thermolysis (pyrolysis) pathways.[5] All these methods have important limitations for practical multi-gram syntheses, often involve unstable (intermediates and) starting materials, and typically require specialized equipment.[1]

A more robust method for preparing ketenes[6] found in several organic transformations is the carbonylation of metal-carbenes[7,8] and "in situ" reaction of the thus produced highly reactive ketenes with suitable reagents such as imines, amines or alcohols.[7] However, a significant drawback of these methods is that the transformations usually rely on the use of Fischer-type carbene complexes (thus leading to fast carbene-carbene dimerization side reactions in many cases), and the reactions are typically stoichiometric. Just a few examples have been reported where the carbonylation is catalysed by a transition metal complex.[7, 8] One of them uses noble metal catalysts in the form of palladium complexes,[7c] while others use base metal catalysts. However, most of these reactions are associated with low yields and rather harsh reaction conditions (i.e. high temperatures and high CO pressures).[8]

The synthesis of reactive ketenes formed during the carbonylation of metal carbenes leads to relevant products, such as β-lactams formed by [2+2] ketene-imine cycloadditions (Scheme 1). The β-lactam skeleton is of great importance for the pharmaceutical industry,[9] as the β-lactam backbone is found in many antibiotics such as penicillins, cephalosporins, carbapenems and monobactams. The β-lactam structure strongly interacts and even covalently binds to the active site of some bacterial proteins, which eventually leads to their apoptosis.[10] The [2+2] cycloaddition between ketenes and imines to yield β-lactams is a reaction discovered by Staudinger, published only two years after isolation of the first ketene.[1] The mechanism of the Staudinger synthesis (Scheme 1) starts with nucleophilic attack of the imine nitrogen to the central carbon of the ketene moiety, forming an enol-type amide intermediate.[11] If the ketene is substituted with electron donating substituents, the cyclization step is fast and due to the default *E*-configuration of the imine and subsequent conrotatory ring closure, the products formed are generally the *cis*-isomers. If the ketene lacks strongly electron-donating substituents, the cyclization step is slower, thus allowing isomerization of the enol intermediate resulting in formation of (thermodynamically favoured) *trans*-β-lactam isomers (Scheme 1).[11]



Scheme 1. The Staudinger synthesis of β-lactams via [2+2] cycloaddition reactions.

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The use of cobalt(II) porphyrins [Co^{II}(por)] as stable metalloradicals with well-defined open-shell doublet d^7-electronic configurations have recently been reported in several transformations involving catalytic carbene transfer reactions[12] via stable Co^{III}-carbene radical intermediates.[13] A relevant example is the efficient carbonylation of diazo compounds using mild temperatures and CO pressures, previously reported in our group.[14] The nucleophilic nature and radical-type character of the carbene radical intermediates involved in these reactions is in marked contrast with that of an electrophilic Fischer-type carbene, thus preventing unwanted carbene dimerization reactions. Therefore, the attack of the nucleophilic carbene radical at the π-accepting carbon monoxide becomes possible, thus allowing "in situ" generation of ketenes. These ketenes are subsequently reacted with imines or amines to obtain amides or respectively β-lactams (Scheme 2). Because the cobalt catalyst and the carbene radical intermediates are not sensitive to the presence of amines or imines, the reactions can be performed in a one-pot catalytic reaction in which the "in situ" generated ketene is trapped by the added nucleophile.

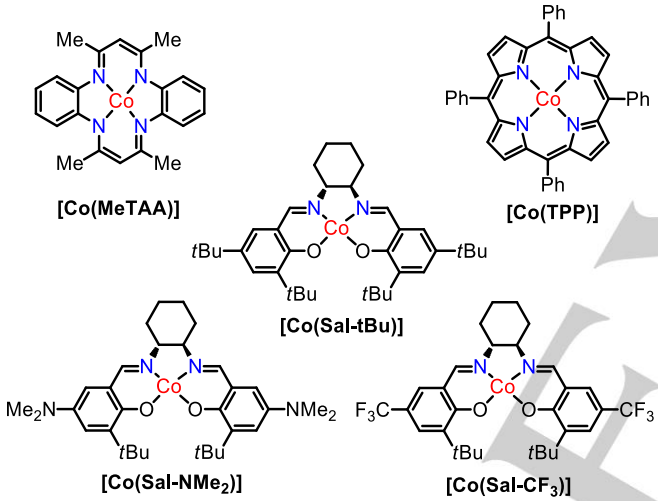
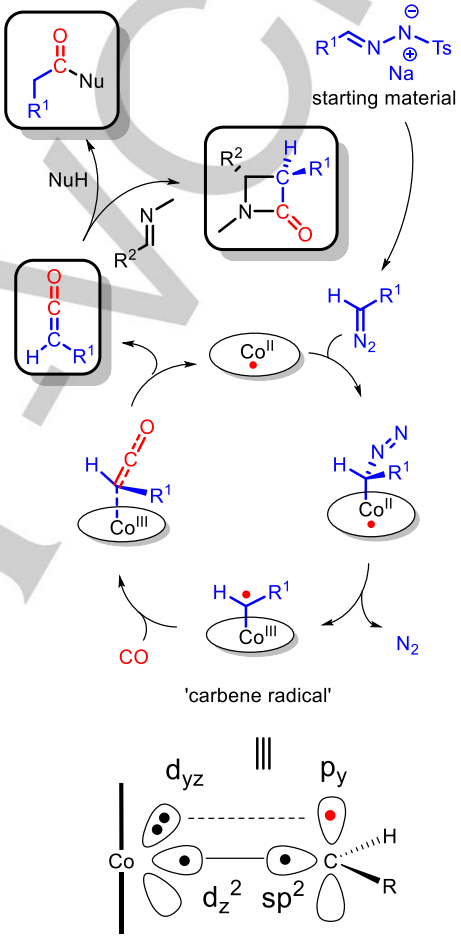


Figure 1. Structures of the cobalt(II) catalysts used in this study.

