C–O Coupling

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Enol Acetal Synthesis through Carbenoid C–H Insertion into Tetrahydrofuran Catalyzed by CpRu Complexes**

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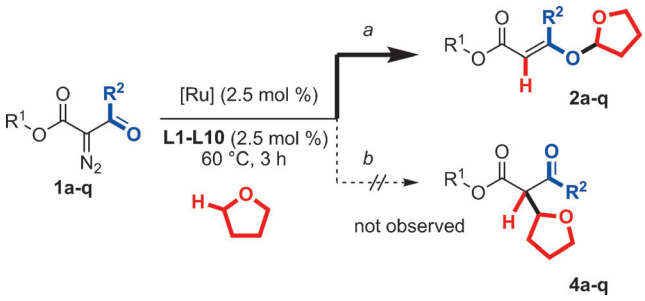
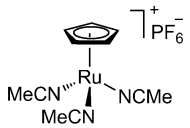
Dedicated to Professor E. Peter Kündig on the occasion of his 65th birthday

Substituted tetrahydrofurans, ubiquitous motifs in biological and natural product chemistry,[1] are accessible by coupling reactions of diazoacetates or aryldiazoacetates with simple tetrahydrofurans.[2,3] These intermolecular carbenoid C–H insertions[4] are efficiently catalyzed by copper, iridium, iron, rhodium, and silver salts or complexes.[2,5] Successful asymmetric versions have also been achieved.[4] In all these instances, a C–C bond is created by insertion of the carbenoid into a C–H bond α to the oxygen ether atom (Scheme 1, route b). Herein, in a new development that uses α-diazo-β-ketoesters **1** as reagents and CpRu (Cp = cyclopentadienyl) moieties as catalysts, we report the kinetically favored formation of C–O instead of C–C bond adducts. The mild reaction conditions yield novel enol acetal motifs **2** through unprecedented 1,3 C–H insertion reactions (Scheme 1, route a).



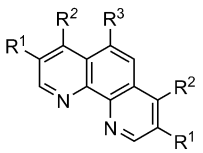
Scheme 1. Favored enol acetal formation through 1,3 C–H insertion of diazocarbonyl compounds into THF. For ligands **L1**–**L10**, see Figure 1.

α-Diazo-β-ketoesters **1**, readily made acceptor/acceptor reagents,[6] are usually characterized by a better chemical stability and a moderate reactivity in comparison to other diazo derivatives.[7] These compounds yet react in the presence of metal catalysts to form electrophilic carbenoid/carbene intermediates. These reactive species undergo many useful transformations, such as cyclopropanation, insertion, dipolar addition, ylide generation, and subsequent rearrangement/macrocyclization reactions.[8] Recently, using combinations of $[CpRu(CH_3CN)_3][PF_6]$ ([**3**][PF_6])[9] and diimine ligands,[10] reagents **1** provided selective O–H insertion and condensation reactions with alcohols, nitriles, ketones, and aldehydes.[11] This result led us to examine the reactivity of other Lewis basic moieties, and THF derivatives in particular, with this catalytic combination.[12]

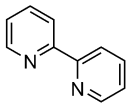


[**3**][PF_6]

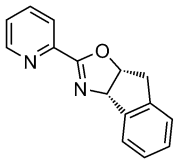
Methyl diazoacetoacetate **1a** ($R^1 = R^2 = Me$, Scheme 1) was thus added to THF solutions of complex [**3**][PF_6] and ligands **L1** to **L10** (Figure 1).[13] Using **L1**, a moderate heating to 60 °C was necessary to induce gas evolution. At that



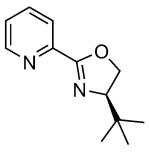
L1: R^1 = H; R^2 = H; R^3 = H; **Conv**: 95 %
L2: R^1 = H; R^2 = Me; R^3 = H; **Conv**: 70 %
L3: R^1 = H; R^2 = OMe; R^3 = H; **Conv**: 48 %
L4: R^1 = H; R^2 = H; R^3 = NO_2; **Conv**: 57 %
L5: R^1 = Me; R^2 = Me; R^3 = H; **Conv**: 50 %
L6: R^1 = H; R^2 = Ph; R^3 = H; **Conv**: 66 %



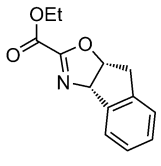
L7; **Conv**: 27 %



L8; **Conv**: 75 %



L9; **Conv**: 22 %



L10; **Conv**: 30 %

Figure 1. Ligands **L1** to **L10**, and conversions of **1a** (0.5 M in THF), using **L** and [**3**][PF_6] (2.5 mol% each), after 2 h (corresponds to 95% conversion for **L1**) at 60 °C (^{1}H NMR, 1,3,5-trimethoxybenzene as internal reference).

