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Nickel-Catalyzed Coupling of Arylzinc Halides with Thioesters

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Abstract: The Pd-catalyzed Fukuyama reaction of thioesters with organozinc reagents is a mild, functional group tolerant method for acylation chemistry. Its Ni-catalyzed variant might be a sustainable alternative to expensive catalytic Pd sources. We investigated the reaction of S-ethyl thioesters with aryl zinc halides with hetero- and homotopic Ni precatalysts and several ligands. The results show that both homo- and heterotopic species may contribute to catalysis. The substrate scope using an operationally homogeneous defined Ni complex was established. Acyl radicals are postulated as short-lived intermediates.

The Fukuyama reaction (FR) allows access to polyfunctional ketones via the cleavage of thioesters by employing mild organozinc reagents in conjunction with Pd catalysis without formation of the corresponding alkanol (Scheme 1a).^[1] Compared to the more sensitive acyl chlorides, simple S-alkyl thioesters are bench- and chromatography-stable acyl transfer reagents.^[2] They are most commonly prepared by active ester methods,^[3] but carbonylative transition metal catalysis offers the possibility to forego the need for stoichiometric activating agents.^[4] The FR has certain advantages for synthetic chemists over acylation reactions using Grignard reagents. It has been employed in the total synthesis of various natural compounds, for example of (+)haplophytine by Fukuyama and of Biotin (52 mmol scale) by Seki and co-workers using Pd/C.^[5] Modern extensions of the FR are continuously being developed, such as the enantioconvergent variant based on a dynamic kinetic resolution of racemic benzylic zinc reagents by chiral catalysts.^[6] Besides Pd/C and the originally employed [PdCl₂(PPh₃)₂], the efficiency of phosphine-free Pd₂dba₃ was demonstrated.^[7] However, it was shown that varying amounts of Pd nanoparticles (NPs) may be present in this apparently homogeneous Pd(0) precursor depending on the supplier.^[8] Other studies using Pd/C and Pd(OAc)₂ led to assumption that the Fukuyama reaction might operate both in homogeneous and heterogeneous mode.^[9]

Despite the usefulness of this transformation, two major issues emerge especially at larger scale: a) Contamination of potentially bioactive products with metals and b) the recovery of Pd metal. To address point b), Ni(II) precursors have been investigated briefly by Seki as a potential substitute for the expensive Pd catalysts in the FR, but a large excess (4 eqv.) of the organozinc reagent was required in combination with long reaction times (20 h).^[10] Rovis has shown a more active system for the Ni-catalyzed FR going to completion within 2 h.^[11] In this case, pyrophoric Ph₂Zn in combination with the air-sensitive Ni(cod)₂ and 4-F-styrene as an additive was required and only

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 Supporting information for this article is given via a link at the end of the document. one example was shown, but the study was focused mainly on the activation of other acyl electrophiles. In addition, the cost of Ni(cod)₂ partially offsets the price advantage of bulk Ni over Pd. Recently, ketones were accessed by Rueping et al. from the more inert aromatic oxoesters and alkylboranes under Ni(cod)₂ catalysis.^[12]

Thus, there is much potential to develop more efficient Nibased version of the Fukuyama coupling. We were interested if the salt effect of Knochel-type arylzinc reagents could be employed to increase reactivity in the Ni-catalyzed Fukuyama reaction allowing for reduced catalyst loadings and shorter reaction times.^[13] Secondly, we wanted to address various entry points into catalysis (molecular, nanoparticulate) (Scheme 1b). Our investigations presented herein led to development of a method featuring the use of a defined complex as catalyst,^[14] which improves the selectivity of the reaction (Scheme 1c).



Scheme 1. a) The Fukuyama reaction. b) The respective catalytic reaction with Ni and its associated open questions. c) Our method using a defined Ni-complex as catalyst.

