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Synthesis of 3-Formylfurans *via* a Silver(I)-Catalyzed Epoxide Ring-Opening/1,2-Acyl Migration/Cyclization Cascade

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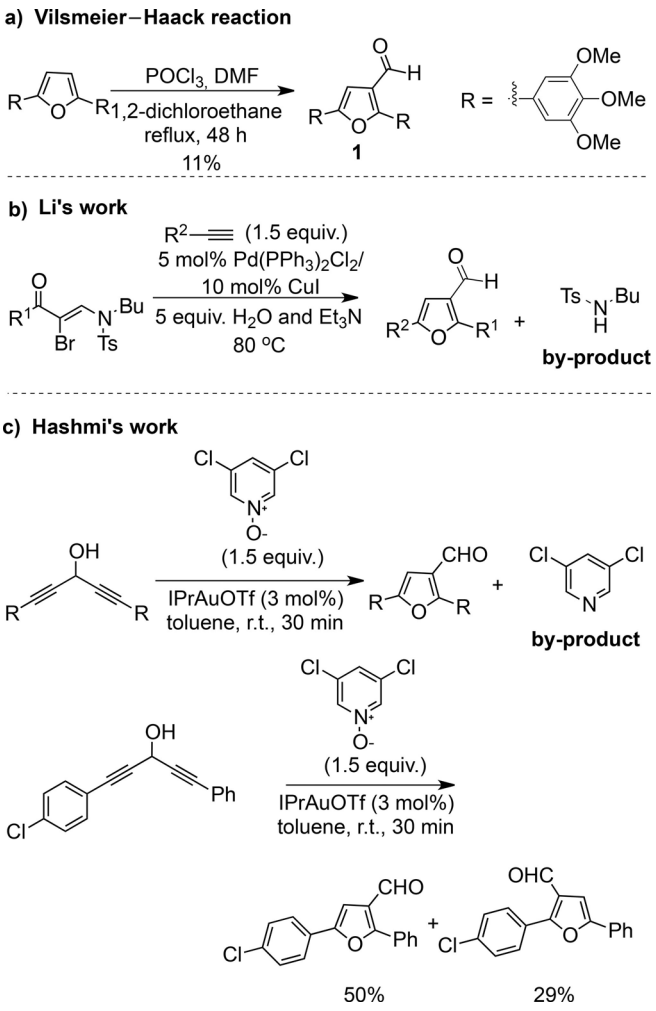
Abstract: By the design of suitable starting materials, a silver(I)-catalyzed epoxide ring-opening/1,2-acyl migration/cyclization cascade has been developed, which allowed us to systematically prepare unsymmetrical 3-formylfurans. Various 3-formylfurans were prepared in good to excellent yields. In addition, the distinct fluorescence properties of 3-formylfurans in solution and the solid state are disclosed.

Keywords: 1,2-acyl migration; cascade reaction; epoxides; 3-formylfurans; silver catalysis