Due to the synthetic challenge in preparing substituted cobalt(II) porphyrins, we decided to expand the catalytic scope of this reaction by screening several cheap and easy to prepare cobalt(II) complexes (Figure 1). Based on our current understanding of the metalloradical mechanism, more electron-rich low-spin cobalt(II) complexes facilitate the carbene reduction and thus the formation of the key carbene radical intermediate. Electron rich carbenes would be nucleophilic, therefore favouring the CO carbonylation pathway. A lead candidate would be the cobalt(II)tetramethyltetraaza[14]annulene complex [Co(MeTAA)] (Figure 1), successfully used in our recent other studies.[15] It is easily prepared from readily available staring materials,[16] and presents a smaller macrocycle than corresponding porphyrins, thereby inducing more electron density at the metal centre. The complex proved to be an excellent catalyst for the activation of diazo compounds and generation of reactive carbene radical species.[15] As such, we argued that [Co(MeTAA)] should be a potent catalyst for carbene carbonylation, with subsequent ketene trapping.

In this paper we report an easy one-pot cascade method to form ketenes starting from tosylhydrazones (which are in turn prepared easily from aldehydes and tosylhydrazine). This strategy expands the scope of previous studies by taking advantage of the outstanding activity of [Co(MeTAA)] to activate diazo compounds, thus forming carbene radicals intermediates which react with carbon monoxide to afford ketenes. The "in situ" catalytically formed ketenes are then trapped with imines, amines or alcohols to afford beta-lactams, amides and esters as the final organic products.

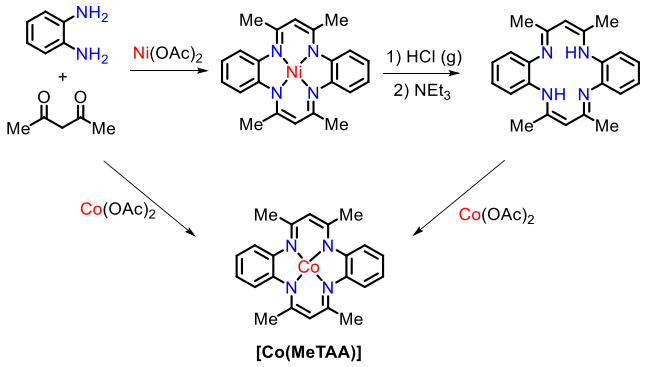


Scheme 2. Proposed mechanism for catalytic ketene synthesis via cobalt(III)-carbene radical carbonylation.

Results and Discussion

The cobalt(II) tetramethyltetraaza[14]annulene complex [Co(MeTAA)] can be synthesized using a template condensation between 2,4-pentandione and 1,2-diaminobenzene in the presence of cobalt(II) acetate tetrahydrate (Scheme 3). However, due the sensitivity of the complex towards oxygen and the low yield of the direct cobalt-template synthesis, a stepwise route is preferred in which the nickel(II) tetramethyltetraaza[14]annulene [Ni(MeTAA)] is first prepared using the template synthesis around nickel.[17] In this case the formed complex is not sensitive to oxygen, and the complex can easily be obtained in high quantities using bulk cheap starting materials. Demetallation using gaseous hydrochloric acid, followed by deprotonation with trimethylamine

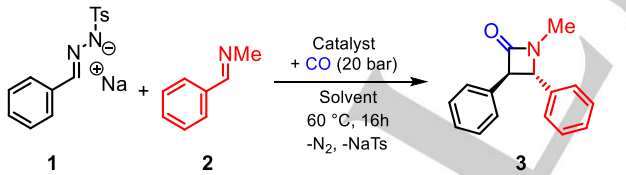
affords the free tetramethyltetraaza- [14]annulene ligand. Complexation using cobalt acetate under reflux for a few minutes produces the crystalline [Co(MeTAA)] complex, which precipitates from solution in high yield. The thus formed [Co(MeTAA)] complex was further used in catalysis screening.



Scheme 3. Synthesis of [Co(MeTAA)].

We decided to first focus on the reaction between the benzaldehyde tosylhydrazone sodium salt and *N*-methylbenzaldimine. In this reaction, phenylketene is generated *in situ*, which together with the imine undergoes a [2+2] cycloaddition resulting in formation of β-lactam **3** as the product (Table 1). This reaction was used as a benckmark to find the optimal catalytic conditions. A comparison of the activity of the planar cobalt(II) complexes depicted in Figure 1 was investigated, using 1.0 eq of tosylhydrazone, 1.2 eq. of imine, toluene as the solvent, a CO pressure of 20 bar, and a reaction temperature of 60 °C as the initial reaction conditions.

Table 1. Optimization of the reaction conditions for the synthesis of β-lactam **3** from benzaldehyde tosylhydrazone sodium salt **1** and *N*-benzylidenemethanamine **2**.