We began our investigation by employing thioester 1 and 1.5 eqv. LiCl-adducted phenyl zinc chloride (4) as coupling partners and NiCl₂ as catalyst (Table 1). As expected, this reaction does not proceed in the absence of a catalyst (Table 1. Entry 4). Ni(acac)₂, described by Seki to be active in the Ni-catalyzed Fukuvama reaction, showed good activity towards product 2 (Table 1, entry 6) comparable to the least expensive Ni source, NiCl₂ (obtained by dehydration of the hexahydrate salt). This salt was reported to be inactive in a previous report.^[10] Both catalysts produced significant amounts of biphenyl (3), which should be suppressed in order to facilitate the purification. While we were pleased that the reaction proceeds with simple NiCl₂, we were curious about the actual catalytic mode since NiCl₂ is insoluble in THF. Thus, at the beginning of the reaction, the reaction mixture is heterogeneous. Less zinc reagent, slow addition of the zinc reagent, or lower reaction temperatures had a detrimental effect on the obtained yields (Table 1, entries 1-3). Nickel salts other than NiCl₂ and Ni(acac)₂ performed worse (see SI), and Fe(acac)₃ was inactive (Table 1, entry 8). Interestingly, Fe(acac)₃ was

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reported to be an active catalyst in the reaction of Grignard reagents with S-phenyl thioesters.^[15]

 Table 1. Selected optimization and control experiments of coupling thioester 1

 with nucleophile 4 under Ni catalysis.



Entry	Deviation from standard	Conv. 1	Yields [%] ^[a]	
	conditions	[/0]. ,	2	3 ^[b]
1	1.2 eqv. 4 instead	82	77	14
2	Dropwise addn. of 4	70	54	7
3	0 °C, 2 h instead	79	63	10
4	No metal, no ligand	0	0	0
5	Addn. of 1 to 4	86	70	16
6	5 mol% Ni(acac) ₂ instead	95	87	15
7	+ 5 mol% dtbbpy (L1)	95	83	19
8	5 mol% Fe(acac)₃ instead	1	1	6
9	10 mol% Ni-NP instead	94	76	12
10	5 mol% Ni(xant)Cl ₂ (C1) instead	61	61	11
11	5 mol% Ni(xant)(oTol)Cl (C2) instead	89	81	9
12	5 mol% Ni(dppf)(oTol)Cl (C3) instead	72	59	10
13	As entry 11, 1.5 h, 1.86 eqv. 4	97	91	5

Reagents and conditions for standard run: **1** (63 mg, 333 µmol, 1 eqv.), PhZnCI+LiCI (1.5 eqv. based on titre [typically 0.25 M], in THF), anhydrous NiCl₂ (2.2 mg, 16.6 µmol, 5 mol%), dry THF (300 µL), RT, 30 min. [a] Determined by quantitative GC-FID analysis. [b] Based on 0.5*nPhZnCl. Acac: Acetylacetonate. dppf: 1,1'-Diphenylphosphinoferrocene. dtbbpy: 4,4'-Di-tert-butyl-2,2'-dipyridyl. NP: Nanoparticles. oTol: *ortho*-Tolyl, Xant: Xantphos

Except dtbbpy (**L1**, Table 1, Entry 7), addition of other diimine ligands lowered the yields (see SI). Such insensitivity to ligand variation can be interpreted as a hint that a heterotopic catalyst is active.^[16] Interestingly, preformed Ni-diimine complexes performed significantly worse than salt/ligand mixtures (see SI), further hinting at catalysis by a heterotopic Ni catalyst under this regime. Furthermore, we observed the formation of dark solutions

and noted dark particles upon aqueous acidic workup, which separated to the organic phase. Additionally, these particles complicated purification of the final products, leading to a black appearance of otherwise NMR-pure products after column. This led us to assume that the catalytically active species or a reservoir for molecular catalysis may be of high molecular weight or nanoparticulate, which was confirmed by successful employment of NiB nanoparticles (10 mol%) as the catalyst (Table 1, Entry 9).^[17]

Our conclusion from these experiments was to employ other well-defined complexes to avoid the complicating factor of possible heterogeneous catalysis. Therefore, we also studied the influence of the relatively (compared to diimine-type ligands) strong-field wide-bite angle ligand xantphos (L2) in the Fukuyama reaction (Table 1, entry 10) in complex C1, but the result was moderate. Jamison has prepared a series of well-defined, airstable organometallic Ni^{II}-phosphine precatalysts, including C2 which is easily prepared from C1. These complexes generally display enhanced solubility in organic solvents compared to L₂NiCl₂ complexes.^[14] At the beginning of the reaction, C2 is activated by a transmetalation/reductive elimination sequence to give a molecular Ni⁰ species. In our case, C2 gave homogeneous - solutions in THF with the thioester present, no black particles upon workup and generally higher product selectivity (Table 1, entries 11 and 13). In this case a distinct ligand effect was noted by comparison to commercially available C3 (Table 1, entry 12).