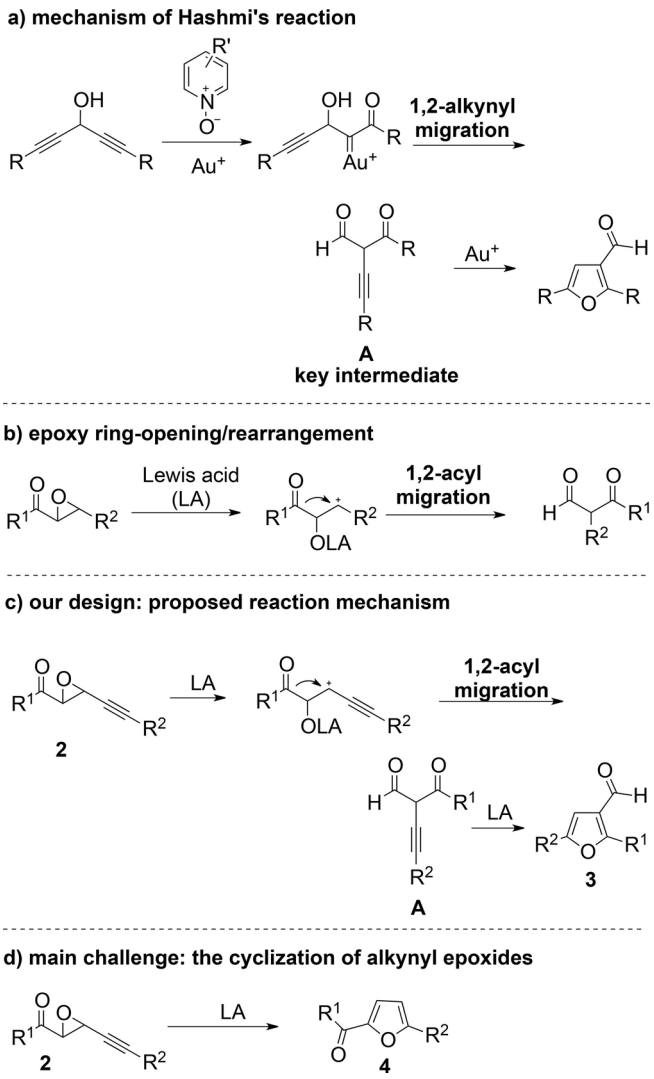
3-Formylfurans are core structures of some bioactive natural products. Examples include Lophotoxin, Lophodiol A, Leptolide and Pukalide.[1] In addition, some of the 3-formylfuran derivatives exhibited anti-proliferation effects against some cancer cells lines.[2] As an functional group, the presence of a formyl group facilities further transformations of the furan moiety. Giving the importance of 3-formylfurans in natural products and organic synthesis, the methodology for their preparation is important in organic synthesis. Traditionally, 3-formylfurans were obtained either through the transformation of other functional groups or by the direct formylation of furans. A typical example is the Vilsmeier–Haack reaction, which was used to prepare 3-formylfuran derivative **1** displaying anti-proliferation effects against two cancer cell lines[2] (Scheme 1a). The product was obtained in very low yield under harsh conditions. In the light of atom economy, the Vilsmeier–Haack reaction is also not satisfactory. In addition, when several electron-rich groups were present, the formylation suffers from the regioselectivity of more than one reaction site. Beside the direct formylation of furans, cascade reactions were also employed. Li reported the Pd/Cu-catalyzed Sonogashira coupling/cyclization cascade to 3-formylfurans (Scheme 1b).[3] In analogy to Vilsmeier–



Scheme 1. Previous methods for the synthesis of 3-formylfurans.

Haack formylation, the reaction also suffered from low atom economy and harsh conditions. In 2014, Hashmi and his co-workers developed an efficient gold-catalyzed[4] method, which gave 3-formylfurans under very mild conditions with high efficiency (Scheme 1c).[5] However, because of the use of pyridine *N*-oxide as oxygen transfer reagent, a stoichiometric amount of pyridine as by-product was unavoidable. In addition, when unsymmetrical starting materials were subjected to the standard conditions, two isomers were obtained due to the lack of regioselectivity (Scheme 1c). As part of our efforts on the synthesis of heterocycles,[6] we herein want to report the synthesis of 3-formylfurans under mild conditions *via* a silver(I)-catalyzed epoxide ring-opening/1,2-acyl migration/cyclization cascade.

Our hypothesis comes from Hashmi's work and the rearrangement of epoxides. As depicted in Scheme 2a, in Hashmi's work, a β-keto aldehyde was the key intermediate for the 3-formylfuran synthesis.[5,7] At the same time, we noticed that the rearrangement of α,β-epoxy ketones under Lewis acidic conditions can afford β-keto aldehydes *via* a 1,2-acyl migration (Scheme 2b).[8] Based on these two transformations, we hypothesized that the rearrangement of alkynyl α,β-epoxy ketones **2** would give the same β-keto aldehyde intermediate **A** and the same final product as in Hashmi's report (Scheme 2c). If this hypothesis could be realized, this reaction would provide an efficient method to systematically prepare unsymmetrical 3-formylfurans. However, a main challenge that this hypothesis meets is the cyclization of alkynyl epoxides, which is very easy to accomplish under mild conditions (Scheme 2d).[9]



Scheme 2. Our design and the main challenge.

