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CpRu-Catalyzed O−H Insertion and Condensation Reactions of α-Diazocarbonyl Compounds

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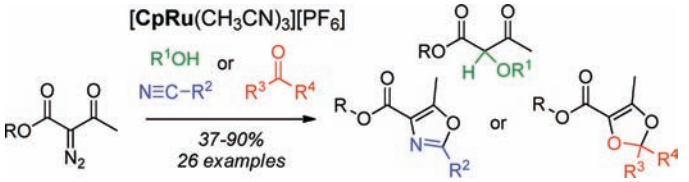
ABSTRACT



[CpRu(CH$_3$CN)$_3$][PF$_6$] and diimine ligands catalyze together the decomposition of α-diazocarbonyl compounds leading to O−H insertion and condensation reactions. In comparison with Rh(II) and Cu(I) complexes, the CpRu catalysts produce rapid and often more selective reactions. Promising enantioselectivities are obtained in dioxole syntheses.

Acceptor/acceptor substituted diazo compounds, in particular those derived from β-ketoesters, are among the most stable diazo reagents.[1,2] They are important building blocks in synthetic organic chemistry as they undergo useful transformations such as cyclopropanation, insertion, dipolar addition, ylide generation, and subsequent rearrangement reactions.[3] Catalytic amounts of metal salts or complexes, in particular those derived from copper and rhodium, are commonly used with these reagents to promote reactions and control reactivity and selectivity.[4−6]

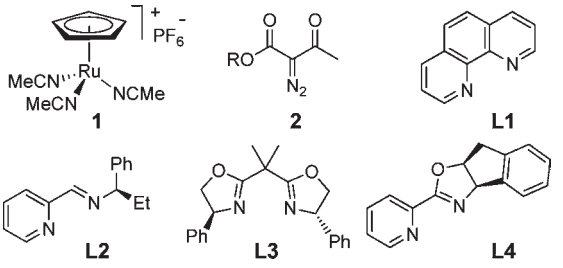


Figure 1

Herein, in a new development, we report that combinations of [CpRu(CH$_3$CN)$_3$][PF$_6$] **1** (Cp = C$_5$H$_5$)[7] and diimine ligands **L1**−**L4** (Figure 1) catalyze also the decomposition of α-diazocarbonyl compounds, and acetoacetates **2** in particular. Products of O−H insertion and condensation reactions with nitriles, ketones, and aldehydes are afforded effectively. Reaction conditions are

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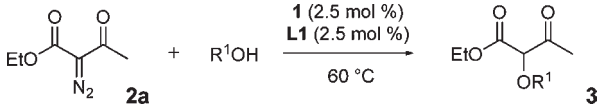
mild and selective, offering the possibility to perform the transformation enantioselectively when feasible.

As mentioned, Cu(I), Cu(II), and Rh(II) salts or complexes are particularly efficient for the decomposition of diazo derivatives. However, other metal sources are active, and ruthenium complexes have become an interesting alternative to these moieties,[8] including CpRu derivatives.[9]

More specifically, $[CpRu(PPh_3)_3Cl_2]$ was shown by Del Zotto and collaborators to promote N−H and S−H insertions into ethyldiazoacetate or the transformation of tertiary amines into ammonium ylides that underwent [1,2]-Stevens shifts or sigmatropic rearrangements.[10] Recently, our group has shown that combinations of $[CpRu(CH_3CN)_3][PF_6]$ **1** and pyridine-imine/pyridine-oxazoline ligands (**L1**−**L4**) are effective catalysts for the enantioselective decarboxylative rearrangements of allylic β-ketoesters and carbonates.[11] In a different context, α-diazo-β-ketoesters **2** (Figure 1) were reacted with cyclic ethers in the presence of dirhodium complexes to yield original 16- to 18-membered macrocycles.[12] Having access to complex **1**, ligands **L** ,and reagents **2**, it was therefore tempting to study their interactions, and this in the context of electrophilic metal carbene chemistry.