Next, the substrate scope was investigated using catalyst **C2** with the aim to evaluate the steric and electronic requirements for effective catalysis (Scheme 2). The thioesters were prepared by Steglich's method and typically isolated before use.^[3b] Initially, the effect of steric bulk proximal to the reactive centre on catalytic activity was studied. Activity increases with decreasing steric hindrance at the thioester moiety (tert. < sec. < prim.), leading to the exemplary products **2** (gram-scale reaction), **19** and **27**.

Cyclic secondary or tertiary thioesters performed significantly worse in catalysis (leading to product 26 and no formation of 28) than their acyclic counterparts (leading to 19 and 27 for comparison). The performance of the aryl substituted thioester (leading to 29) was similar to the cyclic secondary thioester. This effect cannot be solely explained by the thermodynamic trend of product stability, but also by kinetic differentiation during catalysis. By employing NiCl₂/terpy mixtures as a model catalyst for weakfield ligands, a decreased sensitivity to steric bulk was found (see SI); meaning that the preference for primary thioesters is characteristic for C2. Next, the functional group tolerance of the various primary thioesters was investigated. We found that despite the high reactivity of putative Ni⁰ states, electrophilic (e.g. leading to 9, 10) and Lewis basic functional groups were generally well-tolerated (e.g. leading to product 11). Notably, also thioesters containing double bond reacted to corresponding products 15 and 17 in good to excellent yields and the reaction was also applied to convert dehydrocholic acid thioester to 14. In case of 17, isomerization to the thermodynamically more stable alkene isomer occurred most likely by alkene coordination to zerovalent, coordinatively unsaturated (Xant)Ni. Furthermore, steric hindrance on β -carbon atom did not hamper the production of ketone 18.

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Scheme 2. Scope of the Ni-catalyzed Fukuyama reaction of S-alkyl thioesters with aryl zinc halides. Yields given are isolated unless stated otherwise. Reagents and conditions for standard run: Thioester (333 μmol, 1 eqv.), ArZnCl·LiCl (1.86 eqv. based on titre [typically 0.25 M], in THF), C2 (12.7 mg, 16.6 μmol, 5 mol%), dry THF (300 μL), RT, 1.5 h. [a]: 2.86 eqv. of 4 were employed. [b]: The thioester could not be isolated in pure form. Hence, the yield given is over two steps. [c] From 4-Cl-C₆H₄ZnCl under standard conditions. [d] NMR yield.

Next, the effect of organozinc nucleophile on the overall activity was studied using product 19 as a convenient reference point (Scheme 2). While coupling with unhindered, electron rich nucleophiles proceeded well (products 20 to 25), a clear effect of steric bulk on catalytic activity was observed again. No reactions took place with more bulky arylzinc reagents (ferrocenyl-, tolyl-, 1naphthyl zinc halides). Transmetalation is being invoked as the slowest step in the thioester-to-ketone transformation.^[10] Thus, the performance of several electronically differentiated aryl zinc halides was studied. Here, relatively electron-poor nucleophiles gave no appreciable product formation (e.g. 3-CF₃-, 4-cyanophenyl zinc chlorides). The possible negative influence of heteroatoms via coordination was ruled out, since highly coordinating heterocyclic zinc reagents gave the same result. While the electron-rich thiophen-2-yl zinc chloride furnished 25 in 64% yield, the electron-deficient 6-methylpyrid-2-yl zinc chloride provided no product. This is a first experimental indication that transmetalation might be the rate-determining step in the Nicatalyzed FR. Couplings with less reactive alkyl-, alkenyl- or alkynyl zinc halides did not proceed under our optimized conditions. Interestingly, keto-thioether 22 was formed with parachlorophenyl zinc chloride, most likely from the liberated zinc thiolate under Ni catalysis. Stambuli noted a similar effect in the Pd-catalyzed FR, albeit with bromoarenes.[18] Schönebeck also found wide-bite angle diphosphines to be active in the Nicatalyzed trifluoromethylthiolation of chloroarenes.[19]