To prove the hypothesis, alkynyl α,β-epoxy ketone[10] **2a** was prepared and was subjected to various conditions. Although a multi-step procedure was required for the preparation of **2a**, the formation of the epoxide by the use of hydrogen peroxide as stoichiometric oxidant is greener and a synthetic benefit, compared to one equivalent of a pyridine *N*-oxide or metal salts.[11] Lewis acids which were reported to be effective in the rearrangement of α,β-epoxy ketones were examined first (Table 1, entries 1–5). By the use of $Cu(OTf)_2$,[8a] $Bi(OTf)_3$[8b] and $BF_3{\cdot}OEt_2$[8c,d] as catalyst, the reaction indeed afforded 3-formylfuran **3a** as main product. However, the yield was poor due to the decomposition of the starting material. To our delight, no competitive direct cyclization product **4** was observed. Tris(pentafluorophenyl)boron was also examined, however, no desired product was formed (entry 4). $AuCl_3$[8e] gave **3a** in a relative better yield (entry 5). $Fe(OTf)_3$ (entry 6) and AgOTf (entry 7) were also screened, the later one delivered **3a** in moderate yield. This result inspired us to focus on silver salts. Among the silver salts we examined (entries 7–11), $AgBF_4$ showed a great advantage in promoting this reaction (entry 11). Further solvent screening (entries 12–14) revealed that use of a coordinative solvent resulted in deactivation of the catalyst (entry 14). By literature investigation on silver catalysis,[12] we realized that the solubility of the silver salts might affect the reaction dramatically. In addition, the acidity of the catalyst might result in the decomposition of starting material. One method to enhance the solubility of the silver salts, as well as neutralize their acidity, is the use of ligands. Thus a variety of ligands was screened. To our surprise, the addition of ligands in a 1:1 ratio to silver salt totally prevented the reaction (entries 15, 16). We carefully repeated the reaction and it was found that a slight excess of the silver salts over ligands made the reaction possible. In analogy, Shi found that in gold catalysis an excess of silver salts was necessary in some cases.[13] It was also found that in silver catalysis the different ratio of ligands to silver salts resulted in dramatic differences in catalytic activation.[14] For example, Yamamoto and co-workers

Table 1. Optimization of the reaction conditions.[a]

2a **3a**

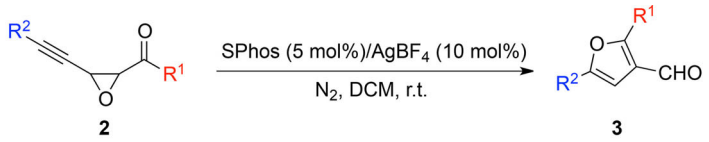
Entry	Catalyst (5 mol%)	Solvent/Time	Yield[b]
1	$Cu(OTf)_2$	DCM/5 h	17%
2	$Bi(OTf)_3$	DCM/7 h	28%
3	$BF_3{\cdot}OEt_2$	DCM/8 h	10%
4	$(C_6F_5)_3B$	DCM/25 h	NR
5	$AuCl_3$	DCM/2 d	33%
6	$Fe(OTf)_3$	DCM/0.5 h	25%
7	AgOTf	DCM/17 h	52%
8	$AgSbF_6$	DCM/16 h	45%
9	$AgNTf_2$	DCM/18 h	49%
10	$AgPF_6$	DCM/7 h	65%
11	$AgBF_4$	DCM/7 h	70%
12	$AgBF_4$	toluene/10 h	20%
13	$AgBF_4$	DCE/12 h	61%
14	$AgBF_4$	CH_3CN/10 h	NR
15	PPh_3(5 mol%) + $AgBF_4$ (5 mol%)	DCM/18 h	NR
16	SPhos (5 mol%) + $AgBF_4$ (5 mol%)	DCM/24 h	NR
17	PPh_3(5 mol%) + $AgBF_4$ (10 mol%)	DCM/5 h	75%
18	SPhos (5 mol%) + $AgBF_4$ (10 mol%)	DCM/18 h	82%
19	$(Cy)_3P$ (5 mol%) + $AgBF_4$ (10 mol%)	DCM/4 h	75%
20	$[4\text{-}MeOC_6H_5]_3P$ (5 mol%) + $AgBF_4$ (10 mol%)	DCM/3 h	66%
21	BINAP (5 mol%) + $AgBF_4$ (20 mol%)	DCM/18 h	74%

