Formate as a CO surrogate for cascade processes: Rh-catalyzed cooperative decarbonylation and asymmetric Pauson–Khand-type cyclization reactions†

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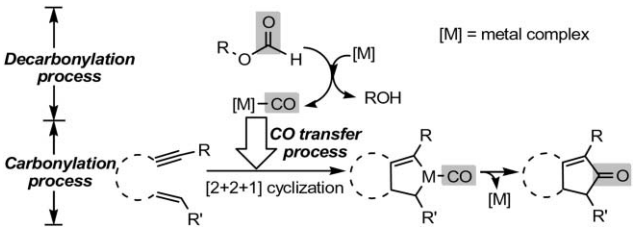
A rhodium-(*S*)-xyl-BINAP complex-catalyzed tandem formate decarbonylation and [2 + 2 + 1] carbonylative cyclization is described; this cooperative process utilizes formate as a condensed CO source, and the newly developed cascade protocol can be extended to its enantioselective version, providing up to 94% ee of the cyclopentenone adducts.

The transition metal-mediated conversion of alkynes, alkenes and carbon monoxide in a formal [2 + 2 + 1] cycloaddition manner, commonly known as the Pauson–Khand reaction (PKR, when Co complexes are employed),[1] is an elegant protocol for the construction of cyclopentenones.[2] These versatile scaffolds are of particular interest in targeting a variety of synthetically useful and pharmaceutically attractive compounds.[3] Recently, notable advancements have been achieved from stoichiometric to catalytic Pauson–Khand-type reactions.[4] The recent enantioselective versions of this reaction catalyzed by Co,[5] Ti,[6] Rh[7] and Ir complexes[8] are of particularly high significance. Although major improvements have been achieved, the use of highly toxic gaseous carbon monoxide signifies a drawback to these versatile procedures. Hence, different operationally simple strategies focusing on the replacement of carbon monoxide within the reaction sequence have been attempted.[9] Recent successful examples have been based on fundamental results from the early 1960s,[10] dealing with the transition metal-catalyzed decarbonylation of organic oxo compounds.[11]

There has been considerable interest in recent years in the chemistry of formate esters.[12] The conversion of methyl formate to methanol and carbon monoxide is particularly desirable for the generation of an easily handled "CO" moiety. However, drastic reaction conditions are usually employed (*e.g.* >180 °C and/or >1 atm pressure).[13] It seemed conceivable to us that the decarbonylation of formates could be achieved under mild reaction conditions with a suitable choice of metal complex.[14] Herein, we report that Rh-diphosphine complexes are effective for dual catalysis (Scheme 1), the cooperative decarbonylation–carbonylation sequence and their enantioselective cycloaddition variants.

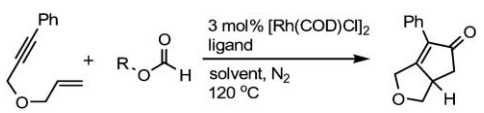
Our prototypical studies focused on the feasibility of the Rh-catalyzed CO transfer process in an alcoholic medium, since the complimentary decarbonylation product of formate is ROH.[15] 2-Pyridylmethyl formate was initially chosen to be the CO surrogate as we expected that the chelating property of the pyridyl ring would assist the intramolecular RO(O)C–H oxidative addition, and thus facilitate the generation of [M]–CO species for the CO transfer hypothesis.



Scheme 1 Cooperative dual catalysis.

Table 1 represents the reaction parameters that we preliminarily examined. Bidentate diphosphine ligands were suitable for the cascade process, and the rigid binaphthyl scaffold gave a better cycloadduct yield (Table 1, entries 1–4). Dioxane was the best solvent of choice among the solvents screened (Table 1, entries 4–7). Commercially available alkyl formates were also investigated (Table 1, entries 8–11). Benzyl formate provided a higher yield than other alkyl analogs. In order to further probe the efficacy of

Table 1 Investigations on catalytic cascade decarbonylation–PKR reactions with formate as the CO surrogate[a]



Entry	R	Ligand	Solvent	Yield (%)[b]
1	2-Pyridylmethyl	dppe	*tert*-Amyl alcohol	23
2	2-Pyridylmethyl	dppp	*tert*-Amyl alcohol	15
3	2-Pyridylmethyl	dppf	*tert*-Amyl alcohol	33
4	2-Pyridylmethyl	(±)-BINAP	*tert*-Amyl alcohol	38
5	2-Pyridylmethyl	(±)-BINAP	Dioxane	47
6	2-Pyridylmethyl	(±)-BINAP	DMF	25
7	2-Pyridylmethyl	(±)-BINAP	Toluene	37
8	*n*-Butyl	(±)-BINAP	Dioxane	20
9	*tert*-Butyl	(±)-BINAP	Dioxane	12
10	*n*-Octyl	(±)-BINAP	Dioxane	23
11	Benzyl	(±)-BINAP	Dioxane	42
12	*para*-Chloro-benzyl	(±)-BINAP	Dioxane	60

[a] Enyne **1a** (0.3 mmol), $[Rh(COD)Cl]_2$ (4.5 μmol), ligand (9.0 μmol), formate (1.5 mmol) and solvent (0.5 mL) under N_2 for 36 h. [b] Isolated yields.