Entry [a]	Catalyst	Solvent	Additive	Catalyst loading	Yield[b] (%)
1	--	PhMe	-		<1
2	$Co(OAc)_2$*$4H_2O$	PhMe	-	5%	<5
3	[Co(Sal-NMe_2)]	PhMe	-	5%	6
4	[Co(Sal-CF_3)]	PhMe	-	5%	10
5	[Co(Sal-tBu)]	PhMe	-	5%	16
6.	[Co(TPP)]	PhMe	-	3.5%	68
7	[Co(MeTAA)]	PhMe	-	2%	71
8	**[Co(MeTAA)]**	**PhMe**	**-**	**3.5%**	**77**
9	[Co(MeTAA)]	PhMe	-	7.5%	78
10	[Co(MeTAA)]	THF	-	4%	34
11	[Co(MeTAA)]	DCE	-	4%	47
12	[Co(MeTAA)]	PhCl	-	4%	48
13	[Co(MeTAA)]	MeCN	-	4%	8
14	[Co(MeTAA)]	Dioxane	-	4%	14
15	[Co(MeTAA)]	$PhCF_3$	-	4%	11
16[c]	[Co(MeTAA)]	PhMe	Pyridine	3%	53
17[c]	[Co(MeTAA)]	PhMe	DMAP	3%	50
18[c]	[Co(MeTAA)]	PhMe	1-Methyl Imidazole	3%	67
19[d]	[Co(MeTAA)]	PhMe	1-Methyl Imidazole	3%	73
20[e]	[Co(MeTAA)]	PhMe	-	3%	46
21[f]	[Co(MeTAA)]	PhMe	-	3%	39
22[g]	[Co(MeTAA)]	PhMe	-	3%	52

[a] Reactions were carried out under 20 bar CO in a sealed autoclave with 1.0 eq. of sodium salt of tosylhydrazone and 1.2 eq. of imine for 16 h. Conc. 0.34 mmol tosylhydrazone/3.0 mL solvent. [b] Isolated yields. [c] stoichiometry catalyst : additive = 1:1 [d] stoichiometry catalyst : additive = 1:2 [e] 10 bar CO [f] 2 bar CO [g] 40 °C

Entries 1-8 from Table 1 present the results of the initial screening experiments, in which [Co(MeTAA)] affords the best yield of 77% (entry 8), better than [Co(TPP)] yielding 68% product (see entry 6). The other cobalt(II) complexes perform poorly, affording a maximum yield of 16% (for [Co(Sal-*t*Bu)], entry 5). Control experiments using no catalyst, as well as the simple $[Co(OAc)_2]$ precursor did not result in products formation, thus showing that the reaction is indeed catalytic and requires a planar low-spin cobalt(II) metalloradical catalyst (entries 1-2). Catalyst loading screening (entries 7-9) indicates an optimum at around 3 mol% [Co(MeTAA)].

Solvent screening (entries 8-15) indicates that toluene is the best solvent for this reaction, producing the product in a yield of 77%. Other solvents such as 1,2-dichloroethane or chlorobenzene lead to lower yields of 47% (entry 11) and 48% respectively (entry 12). Polar solvents (entries 13-15) are not suitable for this reaction as the conversion drops significantly, yielding the product in only 8% using acetonitrile and in 14% using dioxane. In some of our previous reports,[15] coordinating additives had a positive influence on the outcome of the reaction, increasing the activity of the catalyst. However, in this study (Table 1, entries 16-19) the use of pyridine, 4-dimethylaminopyridine and 1-methylimidazole additives led to lower yields than in reactions without these additives.

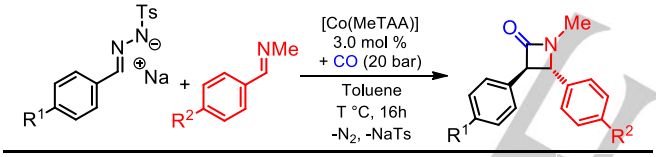
These additives might well hamper the [2+2] cycloaddition of the ketene with the imine. Variation of the CO pressure (entries 20-21) indicates that β-lactams can be formed at 2 bar (39% yield), but higher yields are obtained at higher CO pressures. At 10 bar 46% of the β-lactam **3** is obtained, but the highest yield (77%) is

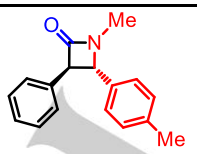
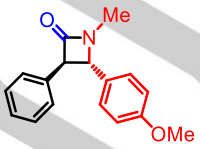
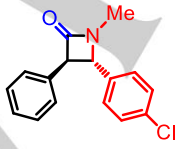
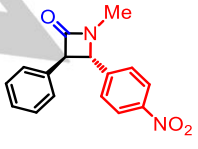
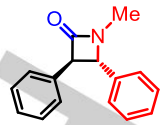
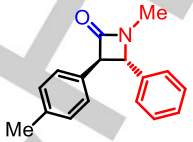
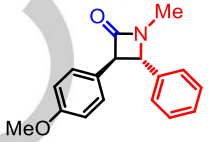
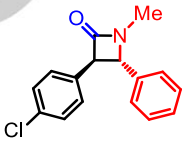
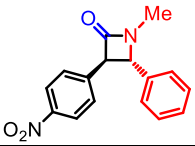
obtained when pressurising the autoclave to 20 bar. Temperature plays also an important role, as it helps formation of the carbene radical intermediate from the benzaldehyde tosylhydrazone sodium salt. Lowering the reaction temperature to 40 °C is possible, but leads to a drop in the product yield to 52% (Table 1, entry 22). The reactions in Table 1 proved to be in all cases highly *trans*-selective, producing *trans* β-lactam product **3** in an excellent diastereoselectivity (>99%).

Based on all information gathered (Table 1), we decided to continue with the following reaction conditions in the initial screening experiments of most of the catalytic reactions described below: 20 bar CO, 60 °C, 3 mol% catalyst and a 1.0:1.2 tosylhydrazone:imine molar ratio. For the more challenging substrates, higher reaction temperatures were used.