[a] All reactions were carried out on a 0.3 mmol scale in 3 mL of solvent at room temperature in the dark, and the reactions were quenched once the TLC analysis showed that the starting material **2a** was completely consumed.
[b] Yields of isolated products.

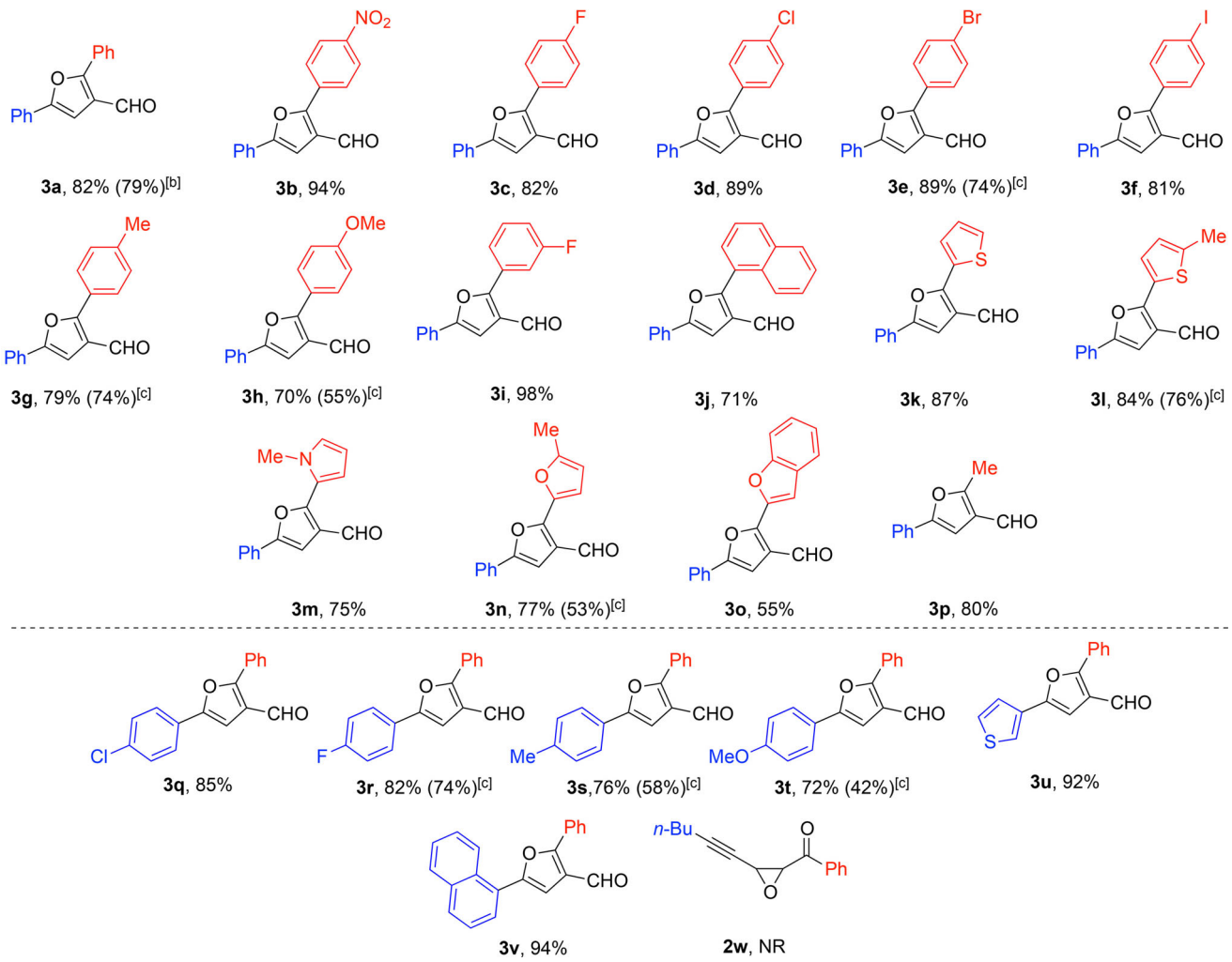
reported that an excess amount of silver salts to the phosphine ligand significantly raised the enantioselectivity of the product in the asymmetric Sakurai–Hosomi allylation.[15] To our delight, when the ligands were added in a 1:2 ratio to silver salts, the reaction worked smoothly to afford **3a** in good yields (entries 17–21). Among the ligands we examined, SPhos (2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl) gave the best result (entry 18). The decomposition of starting material was prevented to some degree due to the addition of ligands. The differences in reaction rate and the yields of product (entries 17–21) indicated that the ligands indeed played some role in the reaction. It was not the silver salt which was added in excess that catalyzed the reaction solely. Table 2 gives the yields of some products which were obtained by the use of SPhos/$AgBF_4$ (1:2) as catalyst and $AgBF_4$ as catalyst, respectively. In some cases, the use of SPhos/$AgBF_4$ (1:2) as catalyst improved the yields dramatically (**3e**, **3h**, **3n**, **3s**, **3t**). We tried to find out the reason for the dramatic difference resulted by ratio changes of ligands to silver salts. ^{31}P NMR experiments were carried out, however, no obvious differences of the chemical shifts were observed, except for some changes in shape.[16] An HR-MS investigation also did not give any clues on the exact catalytic species, which are still not clear.