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temperature, conversion was complete after 3 h for a relatively high concentration of **1a** (0.5 M).[14] NMR spectroscopic analysis of the reaction mixture indicated the formation of a single product **2a**, composed of fragments of **1a** and THF. Its structure was however incompatible with a C–C bond forming reaction, and it was different from that of already known **4a** (Scheme 1).[15] Based on detailed ^{1}H, ^{13}C, and IR analyses, only an original enol acetal structure involving a C–O linkage was consistent with the data; the motif was confirmed by X-ray diffraction studies of **2g** (see below). Of interest was also that the C=C bond of **2a** is *E*-configured.

We then tested the ligands **L2** to **L10**. To our satisfaction, **2a** was the single product in all these experiments. The conversion of **1a** was however lower in all instances (Figure 1).[16] 1,10-Phenanthroline **L1** was therefore selected for the remainder of the study. The results with other cyclopentadienyl ruthenium(II) salts[17] are summarized in Table 1. Complexes with large lipophilic counterions (SbF_6^-, TRISPHAT (=$P(O_2C_6Cl_4)_3^-$))[18] had a reactivity similar to that of [**3**][PF_6]. Lower conversions were however noticed with anions able to coordinate at the metal center (OTf, TRISPHAT-N).[19] Complex [Cp*Ru(CH_3CN)$_3$][PF_6] (Cp* = pentamethylcyclopentadienyl)[20] was also effective, but the reaction was accompanied by concurrent polymerization of THF. Complex [**3**][PF_6] was therefore used in all further experiments.

Table 1: Metal complex selection.[a]

Entry	[Ru]	Anion	Conv.[b]
1	CpRu(CH_3CN)$_3$	PF_6	95
2	CpRu(CH_3CN)$_3$	SbF_6	95
3	CpRu(CH_3CN)$_3$	TRISPHAT	80
4	CpRu(CH_3CN)$_3$	TRISPHAT-N	43
5	CpRu(CH_3CN)$_3$	OTf	30
6	Cp*Ru(CH_3CN)$_3$	PF_6	90

[a] Reaction conditions: diazo **1a** (0.32 mmol), [Ru] and **L1** (2.5 mol % each), THF (0.6 mL), 2 h, 60 °C. [b] Conversion of **1a** (^{1}H NMR, 1,3,5-trimethoxybenzene as internal reference).

To investigate the scope of the reaction, substrates with different ester groups (alkyl, aryl, allyl) were tested and reactions were allowed to run until full conversion (Table 2). With bulkier alkyl esters, moderate to good yields of **2** were afforded after prolonged reaction time (Table 2, entries 2–5).[21] A series of aryl esters was also studied (Table 2, entries 6–12). In essentially all cases, products of type **2** were obtained. After 24 h, complete conversions were achieved with reagents carrying either electron-donating or electron-withdrawing substituents at the *para* position; this indicates a global lack of electronic effects. Only the highly hindered *o-tert*-butylphenyl reagent did not lead to any insertion reaction (Table 2, entry 12).[22] Product **2g** was found to be moderately soluble in a 4:1 mixture of hexane and Et_2O, which made X-ray-quality crystals accessible. The result of the X-ray analysis is shown in Figure 2. For compounds **2j** and **2k**, although predominant in the crude mixtures, decomposition occurred upon chromatographic purification (on SiO_2 or Al_2O_3). Another substrate, **1m** (R^1 = PhCH=CHCH$_2$, R^2 = Me), was also tested. In this case, the product of intramolecular cyclopropanation (65%) predominated and the corresponding enol acetal **2m** was isolated in 15% yield only (Table 2, entry 13).[23]

Table 2: Substrate scope.[a]

Entry	R^1	R^2	Product	Yield[b]	Time [h][c]
1	Me	Me	**2a**	80	3
2	Et	Me	**2b**	80	3
3	Ph(CH_2)$_2$	Me	**2c**	63	15
4	PhCH$_2$	Me	**2d**	85	20
5	*t*Bu	Me	**2e**	70	20
6	Ph	Me	**2f**	89	24
7	4-ClC_6H_4	Me	**2g**	80	24
8	4-$NO_2C_6H_4$	Me	**2h**	81	24
9	4-*t*BuC_6H_4	Me	**2i**	60	24
10	4-MeOC_6H_4	Me	**2j**	–[d]	24
11	4-$CF_3C_6H_4$	Me	**2k**	–[d]	24
12	2-*t*BuC_6H_4	Me	**2l**	0	24
13	PhCH=CHCH$_2$	Me	**2m**	15[e]	24
14	Et	Pr	**2n**	65	3
15	Me	CH_2Ph	**2o**	44	24
16[f]	Et	Ph	**2p**	27	24
17	Et	CF_3	**2q**	–[d]	3