The occurrence of reactivity was established using a classical reaction of diazo reagents, i.e., the insertion in the O−H bond of alcohols.[13] The results are summarized in Table 1. Ethyl 2-diazo-3-acetoacetate **2a** was dissolved in various alcohols (R^1OH) along with **1** (2.5 mol %) and 1,10-phenanthroline **L1** (2.5 mol %).[14] After 45 min at 60 °C, full conversion was achieved in all cases, and products of insertion **3a**−**3d** (R^1 = Et, allyl, *t*-Bu, benzyl) were obtained in good to excellent isolated yields (entries 1−4, 75−90%). No

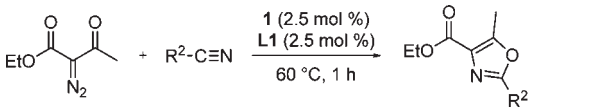
Table 1. Reaction Scope with Alcohols



entry[a]	**1**	**L1**	R^1	**3**	*t* (h)	conv (yield %)[b,c]
1	2.5	2.5	Et	**3a**	0.75	>97 (90)
2	2.5	2.5	allyl	**3b**	0.75	>97 (78)
3	2.5	2.5	*t*-Bu	**3c**	0.75	>97 (85)
4	2.5	2.5	Bn	**3d**[d]	0.75	>97 (75)
5	–	–	Et	**3a**	24	<3
6	2.5	–	Et	**3a**	1	>97
7	2.5	2.5	Et	**3a**	1	>97

[a] Catalyst combination **1** (*x* mol %) and ligand **L1** (*x* mol %), 60 °C, [diazo] 0.5 M in R^1OH. [b] Conversion determined by ^1H NMR (400 MHz). [c] Isolated yield after column chromatography. [d] Purified by bulb to bulb distillation.

Scheme 1. Reaction Scope with Nitriles



4a, R^2 = Me (54%) **4c**, R^2 = *i*-Pr (60%)
4b, R^2 = Et (75%) **4d**, R^2 = Ph (60%)

conversion of **2a** was detected after 24 h at 60 °C in the absence of **1** (entry 5). Reactions were also performed in EtOH with and without **L1**. Whereas only 15 min was necessary to reach full conversion with the ligand, 1 h was required to reach the same result without it (entries 6 and 7).[15]

With this result in hand, other classical transformations were investigated and condensation reactions with nitrile[16,17] or carbonyl[18,19] moieties in particular.

For instance, diazoacetoacetate **2a** was dissolved in nitriles R^2CN in the presence of **1**/**L1** (2.5 mol %). After 1 h at 60 °C, full conversion of the starting material was achieved and oxazoles **4a**−**4d** (R^2 = Me, Et, *i*-Pr, Ph) were

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(14) The alcohols and other solvents need to be anhydrous.

(15) This reaction was tested only in racemic series with **L1** as ligand because of the existence of a fast tautomerization between keto and enol forms and hence a rapid racemization.

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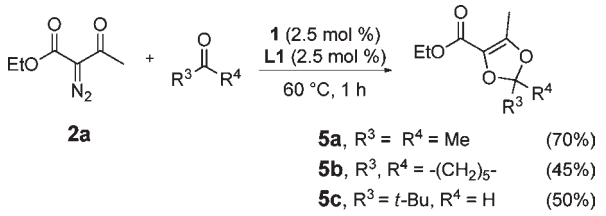
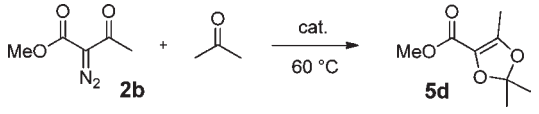
Scheme 2. Initial Study of the Reaction with Aldehydes and Ketones



5a, $R^3 = R^4 = Me$ (70%)
5b, $R^3, R^4 = -(CH_2)_5-$ (45%)
5c, $R^3 = t\text{-Bu}$, $R^4 = H$ (50%)

Table 2. Optimization of Reaction Conditions



entry	catalyst	cat. loading (mol %)	acetone (equiv)	t (h)	yield (%)[a]
1	**1**, **L1**	2.5	27	0.5	73
2	**1**, **L1**	2.5	13.5	0.5	69
3	**1**, **L1**	1	13.5	0.5	73
4	**1**, **L1**	1[b]	1	7	70
5	$Rh_2(Oct)_4$	1[b]	1	7	40
6	$[CuOTf]_2 \cdot C_7H_8$	1[b]	1	70	58

[a] Isolated yield after column chromatography. [b] CH_2Cl_2 was used as solvent; [diazo] 1 M.

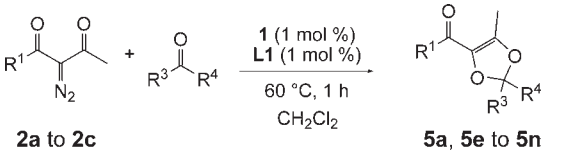
the only detectable products. These compounds were purified on silica gel and thereafter obtained in lower yields (50−75%, Scheme 1).[20]

Related reactions were carried out in the presence of carbonyl compounds as reagents. Initially, **2a** was reacted in the presence of an excess of aldehyde and ketones (ca. 30 equiv, Scheme 2). Clean reactions occurred in less than 1 h at 60 °C, and the corresponding dioxoles **5a**−**5c** were obtained as single products as well. Also in this case, somewhat low yields of isolated products were obtained, this being possibly related to an instability of **5a** to **5c** during the purification.