With the optimized conditions in hand, the scope of the substrates was explored (Table 2). The epoxide ring-opening/1,2-acyl migration/cyclization cascade proved feasible for a variety of substrates. For substrates prepared from a variety of ethanone derivatives (**2a**–**2p**), the reaction afforded 3-formylfurans **3** in good to excellent yields (55–98%). For substrates derived from acetophenones with various substituents in the benzene ring (**2a**–**2i**), those bearing electron-withdrawing groups delivered the products (**3b**, **3c**, **3d** and **3i**) in better yields than those bearing electron-donating groups (**3g** and **3h**). Beside the acetophenone derived substrates, 2-acetothiophene (**2k** and **2l**), 2-acetyl-1-methylpyrrole (**2m**), 2-acetofuran (**2n**) and 2-acetobenzofuran (**2o**) derived substrates also worked smoothly affording the corresponding products in good to excellent yields, respectively (**3k**–**3o**). To our delight, an acetone derived starting material **2p** also worked well giving **3p** in very good yield. The substituents at the acetylenic terminus could be substituted by phenyl (**3q**–**3t**), thienyl (**3u**) and naphthyl

Table 2. Substrate scope for the reaction.[a]



2 **3**



[a] Unless otherwise noted, reactions were performed on 0.3 mmol scale in 3 mL of DCM with Sphos (5 mol%) and $AgBF_4$ (10 mol%) at room temperature in the dark; the yields given are isolated yields.

[b] The reaction was carried out on the gram scale; 0.811 g of **3a** were obtained from 1.026 g of **2a** under the standard conditions.