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the formates, we found that the electron-withdrawing *para*-chlorobenzyl formate donated a CO moiety more effectively (Table 1, entry 12). This is consistent with the general tendency of alkyl groups to migrate from acyl complexes, leading to the formation of metal carbonyls.[16] Interestingly, for all formates examined, the catalyst abstracted a CO moiety from formates and transferred them to the enyne without hydroacylating the alkene and/or the alkyne portions of enyne, as judged by GC-MS analysis.

Although 2-pyridylmethyl and *para*-chlorobenzyl formates afforded better yields of the cyclopentenone product, we chose the inexpensive and commercially available benzyl formate as the CO source for our further investigations.[17] In fact, the electronic properties of the substituted benzyl formates did not affect the ee of the cyclopentenone products. Cationic $Rh(COD)_2BF_4$ and $[Rh(COD)Cl]_2/AgPF_6$ were inferior to the neutral $[Rh(COD)Cl]_2$ in the cooperative process.[18] When Ru and Ir complexes were applied to the cascade catalysis, a CO transfer process from formate was observed. However, the effectiveness was inferior to that found for the Rh complexes.[18]

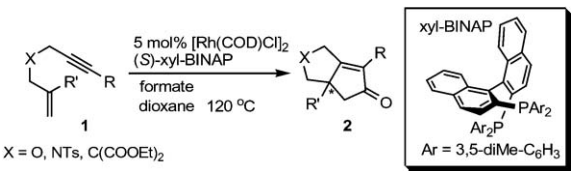
Encouraged by the capability of the formate CO transfer process and our previous success in asymmetric catalysis using chiral atropisomeric ligands,[19] we were attracted to investigate the enantioselective version of this dual catalysis, and some commercially available diphosphine ligands were probed in the process. BisbenzodioxanPhos/SYNPHOS[20] and P-Phos[21] afforded the desired cycloadduct **2a** in low enantioselectivities, 41 and 23% ee, respectively. However, the state-of-the-art BINAP class ligand showed a significantly better product enantioselectivity. Among the enantiomerically pure BINAPs we have examined, the sterically demanding (*S*)-xyl-BINAP provided the best stereocommunication in the [2 + 2 + 1] cycloaddition (75% ee).[22]

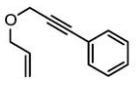
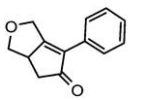
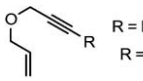
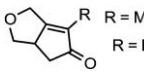
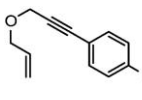
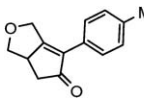
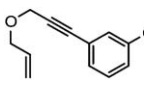
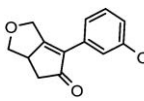
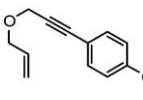
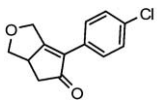
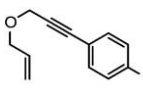
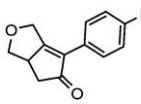
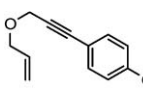
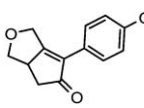
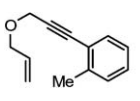
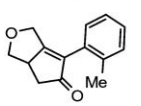
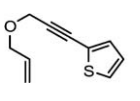
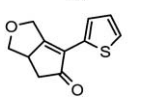
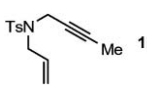
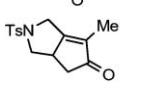
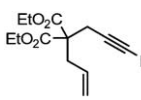
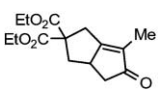
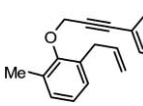
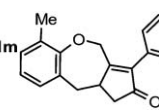
To further test the effectiveness of the Rh-xyl-BINAP catalytic system, we studied a variety of oxygen-tethered 1,6-enynes for enantioselective PKR (Table 2). Alkyl-substituted alkynes gave excellent enantioselectivities (94% ee) of the corresponding products (Table 2, entries 2–3). Various aromatic enynes, possessing different electronic properties, were prepared and subjected to carbonylative cyclization (Table 2, entries 5–8). The substituents on the enyne, having different electronic natures, apparently did not affect the ee of the carbonylative cycloadducts.[23] A sterically hindered, *ortho*-substituted aromatic enyne afforded a low yield of the product; presumably the *ortho*-methyl group hindered the coordination of yne moiety to the Rh center (Table 2, entry 9). Of particular note is that we have demonstrated for the first time the successful transformation of a heterocyclic-substituted enyne to the corresponding cyclopentenone (Table 2, entry 10).

These reaction conditions were also applied to other nitrogen- and carbon-tethered enynes (Table 2, entries 11–12), and moderate to good enantioselectivities of the products were observed. However, when a 1,8-enyne was applied in this cascade process, only a trace amount of the desired product was obtained, as judged by GC-MS analysis.