To explore the versatility of the reaction, the substrate scope was investigated (Table 2). First, the coupling of a variety of para-substituted *N*-methylbenzaldimines to benzaldehyde tosylhydrazone sodium salt was explored (Table 2, entries 1-5). The non-substituted imine afforded the highest yield of 77% (entry 5), followed by electron-donating substituents (Me: 62% yield, entry 1; MeO: 57% yield, entry 2). Introducing electron-withdrawing substituents at the para-position of the benzaldimines leads substantial lowering of the product yields (Cl: 52% yield, entry 3; NO_2: 36% yield, entry 4).

Table 2. Substrate scope screening [Co(MeTAA)] catalysed trans-selective β-lactam synthesis from substituted tosylhydrazone sodium salts and substituted imines.



Entry[a]	-R^1	-R^2	Temp (°C)	Product	Yield[b] (%)
1	-H	-Me	60		62
2	-H	-OMe	60		57
3	-H	-Cl	60		52
4	-H	-NO_2	60		36
5	-H	-H	60		77
6[c]	-H	-H	140		69
7	-Me	-H	60		20
8[c]	-Me	-H	140		46
9	-OMe	-H	60		33
10[c]	-OMe	-H	140		60
11	-Cl	-H	60		61
12[c]	-Cl	-H	140		62
13	-NO_2	-H	60		<5
14[c]	-NO_2	-H	140		<5

[a] Reactions were carried out under 20 bar CO in a sealed autoclave with 1.0 eq. of tosylhydrazone salt, 1.2 eq. of imine and 0.03 eq. [Co(MeTAA)]. Conc: 0.34 mmol tosylhydrazone salt/3.0 mL toluene. [b] Isolated yields. [c] 1.0 eq. tosylhydrazone salt, 2.0 eq. imine and 0.04 eq. [Co(MeTAA)]. Conc: 0.34 mmol tosylhydrazone salt/2.0 mL toluene.

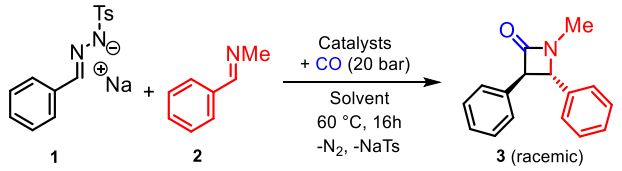
Next, the effect of para-substitution on the tosylhydrazone salt was investigated (entries 6-14). These substrates proved to be challenging, and thus we needed to increase the reaction temperature to 140 °C. Apart from that, both electron donating substituents (Me: 46%, entry 8; OMe: 60%, entry 10) and the electron withdrawing chloro-substituent (62% yield, entry 12) are tolerated. Unfortunately, a nitro substituted on the tosylhydrazone proved to be too challenging, and did not produce any β-lactam. Remarkably, reactions are possible in pressurized systems at elevated temperatures of 140 °C showing the stability of the catalytic system, in contrast to normal [2+2] Staudinger cycloadditions that are usually performed bellow 0 °C. In all cases, the reactions proved to be highly *trans*-selective, producing the *trans* β-lactam products in excellent diastereoselectivities >99%.

The reactions in Table 1 and 2 afforded the *trans* products in excellent diastereoselectivities (>99%), but as racemic mixtures. Utilization of chiral cobalt(II) catalysts has no influence on this reaction, because the ketene is dissociated from the metal centre before reacting with the imine.[14] This was confirmed in reactions using chiral catalyst [Co(Sal-*t*Bu)] (Table 3, entry 6). Therefore, we argued that a chiral co-catalyst could perhaps be used to induce chirality in the [2+2] ketene-imine cycloaddition. Hence, we decided to investigate a cascade one-pot reaction that uses the cobalt(II) catalyst for ketene formation, and subsequently a chiral co-catalyst that favours the β-lactam formation (Table 3).

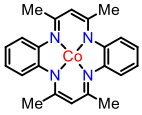
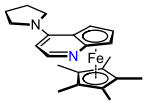
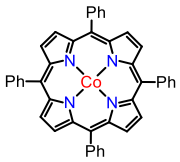
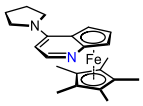
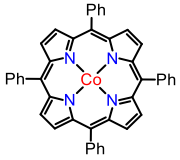
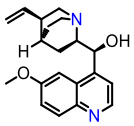
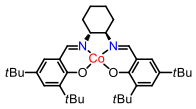
Two chiral co-catalysts have been tested, the iron based (–)-PPY* used successfully in enantioselective [2+2] cycloadditions as reported by Fu and coworkers[18] (entries 2, 4),

and quinidine which is a well-known organocatalyst used in a variety of reactions (entry 5).[19]

Table 3. Cocatalyst screening in attempts to enable asymmetric β-lactam cascade synthesis from benzaldehyde tosylhydrazone sodium salt **1** and *N*-benzylidenemethanamine **2**.