[a] Reaction conditions: diazo **1** (0.32 mmol), [**3**][PF_6] and **L1** (2.5 mol % each), THF (0.6 mL), 60 °C. [b] Yield of isolated product. [c] Reaction time at 100% conversion. [d] Decomposition upon chromatography. [e] Intramolecular cyclopropanation adduct (65%) as major component. [f] Incomplete reaction. Conversion not measurable by ^{1}H NMR spectroscopy.

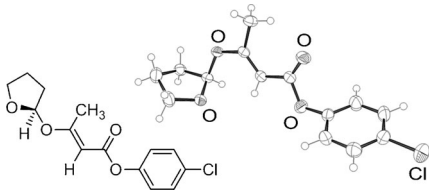
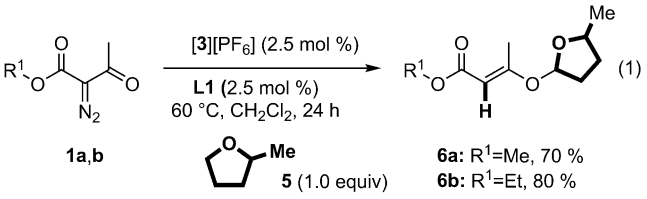


Figure 2. ORTEP view of the structure of (*E*)-**2g** in the crystal. Thermal ellipsoids are drawn at 50% probability level.

With 2-methyltetrahydrofuran (**5**) instead of THF, one equivalent was used as the reaction proceeded well in CH_2Cl_2 as solvent [Eq.(1)]. A longer reaction time was necessary (24 h instead of 3 h), but the isolation of the products (**6a** and



6b) was easier than for reactions performed with **5** as solvent. The C–O bond formation occurred only on the secondary CH_2 carbon atom; no evidence was found in the crude mixture for an insertion on the more hindered tertiary CH site.[25] In line with previous studies, this regioselectivity can be rationalized on steric grounds.[2b] Compounds **6a** and **6b** are obtained as 3.3:1 mixtures of diastereomers due to a lack of discrimination at the anomeric carbon atom.

To gain some insight into the nature of the transformation, a series of experiments was performed using reagents **1a**, **1f**, and **1h** in 1:1 mixtures of THF and [D_8]THF [Eq. (2)]. Mass spectrometry indicated the predominant formation of homocoupling products **HH** and **DD** (>90%) over cross-coupling products **HD** and **DH** (<10%).[26] A larger proportion of **HH** over **DD** was also denoted (Table 3).

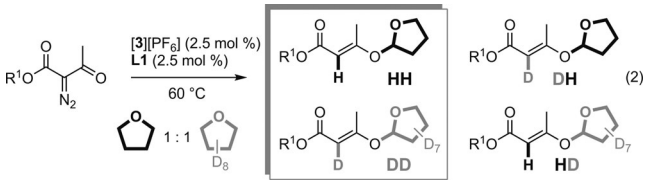


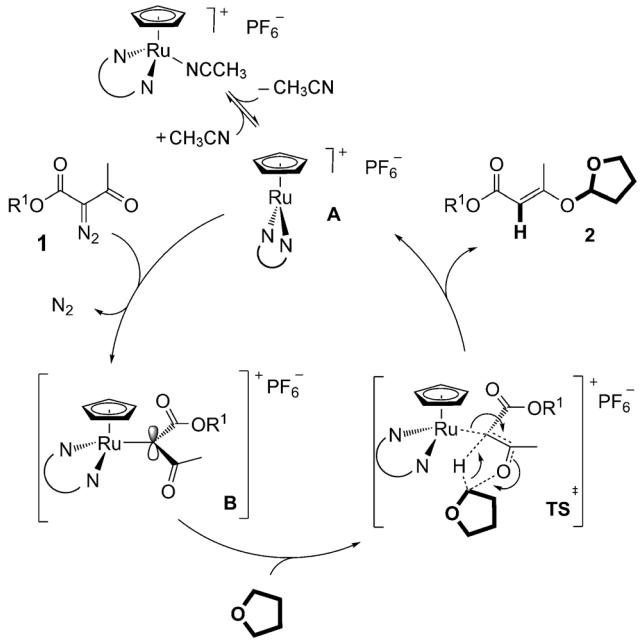
Table 3: Homocoupling and kinetic isotope effects.