Fig. 1 shows the suggested mechanism for the Rh-catalyzed cascade decarbonylation—Pauson–Khand-type reaction. The coordination of formate, followed by a subsequent C–H oxidative addition, generates a hydrido-Rh-acyl complex. Independent NMR experiments showed the presence of a Rh-hydride species during the course of the reaction (^{1}H NMR, −6.3 ppm). After the reductive elimination of ROH, the Rh-carbonyl complex **A** is generated, which presumably is the key intermediate of PKRs. The carbonylation cycle starts from the coordination of enyne **1a** to complex **A**, giving the Rh-enyne complex **B**. The chiral diphosphine ligand exerts stereoinduction on the coordinated enyne and finally gives the stereo-determining rhodacycle **C**. After insertion of

Table 2 Rh-catalyzed cascade decarbonylation–asymmetric Pauson–Khand-type reactions[a]



Entry	Substrate	Product	Yield (%)[b]	ee (%)[c]
1	 **1a**	 **2a**	43	75
2	 R = Me, **1b**	 R = Me, **2b**	16	92
3	R = Et, **1c**	R = Et, **2c**	20	94
4	 **1d**	 **2d**	44	81
5	 **1e**	 **2e**	37	84
6	 **1f**	 **2f**	40	84
7	 **1g**	 **2g**	61	76
8	 **1h**	 **2h**	38	77
9	 **1i**	 **2i**	11	65
10	 **1j**	 **2j**	59	80
11	 **1k**	 **2k**	65	74
12	 **1l**	 **2l**	40	87
13	 **1m**	 **2m**	Trace	not determined

[a] Enyne **1** (0.3 mmol), $[Rh(COD)Cl]_2$ (7.5 μmol), (*S*)-xyl-BINAP (0.015 mmol), benzyl formate (1.5 mmol) and anhydrous dioxane (0.5 mL) under N_2 for 3 d. [b] Isolated yields. [c] Determined by chiral HPLC analysis using Daicel® AS-H, AD-H and OD-H columns.

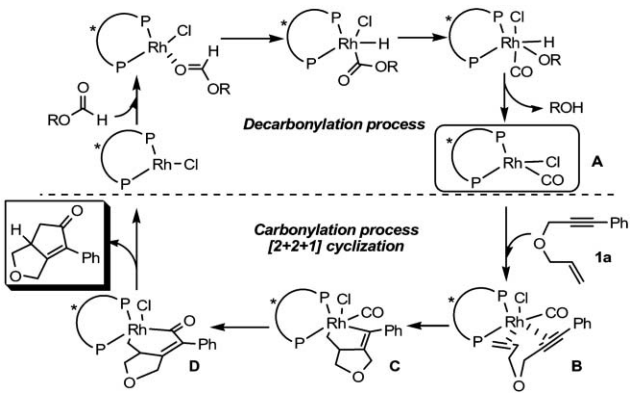
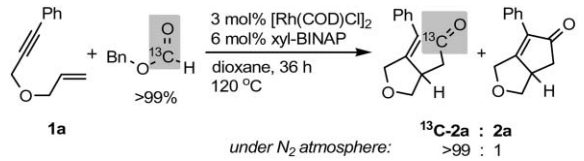


Fig. 1 Proposed catalytic cycles for the cascade processes.



Scheme 2 Labelling experiments for the direct CO transfer process.

the CO moiety and reductive elimination of complex **D**, the desired cyclopentenone is obtained along with the regenerated Rh(I) complex.

In order to originate the CO transfer process, we prepared the ^{13}C-labelled benzyl formate (from benzyl alcohol and acetic anhydride with ^{13}C-labelled formic acid) for the decarbonylation–carbonylation sequence (Scheme 2). It was obvious that, under the nitrogen atmosphere, over 99% of the corresponding ^{13}C-cyclopentenone was obtained, as judged by NMR spectroscopy. These informative results show that the CO moiety for the carbonylative coupling is mainly provided by the Rh-carbonyl complex **A** (Fig. 1). Thus, it is feasible to apply formate as a convenient CO surrogate in a direct CO transfer process.

In summary, we have demonstrated the capability of replacing "external" gaseous carbon monoxide by formate transfer carbonylation using suitable Rh-diphosphine complexes. This versatile reaction was found to be a suitable cooperative partner in cascade decarbonylation—Pauson–Khand-type cyclization. Notably, apart from the initial achiral synthesis, the asymmetric version of this dual catalysis was successfully achieved. Various 1,6-enynes were transformed into corresponding cyclopentenones in good enantioselectivities (up to 94% ee) in the presence of Rh-(*S*)-xyl-BINAP catalyst. ^{13}C-labelling experiments indicated that the CO moiety, generated by the decarbonylation of formate, was directly incorporated into the carbonylative cyclization. To our best knowledge, this represents the first example of asymmetric CO transfer carbonylation using a formate ester as a CO surrogate.

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