After these initial reactions, an optimization study was conducted to decrease the amount of reactants and catalysts used. The results are summarized in Table 2. Methyl 2-diazo-3-acetoacetate **2b** and acetone were selected for the study (Table 2). Using previous conditions, dioxole **5d** was isolated as a single product (73%, entry 1), a slightly lower yield being obtained under more concentrated conditions (entry 2). Catalyst loading was decreased to 1 mol % without any impact (entry 3). Using dichloromethane as solvent, a single equivalent of acetone can be used and it afforded **5d** with essentially the same yield (70%, entry 4). Finally, a comparison with other "classical" catalysts was

(20) The lower yields seem related to purification issues as absolutely clean reaction mixtures containing only the oxazoles are obtained at full conversion in each case.

Table 3. Reaction Scope of Dioxole Formation[a]



entry	R^1	diazo	R^2	R^3	dioxole	yield (%)[b]
1	OEt	**2a**	Me	Me	**5a**	72
2	OMe	**2b**	Me	Me	**5d**	70
3	OMe	**2b**	Et	H	**5e**	77
4	OMe	**2b**	Pr	H	**5f**	71
5	OMe	**2b**	Bu	H	**5g**	75
6	OMe	**2b**	t-Bu	H	**5h**	73
7	Ot-Bu	**2c**	Me	Me	**5i**	73
8	Ot-Bu	**2c**	Et	H	**5j**	68
9	Ot-Bu	**2c**	Pr	H	**5k**	70
10	Ot-Bu	**2c**	Bu	H	**5l**	70
11	Ot-Bu	**2c**	t-Bu	H	**5m**	71
12	Me	**6**	Me	Me	**5n**	37

[a] Catalyst combination **1** (1 mol %) and **L1** (1 mol %), carbonyl compounds (1 equiv), 60 °C, [diazo] 1 M in CH_2Cl_2. [b] Isolated yield after column chromatography.

performed. Reactions were not as clean with either $Rh_2(Oct)_4$ or $[CuOTf]_2 \cdot C_7H_8$,[18] the dioxole being isolated with lower yields as well (40% and 58%, respectively, entries 5 and 6). Moreover in the case of the Cu(I) catalyst, the reaction was slower as 70 h was necessary to reach full conversion of diazo ester **2b**.

With conditions highlighted in entry 4 (1 mol % **1**/**L1**, 1.0 equiv of aldehyde or ketone, CH_2Cl_2), the scope of the reaction was studied. As expected, reaction of diazo compound **2a** with acetone proceeded well (72%, entry 1, Table 3). Then, diazoacetoacetate **2b** was reacted with a series of aliphatic aldehydes to afford the expected products **5e**−**5h** in good yields (71−77%, entries 3−6). Bulkier *tert*-butyl derivative **2c** was used, and significantly, dioxoles **5i** to **5m** were obtained with very similar output (68−73%, entries 7−11). Diazodiketone **6** was also reacted in presence of acetone and afforded **5n** in lower yield (37%), mainly because of volatility and lower stability of the adduct (entry 12).

The results are indeed interesting as, under the same conditions but using $Rh_2(Oct)_4$ as catalyst, **2c** afforded predominantly lactone **7** in the crude reaction mixtures instead (Scheme 3). Using various amounts of acetone (1, 2, 5, and 10 equiv), different ratios between **7** and **5i** were obtained (6.0:1, 5.1:1, 2.1:1, and 1.5:1 respectively), which indicates a competition between an intramolecular C−H insertion leading to **7** and an intermolecular carbonyl ylide formation resulting in compounds **5**.[21] Herein, with **1**/**L1** catalyst combination, adduct **7** is totally absent from crude reaction mixtures.

(21) For related lactone formations, see: Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958. Wee, A. G. H.; Yu, Q. *J. Org. Chem.* **1997**, *62*, 3324.