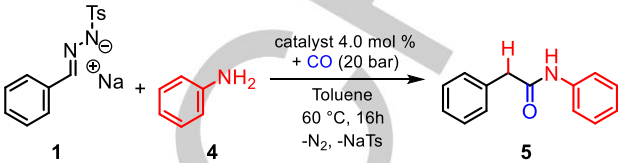
1 2 3 (racemic)

Entry [a]	Catalyst	Cocatalyst	Yield[b] (%)	*ee* [c]
1	[Co(MeTAA)]	-	77	-
2	 [Co(MeTAA)]	 (-)-PPY*	53	<1%
3	[Co(TPP)]	-	68	-
4	 [Co(TPP)]	 (-)-PPY*	62	<1%
5.	 [Co(TPP)]	 Quinidine	58	<1%
6	 [Co(Sal-*t*Bu)]	-	16	<1%

[a] Reactions were carried out under 20 bar CO in a sealed autoclave with 1.0 eq. tosylhydrazone, 1.2 eq. imine, 0.03 eq. catalyst and 0.03 eq. cocatalyst for 16h. Conc. 0.34 mmol tosylhydrazone salt/3.0 mL solvent. [b] Isolated yields. [c] enantiomeric excess determined by chiral HPLC analysis.

Although the cascade dual catalytic reactions were compatible in both cases, affording the *trans* β-lactams in decent yields (Table 3), no chirality transfer was observed when using [Co(MeTAA)] or [Co(TPP)] in combination with quinidine or (–)-PPY*. A possible reason for the lack of chirality transfer is the high reaction temperature of 60 °C used in these reactions, as chirality transfer with organocatalysts or (–)-PPY* typically requires low temperatures (0 °C or below). Unfortunately we were unable to reduce the reaction temperature to such required temperature for efficient chirality transfer, as the ketene formation is too slow at such a low temperature. However, the reactions do show that a one-pot bi-catalytic system is possible, and the reactions are quite tolerant to a variety of additives despite formation of reactive intermediates such as cobalt(III) carbene radicals and ketenes in these reactions.

Table 4. Reaction optimizations for the synthesis of *N*-benzylbenzamide **5** from benzaldehyde tosylhydrazone sodium salt **1** and *N*-benzylidenemethanamine **4**.



1 4 5

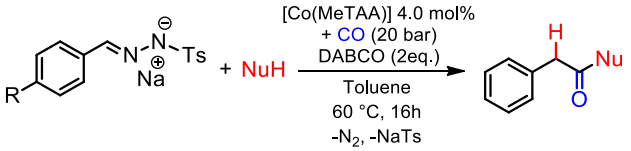
Entry[a]	Catalyst	Additive	Eq. of additive	Yield[b] (%)
1	-	-	-	<1
2	[Co(TPP)]	K_3PO_4	3	75
3	[Co(MeTAA)]	-	-	40
4	[Co(MeTAA)]	K_3PO_4	2	44
5	[Co(MeTAA)]	Pyridine	2	51
6	[Co(MeTAA)]	K_3PO_4 : pyridine	1:1	46
7	[Co(MeTAA)]	DMAP	2	44
8	**[Co(MeTAA)]**	**DABCO**	**2**	**95**
9	[Co(MeTAA)]	DABCO	1	73
10	[Co(MeTAA)]	DABCO	0.5	61
11	[Co(MeTAA)]	DABCO	0.25	74
12	[Co(MeTAA)]	DABCO	0.1	75
13	[Co(Sal-tBu)]	DABCO	2	40
14	[Co(Sal-CF_3)]	DABCO	2	37
15	[Co(Sal-NMe_2)]	DABCO	2	73

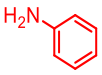
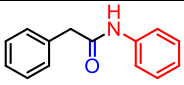
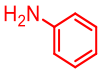
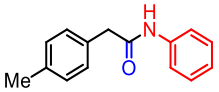
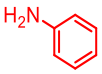
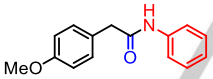
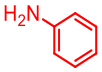
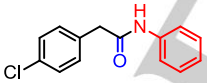
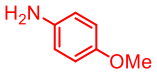
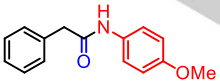
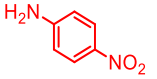
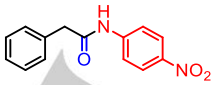
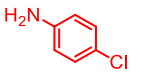
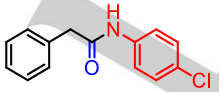
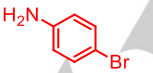
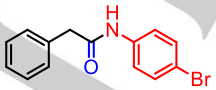
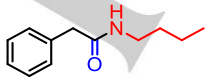
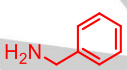
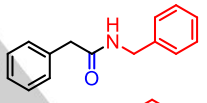
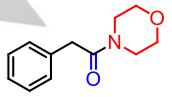
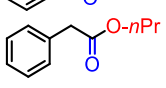
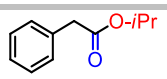
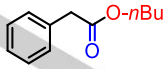
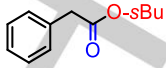
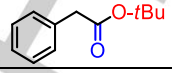
[a] Reactions were carried out under 20 bar CO in a sealed autoclave with 1.0 eq. tosylhydrazone, 2.2 eq. aniline, 0.04 eq. catalyst and additive for 16h. Conc. 0.4 mmol tosylhydrazone/3.0 mL toluene. [b] Isolated yields.