Next, we investigated the possible radical character of the reaction. Single electron reduction of thioesters by a low-valent Ni

complex might lead to fragmentation resulting in a thiolate and a neutral acyl radical. A ketyl radical anion equivalent has been postulated by Skrydstrup in a Sml2-mediated C-C bond-forming reaction of thioesters with electron-deficient alkenes.[20] Interestingly, a Ni(I)-Me terpyridine complex has been reported to have a reducing power similar to Sml₂.^[21] If an acyl radical is formed, a decarbonylative pathway can be envisioned. The decomposition of benzylic acyl radicals compared to primary ones is thermodynamically favoured and fast.^[22] Thus, we employed benzylic thioester 30 under a) our reaction conditions using C2 and b) under conditions that have been optimized for the decarboxylative coupling of redox active esters (RAE) under Nicatalysis (Scheme 3a).^[23] Under RAE conditions, an appreciable amount of decarbonylated product 32 is formed whereas under our conditions, only small amount of 32 was formed together with the expected 31. Our initial conclusion from these experiments was that C2 operates by a 2-valence electron redox classical cross-coupling mechanism which is distinct of the mechanism under RAE conditions. However, a catalytic reaction of the model substrate in the presence of TEMPO (75 mol% relative to the thioester) and C2 or NiCl₂ showed only minimal product formation, implying radical pathways operative with both catalysts. The adduct from these experiments could not be detected. However, in the presence of ethyl acrylate (2 eqv. relative to the thioester), the putative acyl radical was trapped, as shown by the detection of product 33 (see SI for details) of a formal hybrid Fukuyama-Giese reaction either with C2 or NiCl₂ (Scheme 3b), which however proceeded sluggishly and also produced 2.

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Scheme 3. a) Testing for decarbonylative pathways by generation of benzylic acyl radicals from benzylic thioesters. b) Trapping acyl radicals by a hybrid Fukuyama-Giese reaction. c) Proposed mechanism.

In our proposed mechanism, activation of C2 by ArZnCI leads to a zerovalent Ni species (Scheme 3c),[14] which undergoes a single electron transfer-type stepwise oxidative addition into the thioester. A short-lived acyl radical 34, which can undergo capture by radical acceptors or decomposition by decarbonylation, is formed. The acyl or alkyl radical recombines with the Ni(I) species, providing a Ni(II) oxidative addition complex (Scheme 3c). This is followed by the classical steps of transmetalation and reductive elimination to close the cycle. Thus, an apparent classical 2valence electron cross-coupling mechanism involves SET steps as proven by capture or decarbonylation of acyl radical intermediates. Other mechanisms such as a Ni(I/II/III) cycle may be possible as well.^[24] The difference in the propensity to decarbonylate 30 (to give 32) between C2 and other Ni/diimine ligand combinations can be accounted to a lower tendency of Xantphos-ligated Ni acyl species to undergo migratory deinsertion of CO (non-radical on-metal decarbonylation). Stoichiometric experiments by the groups of Love and Riordan on the oxidative addition of defined, bidentate-phosphine ligated Ni⁰ complexes into thioesters have shown that decarbonylation of the resulting acylnickel(II) thiolates occurs readily to give alkylnickel(II) thiolates.[25]

In conclusion, we have shown that an operationally homogeneous precatalyst **C2** is an efficient and functional group tolerant catalyst for the Ni-catalyzed Fukuyama reaction. Both homogeneous precatalysts such as **C2** and Ni nanoparticles can be entry points into catalysis. Thus, a picture similar to the Pd-catalyzed FR emerges where hetero- and homotopic catalytic cycles may coexist.^[26] We provide the first experimental proof that the Ni-catalyzed FR proceeds *via* acyl radical intermediates (and/or synthons thereof), which were previously accessible from thioesters only by neutral photo- and thermolysis as well as reductive electrolysis and in a catalytic manner by photoredox catalysis.^[27] We wish to harness these catalytically generated reactive intermediates in related Ni-catalyzed transformations to gain further proof of this concept.

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Keywords: Nickel catalysis • Acyl radicals • Fukuyama coupling • Thioester • Ketones

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Herein, we report coupling of thioesters with arylzinc reagents using a defined bidentate phosphine ligand-based nickel complex as catalyst. A discussion on mechanism using different homo- and heterotopic Nickel precursors is included.

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