Entry	R^1	Product[a]	Ratio **HH**/**DD**[b]
1	Me	**2a**	3.0:1.0
2	Ph	**2f**	3.3:1.0
3	4-$NO_2C_6H_4$	**2h**	3.4:1.0

[a] Reaction conditions: diazo **1** (0.32 mmol), [**3**][PF_6] and **L1** (2.5 mol %), 1:1 THF:[D_8]THF (0.6 mL), 60 °C. [b] Measured by 400 MHz ^{1}H NMR spectroscopy and confirmed by ESI mass spectrometry.

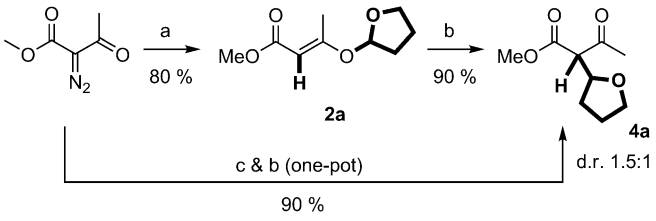
The predominant formation of the homocoupling products **HH** and **DD** advocates for a concerted hydrogen transfer mechanism. The higher proportion of **HH** over **DD** indicates the occurrence of a primary kinetic isotope effect.[27] The measured k_H/k_D values, from 3.0 to 3.4, are in accordance with previously reported results for C–C bond forming reactions.[2b] A mechanistic rationale coherent with these results is proposed in Scheme 2.[28]

In detail, catalyst precursor [**3**][PF_6] reacts with **L1** to generate a [Cp(**L1**)(CH_3CN)$_2$Ru][PF_6] species, which, upon dissociation of the monodentate ligand, forms the catalytically active 16-electron complex **A**.[10] This electron-deficient entity probably reacts with diazo reagent **1** to afford metal carbenoid intermediate **B**. At this stage, in contrast to classical C–H insertions, which proceed via 3-membered transition states,[7] a concerted reaction occurs that involves the keto group of carbenoid **B** and the more accessible C_α–H bond of the ether moiety.[29] A concomitant formation of the novel C–O and C–H bonds occurs in a 5-membered transition state **TS**‡ to release both product **2** and catalyst **A**. This step is stereo-determining as the s-*cis* conformation of the carbonyl group in intermediate **B** is conserved to form the *E*-configured enol.



Scheme 2. Mechanistic rationale. NN corresponds to 1,10-phenatroline (**L1**).

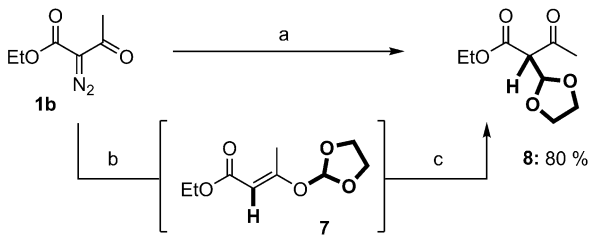
Finally, with compounds **2** in hand, we were able to also synthesize the products of "classical" C–C bond formation. Based on literature precedents,[30] we expected that the enol fragment of **2** would behave as a good leaving group in the presence of Lewis acids. After an induced dissociation, a recombination within the oxocarbenium/enolate ion pair would form adducts **4**. This assumption was validated in the transformation of **2a** into **4a** using catalytic amounts of $Cu(OTf)_2$ or TMSOTf (5 mol%, Scheme 3).[31,32] By using



Scheme 3. a) [**3**][PF_6] (2.5 mol%), **L1** (2.5 mol%), THF, 60 °C, 3 h; b) TMSOTf or $Cu_2(OTf)_2$ (5 mol%), CH_2Cl_2, 0→25 °C, 1 h; c) [**3**][PF_6] (2.5 mol%), **L1** (2.5 mol%), THF (1 equiv), CH_2Cl_2, 60 °C, 24 h.

only one equivalent of THF, the C–H insertion and rearrangement steps can be combined into a single-pot process. In this tandem fashion, a higher yield of **4a** was obtained (90 vs. 72% for two steps).

Using 1,3-dioxolane instead of THF as reactive ether, the classical C–C bond formation occurs under thermal conditions (Scheme 4). At 60 °C, decomposition of **1b** in the presence of the acetal affords **8** as the single adduct. The product of C–O bond forming reaction, **7**, is however observed after 1 hour at 25 °C. Two hours at 60 °C are then sufficient to induce the rearrangement into **8**, and this without



Scheme 4. [**3**][PF_6] (2.5 mol%), **L1** (2.5 mol%), 1,3-dioxolane (solvent): a) 60°C, 3 h; b) 25°C, 1 h; c) 60°C, 2 h.

any added Lewis acid. This result indicates that C–O bond forming is kinetically preferred over C–C bond forming using the current catalyst combination.