To show that not only β-lactams can be obtained as products using the [Co(MeTAA)-catalyzed ketene formation protocol, we decided to also investigate the possibility to trap the ketene intermediates with amines and alcohols, in order to form amides or esters in one-pot reactions. As a benchmark reaction, benzaldehyde tosylhydrazone sodium salt **1** and aniline **4** were used as substrates to form *N*-benzylbenzamide **5**. Table 4 shows the condition screening study, in which different bases are tested together with [Co(MeTAA)] (entries 3-12). The best yield of 95% was obtained when using 2.0 eq. of DABCO (entry 8). Investigating different molar ratios of DABCO proved less successful (entries 9-12), revealing that at least 2.0 equivalents are needed to obtain the product in almost quantitative yield. The bases 4-dimethylaminopyridine, pyridine and potassium phosphate were also tested, but in these cases the desired

product was obtained in moderate yields (44%, 51% and 44%, respectively; see Table 4, entries 4-7). The best conditions for [Co(TPP)] have been screened in a previous study,[14] and the result is presented in Table 4, entry 2 for comparison. The afforded yield of 75% was obtained using 3.0 equivalents of potassium phosphate, and is significantly lower than the 95% one obtained using [Co(MeTAA)] and DABCO (entry 8). The salen based cobalt(II) complexes (Figure 1) produced the desired product in only moderate yields of 40%, 37% and 73% for [Co(Sal-*t*Bu)], [Co(Sal-CF_3)] and [Co(Sal-NMe_2)] respectively (entries 13-15), further confirming that a more electron rich catalyst is better suited for these radical-type transformations proceeding via carbene radical intermediates.

Table 5. Substrate scope screening in [Co(MeTAA)] catalysed amides and ester synthesis from tosylhydrazone salts and corresponding nucleophiles.



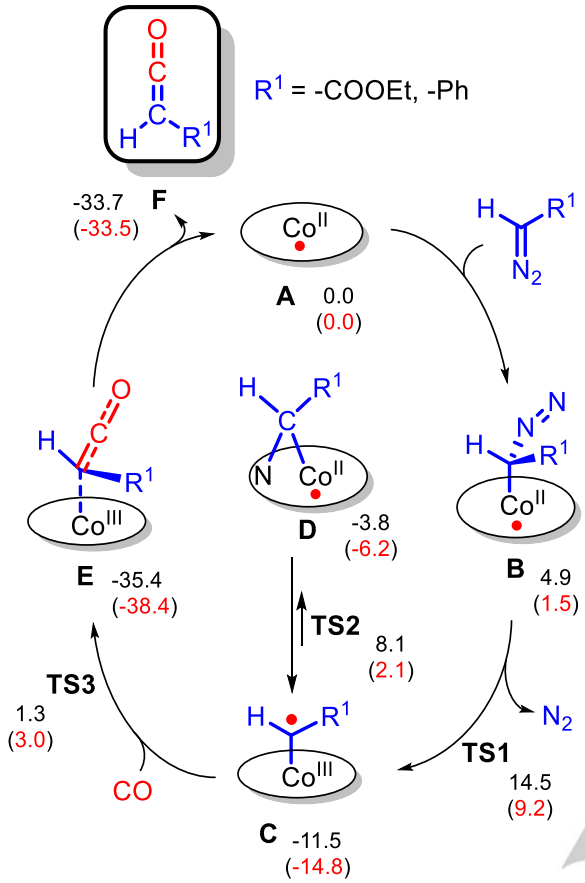
Entry [a]	-R	NuH	Product	Yield [b] (%)
1	-H			95
2	-Me			90
3	-OMe			81
4	-Cl			82
5	-H			90
6	-H			50
7	-H			61
8	-H			84
9	-H	*n*Bu-NH_2		48
10	-H			86
11	-H			79
12	-H	*n*Pr-OH		55
13	-H	*i*Pr-OH		46
14	-H	*n*Bu-OH		70
15	-H	*s*Bu-OH		43
16	-H	*t*Bu-OH		15

[a] Reactions were carried out under 20 bar CO in a sealed autoclave with 1.0 eq. tosylhydrazone, 2.2 eq. aniline, 0.04 eq. catalyst and additive for 16h. Conc. 0.4 mmol tosylhydrazone/3.0 mL toluene. [b] Isolated yields.

Using the abovementioned optimized reaction conditions, we proceeded to further screen the substrate scope (Table 5). We first investigated the reaction of para-substituted tosyhydrazone salts, carbon monoxide and aniline catalysed by [Co(MeTAA)] (Table 5, entries 1-4). The unsubstituted benzaldehyde tosylhydrazone sodium salt afforded the desired amide product in the highest yield (95%), followed by the Me-substituted hydrazone (90%, entry 2), Cl-substituted hydrazone (82%, entry 4) and MeO-substituted hydrazone (81% yield, entry 3). Next, reactions using several para-substituted anilines were investigated (entries 5-8), and as expected the results show that an electron-donating alkoxy substituent on the nucleophile is beneficial (yield 90%, entry 5). Electron withdrawing substituents such as an NO_2 (50% yield (entry 6) or chloro- (61%) and bromo-group (84%) lead to somewhat lower yields (entries 7-8). Aliphatic and benzylic amines are also suitable for this reaction (entries 9-11), with benzylamine affording the amide product in 86% isolated yield. The last entries in Table 5 show ester formation using differently substituted alkyl alcohols (entries 12-16). Due to the lower nucleophilic nature of alcohols as compared to amines, the yields of these reactions are somewhat lower, with n-butanol affording the ester product in 70% yield (entry 14), while tert-butanol reacts poorly producing only 15% of the desired ester product (entry 16). As can be expected, the more sterically congested and hence less nucleophilic alcohol produced the ester product in a lower yield as compared to the linear alcohols.