Scheme 3. Competitive Formation of Lactone **7**

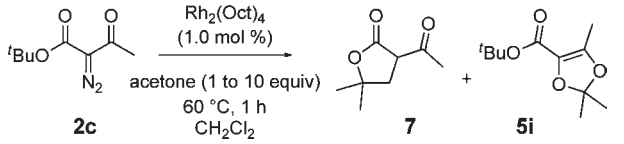


Table 4. Enantioselective Condensation: Ligand Screening[a]

entry	dioxole	ligand	t (h)	conv (%)[b]	ee (%)[c]
1	**5c**	**L1**	22	>97	–
2	**5c**	**L2**	48	<3	–
3	**5c**	**L3**	16	>97	0
4	**5c**	**L4**	48	84	(−)-35
5	**5c**	**L4**	72	>97[d]	(−)-27

[a] Catalyst combination **1** (2.5 mol %) and ligand **L** (2.5 mol %), pivalaldehyde (1 equiv), 25 °C, [diazo **2a**] 0.5 M in CH_2Cl_2. [b] Conversion determined by ^{1}H NMR (400 MHz). [c] ee measured by CSP-GC. [d] Isolated yield 75%.

Finally, we took notice of the presence of a stereogenic center in many of the prepared dioxoles **5** and that derived from aldehydes in particular. Care was thus taken to attempt the preparation of these chiral derivatives in an enantioselective manner. For this, we used chiral ligands **L2**−**L4** that had been shown to be efficient in CpRu-catalyzed decarboxylative transformations[11] and screened reaction conditions with diazo compound **2a** and pivalaldehyde. To possibly enhance the enantioselectivity, reactions were performed at 25 °C instead of 60 °C. At this temperature, 2.5 mol % of both complex **1** and ligands were necessary. The results are summarized in Table 4.

With **L1**, full conversion was achieved after 22 h (entry 1). Whereas pyridine imine **L2** inhibited totally the process (less than 3% conversion after 48 h, entry 2), box-ligand **L3** effected the reaction noticeably. After 16 h, diazo ester **2a** was totally consumed, but product **5c** was recovered as a racemate (entry 3). Finally, with pymox ligand **L4**, an enantioselectivity was detected, the dioxole being isolated with 35% ee (84% conversion in 48 h, entry 4). Extension of the reaction time to reach full conversion (72 h) led to a 75% isolated yield of **5c** with yet a lower enantiomeric excess (27% ee, entry 5).[22]

(22) The loss of enantiomeric purity might be due to a postreaction racemization involving a cleavage of the O(1)−C(2) bond of the dioxole to form an achiral enolate/oxycarbenium intermediate; the cationic part is stabilized by donating groups on the aryl moiety of the benzaldehyde and hence the result of entry 3, Table 5.

Table 5. Enantioselective Condensation: Substrate Scope[a]

entry	**5**	R^3	R^4	t (h)	yield (%)[b] (conv %)[c]	ee (%)[d]
1	**5o**	Ph	H	24	76 (>97)	(−)-24
2	**5p**	4-CF_3Ph	H	24	40 (45)	(−)-36
3	**5q**	4-MeOPh	H	24	80 (>97)	0
4	**5r**	Ph	Me	24	(20)	50

[a] Catalyst combination **1** (2.5 mol %) and ligand **L4** (2.5 mol %), aldehyde (1 equiv), 25 °C, [diazo **2a**] 0.5 M in CH_2Cl_2. [b] Isolated yield after column chromatography. [c] conversion determined by ^{1}H NMR (400 MHz). [d] ee determined by CSP-GC or CSP-HPLC.

A series of aldehydes and ketone was then tested with **L4** (and diazo compound **2a**) to achieve possibly better selectivity (Table 5). With simple benzaldehyde, good reactivity was observed (76% isolated yield after 22 h, entry 1), but product **5o** was obtained with only a moderate ee value (24%, entry 1). Next, rather strong effects were seen upon introduction of electron-withdrawing and -donating groups at the para position of the benzaldehyde (CF_3 and MeO, respectively). In the first instance, a higher enantioselectivity was noticed (ee 36%), contrasting interestingly with a lower conversion and isolated yield.[23] With *p*-anisaldehyde, full conversion was this time achieved, but desired product **5q** was obtained as a racemate (entry 3).[22] Finally, acetophenone was tested. Although a low reactivity was observed, a noticeable enhancement of the enantioselectivity was seen (ee 50%, 20% conversion in 24 h, entry 4).

In summary, we have shown that combinations of $[CpRu(CH_3CN)_3][PF_6]$ **1** and diimine ligands, in particular, 1,10-phenanthroline **L1**, can efficiently catalyze O−H insertion and condensation reactions of α-diazocarbonyl compounds. In the formation of dioxole products, we have noticed that reactions are either more selective or faster than with classical dirhodium and copper catalysts. Further studies are being performed to improve the enantioselectivity of the reaction.

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Supporting Information Available. Experimental procedures and spectroscopic data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(23) The lower yield and conversion are probably the result of the poorer nucleophilicity of the CF_3-substituted benzaldehyde.