In conclusion, we have reported a new reactivity in the CpRu-catalyzed decomposition of diazo compounds and, as a consequence, a novel functionalization of tetrahydrofurans. To our knowledge, it is the first one-step synthesis of enol acetal moieties by direct C–H activation.

Experimental Section

Representative procedure: In a 2 mL screw-cap vial equipped with a magnetic stirring bar, **L1** (1.5 mg, 8 μmol, 2.5 mol%) and [CpRu-$(CH_3CN)_3$][PF_6] (3.5 mg, 8 μmol, 2.5 mol%) were dissolved in 0.60 mL of dry THF. The vial was flushed with argon and capped. The resulting deep red solution was stirred for 20 min at 25°C and then diazoketoester **1** (0.32 mmol) was added. The solution was stirred at 60°C until full conversion (^{1}H NMR monitoring). The crude mixture was purified by column chromatography (Hexane/Et_2O, SiO_2) to afford insertion product **2**.

Crystal structure analysis of **2g**: CCDC 867253 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[12] CpRu complexes with cyclooctadiene and diphosphine ligands, known to catalyze the decomposition of certain diazo derivatives, were unreactive in the titled chemistry: W. Baratta, A. DelZotto, P. Rigo, *Chem. Commun.* **1997**, 2163 – 2164; W. Baratta, W. A. Herrman, R. M. Kratzer, P. Rigo, *Organometallics* **2000**, *19*, 3664 – 3669; M. Basato, C. Tubaro, A. Biffis, M. Bonato, G. Buscemi, F. Lighezzolo, P. Lunardi, C. Vianini, F. Benetollo, A. Del Zotto, *Chem. Eur. J.* **2009**, *15*, 1516 – 1526.
[13] The Supporting Information contains optimization studies with **L1** and conversion results with less-performing and even inhibiting ligands.
[14] Without ligand, only 12% conversion is observed and polymerization of THF occurs.
[15] Compound **2a** is characterized by ^{1}H NMR signals at 5.66 (d, $J =$ 4 Hz, OCHO) and 5.32 (s, C=CH) ppm that are at quite higher frequency than the most deshielded proton of **4a** (m, $\delta =$ 4.43 ppm). The configuration of the double bond is readily determined by a NOESY experiment; see: R. Bihovsky, M. U. Kumar, S. Ding, A. Goyal, *J. Org. Chem.* **1989**, *54*, 4291 – 4293; O. Moriya, Y. Urata, Y. Ikeda, Y. Ueno, T. Endo, *J. Org. Chem.* **1986**, *51*, 4708 – 4709.
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[17] Other metal sources were also tested. Whereas copper salts did not induce the formation of **2a**, a small amount (10%) of **2a** is observed in the reaction catalyzed by $[Rh_2(OAc)_4]$. Interestingly, this Rh^{II} complex does not promote the C–O to C–C rearrangement detailed in Scheme 3.
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[25] Preferential C–H insertion on the tertiary carbon atom could be expected based on electronic grounds.
[26] The minimal amounts of products with $M+1$ and $M+7$ masses might be due to the formation of the corresponding cross-coupling products of type **4** according to a dissociation/reassociation mechanism.
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[31] Product **4a** is highly volatile and hence the yield of 90% corresponds to a quantitative reaction.
[32] Compound **6a** also rearranges under these Lewis acidic conditions, but the reaction generates a complex mixture of diastereomers that was not deconvoluted.

Communications

C–O Coupling

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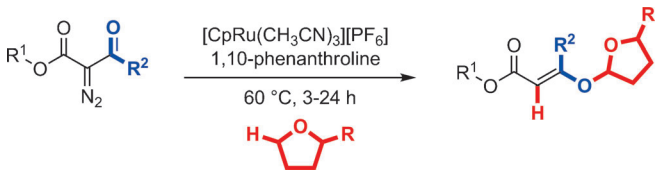
M. Austeri, L. Guénée,
J. Lacour* _____ ▮▮▮▮–▮▮▮▮



Enol Acetal Synthesis through Carbenoid C–H Insertion into Tetrahydrofuran Catalyzed by CpRu Complexes

Intermolecular C–O instead of C–C bond formation is achieved with [CpRu-$(CH_3CN)_3$][PF_6] and diimine ligands as catalysts of the decomposition of α-diazo-β-ketoesters in THF leading to original products of 1,3 C–H insertion (see scheme).