Computational Studies

The mechanism of the [Co(MeTAA)]-catalyzed carbene carbonylation reaction was also investigated computationally, using DFT (see Supporting Information for details). In line with similar systems that have previously been studied extensively, the computations were performed at the BP86 and def2-TZVP level, using Grimme's version 3 dispersion corrections (Scheme 4). The mechanism is similar to the one reported for related [Co(por)]-catalyzed reactions.[14] The pathway starts with activation of the diazo compound (which is generated *in situ* from the tosylhydrazone salt in an uncatalyzed step) by the catalyst, involving binding of the diazo compound via its carbon atom to cobalt (**B**), followed by N_2-loss (**TS1**) to form carbene radical intermediate **C** (see Scheme 4 and Figure 2). This step has a transition state barrier **TS1** of +9.5 kcal mol^{-1} for R^1 = -COOEt and +7.7 kcal mol^{-1} when R^1 = Ph. This step has a lower energy barrier when compared to [Co(por)].[14]



Scheme 4. DFT calculated pathway of the [Co(MeTAA)]-catalysed carbene carbonylation (DFT-D3, BP86, def2-TZVP). All energies (also the transition states) are in kcal mol^{-1} and relative to **A** + diazo compound; **in black** are represented the energies for R^1= -COOEt and in red the energies for R^1= -Ph.

Carbene radical **C** can form a bridging carbene **D** via **TS2** which has a barrier of +19.6 kcal mol^{-1} for R^1 = -COOEt and +16.9 kcal mol^{-1} when R^1 = Ph. Unlike what was observed for the [Co(por)] system, species **C** is however more stable than species **D** for the [Co(MeTAA)] system, thus leading to lower barriers of the follow-up carbene carbonylation step (see also Figure S1 in the supporting information). Carbonylation of carbene radical intermediate **C** proceeds *via* CO addition to the carbene moiety with a significantly lower **TS3** transition state barriers (+12.8 kcal mol^{-1} for R^1 = -COOEt and +11.8 kcal mol^{-1} for R^1 = Ph) than previously reported for [Co(por)] (+23.7 kcal mol^{-1} for R^1 = -COOMe). For the [Co(MeTAA)] system, **TS3** connects species **C** with species **E**. This is somewhat different from what was observed for the [Co(por)]-catalyzed reaction in which the ketene spontaneously dissociates from the metal following the carbonylation step. For the [Co(MeTAA)] system the ketene adduct **E** is formed as an intermediate. However, ketene dissociation (**F**) from ketene adduct **E** requires only a few kcal mol^{-1}. The computed **TS3** energy barriers of the carbene carbonylation steps and the **TS1** barriers for carbene radical formation are very similar, and the CO concentration (non-standard conditions) could well have a significant influence on the relative barriers of these steps (see Figure 2). As such, it is not possible to predict what is/are the actual rate limiting step(s) of the catalytic cycle based on these DFT calculations. The free ketene generated in this manner reacts subsequently with nucleophiles or imines present in solution, leading to the final ester, amide or β-lactam products.

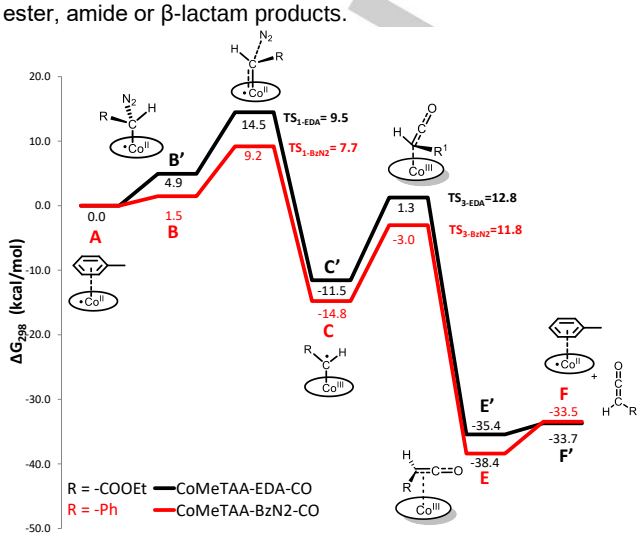


Figure 2. Energy diagram comparison of the [Co(MeTAA)] catalyzed ketene formation starting from ethyldiazoacetate and BzN_2. All energies relative to **A** (transition state barriers relative to the preceding intermediate also reported).

Conclusions

In summary, we have shown an efficient synthetic strategy of producing diastereoselective β-lactams, amides and esters using [Co(MeTAA)] as an effective metalloradical catalyst able to activate tosyhydrazones to generate carbene radicals, which are carbonylated to produce ketenes and subsequently trapped by the applied nucleophile in one-pot reactions. The cheap and highly active [Co(MeTAA)] catalyst proved to be compatible with several different reaction conditions, including dual cascade catalysis, tolerating many functional groups, coordinating additives and high reaction temperatures. The protocol presented in this paper provides a reliable method to produce ketenes in a single pot starting from tosylhydrazone salts and carbon monoxide. The reactions proceed via formation of carbene radical intermediates which react with CO to form ketenes. The intrinsic reactivity of ketenes requires *in situ* trapping of these reactive intermediates with amines, alcohols or imines to obtain useful organic building blocks. The substrate scope has been explored, showing that this method can be applied to several different substrates bearing a variety of substituents.

Experimental Section

General Procedures. All manipulations, except the carbonylation reactions, were performed under a nitrogen atmosphere using standard Schlenk techniques. All solvents used for catalysis were dried over and distilled from sodium (toluene, tetrahydrofuran, diethyl ether) or CaH_2 (dichloromethane, hexane, ethyl acetate, methanol, acetonitrile). Unless specified, all chemicals were purchased from commercial suppliers (Sigma Aldrich, Acros or Strem) and used without further purification. NMR spectra (^{1}H, and ^{13}C{1H}) were measured on a Bruker AV400, AV300, DRX 500 or

DRX 300 spectrometer or on a Varian Mercury 300 spectrometer, referenced internally to residual solvent resonance of $CHCl_3$ (δ = 7.26 ppm for ^1H, δ = 77.2 ppm for ^{13}C) or DMSO (δ = 2.50 ppm for ^1H, δ = 39.5 ppm for ^{13}C). Unless noted otherwise, the NMR spectra were measured in $CDCl_3$. Individual peaks are reported as: multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant in Hz. Mass spectra of the synthesized compounds were recorded on an Agilent-5973 GC-MS spectrometer, and the corresponding HRMS data were recorded on a JEOL AccuTOF 4G via direct injection probe using either EI or ESI. Chirality was determined using a Shimadzu HPLC setup equipped with an UV-Vis detector (SPD-10Avp).

Catalyst preparation. [Co(MeTAA)] has been synthesized according to reported procedures.[20] [Co(TPP)] and [Co(salens)] have been purchased from Sigma-Aldrich or Strem and used without further purification.

General Procedure for Synthesis of the *N*-tosylhydrazone salts.[21] An equimolar mixture of corresponding aldehyde and N-tosylhydrazide was placed in a round bottom flask and dissolved in methanol (2 mL/mmol). The reaction mixture was stirred overnight at room temperature. The white precipitate was collected by filtration, and washed with cold methanol and hexane to obtain the pure product. The formed N-tosylhydrazone was then deprotonated in methanol using 1 equivalent of sodium methoxide. After evaporation of methanol, the pure product was obtained as a white powder.

Typical Carbene Carbonylation Procedures. In a typical carbonylation experiment a stainless steel autoclave (150 mL) equipped with inserts suitable for five glass vials (4 mL) was employed. The vials were charged with appropriate amounts of solvent, substrates (N-tosylhydrazone sodium salts and nucleophiles or imines) and catalyst, together with Teflon stirring bars. Before starting the catalytic reactions, the charged autoclave was purged three times with CO and then pressurized to the desired pressure. After catalysis, the autoclave was cooled to room temperature, and purged with nitrogen so that any excess CO was removed. The reaction mixture is then analysed and purified using typical organic work-up, preparative TLC or flash column chromatography.

Co^{II}-catalysed β-lactam synthesis using different N-tosylhydrazone sodium salts and imines. Under a nitrogen atmosphere, [Co(MeTAA)] (3 mol%), and the desired *N*-tosylhydrazone sodium salt (1.0 eq, 0.34 mmol) were added to a flame-dried 4 ml glass vial. Then the vial was sealed with a stopper and evacuated. The desired imine (1.2 eq., 0.408 mmol) in 3.0 ml of toluene were added via syringe. A small needle was inserted at the top of the vial. The vials were then inserted into an autoclave (150 mL) equipped with inserts suitable for five such glass vials and pressurized to 20 bar of CO. The pressurized autoclave was then stirred at 60° C for 16h. The autoclave was subsequently cooled to room temperature, and purged with nitrogen so that any excess CO is removed. The resulting mixture was concentrated and the residue was purified by preparative TLC or flash silica gel chromatography.

Co^{II}-Catalysed amide/ester synthesis using N-tosylhydrazone sodium salt and different nucleophiles. Under a nitrogen atmosphere, [Co(MeTAA)] (4 mol%), DABCO (2.0 eq., 0.8 mmol), and the desired *N*-tosylhydrazone sodium salt (1.0 eq., 0.4 mmol) were added to a 4 ml flame-dried glass vial. Then the vial was sealed with a stopper and evacuated. Anhydrous toluene (3.0 mL) and the desired nucleophile (alcohol or amine) (2.2 eq., 0.88 mmol) were added *via* syringe. A small needle was inserted at the top of the vial. The vials were then inserted into an autoclave (150 mL) equipped with inserts suitable for five such glass vials and pressurized with 20 bar of CO. The pressurized autoclave was then stirred at 60 °C for 16h. The autoclave was subsequently cooled to room temperature, and purged with nitrogen so that any excess CO is removed. The resulting mixture was concentrated and the residue was purified by preparative TLC or flash silica gel chromatography.

Acknowledgements

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Keywords: Ketene • Cobalt • Catalysis • Carbonylation • Metalloradical • Carbene Radical • *N*-Tosylhydrazone

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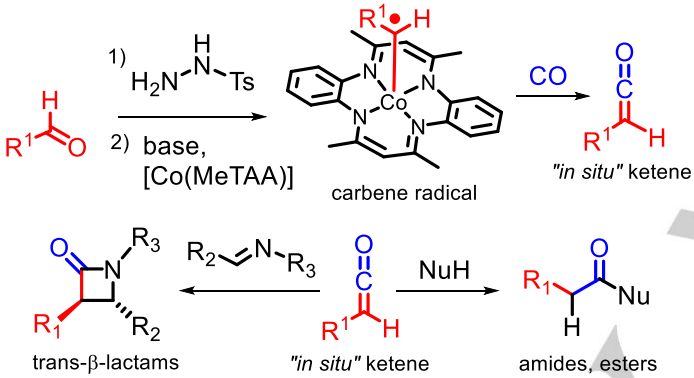

Carbonylation of carbene radical intermediates generated using the highly active cobalt(II) catalyst [Co(MeTAA)] provides a convenient one-pot synthetic protocol towards substituted ketenes. Subsequent trapping with nucleophiles leads to beta-lactams, amides and esters.

Ketenes by metalloradical Catalysis

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[Co(MeTAA)] Metalloradical Catalytic Route to Ketenes via Carbonylation of Carbene Radicals