[c] The yields given in the parentheses are isolated yields by the use of $AgBF_4$ (5 mol%) as catalyst without addition of SPhos as ligand.

groups (**3v**). In analogy to the above-mentioned results, the electron-deficient substrates afforded 3-formylfuran products (**3q** and **3r**) in better yields than the electron-rich ones (**3s** and **3t**). Unfortunately, when aromatic groups were replaced by an aliphatic group (**2w**), no reaction was observed under the standard conditions. Phenylhydrazine and hydroxylamine hydrochloride were added, respectively, to capture the β-keto aldehyde intermediate **A** (Scheme 2c), however only complex mixtures were obtained due to the high reactivity of the starting material. A gram scale reaction of **2a** was also carried out, delivering **3a** in 79% yield.

Interestingly, the obtained 3-formylfuran products showed distinct fluorescence properties both in solution and in the solid state. Figure 1 and Figure 2 show the emission spectra in ethanol solution and the solid-state fluorescence of selected samples. As is demon-

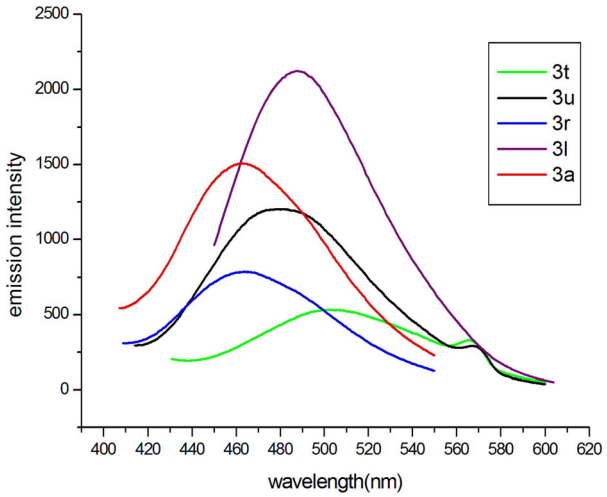


Figure 1. Normalized fluorescence emission spectra of selected samples in EtOH (2×10^{-5} mol L^{-1}).

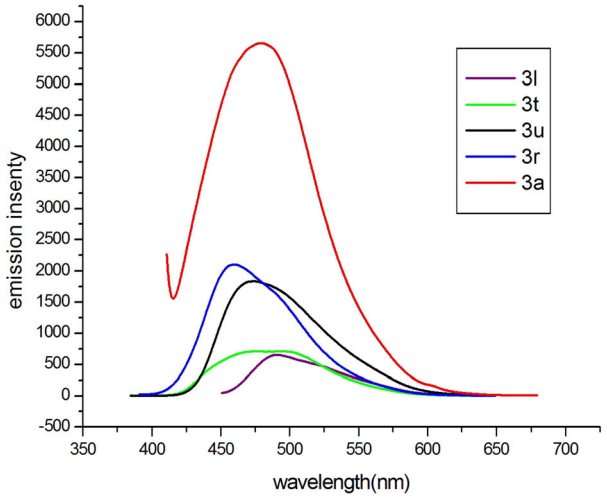


Figure 2. Normalized fluorescence emission spectra of selected samples in the solid state.

strated, these compounds show the green-blue fluorescence both in ethanol and in the solid-state with the emission maxima ranging from 460 nm to 520 nm. The existence of an electron-donating substituent on the product resulted in a bathochromic shift of the fluorescence emission spectrum both in solution and in the solid state. For an example, the emission maxima of **3t** (503 nm) was observed with a 40-nm red shift over **3a** (463 nm) in ethanol solution. Given the fact that the substituents on the 2- and 5-positions of 3-formylfurans are diversified and easily changed, the development of compounds with significant fluorescence properties should be feasible by modification of 3-formylfurans.

In conclusion, we have developed an efficient method to systematically prepare unsymmetrical 3-formylfurans. The addition of a phosphorus ligand to silver salt in a 1:2 ratio was crucial for the generation of the catalytic species. Various 3-formylfurans were prepared in good to excellent yields. Interestingly, the products showed distinct fluorescence properties both in ethanol solution and in the solid state. The interaction between ligands and silver salts, and investigations on 3-formylfurans with significant fluorescence properties are currently in progress.

Experimental Section

General Procedure for the Synthesis of 3-Formylfurans

SPhos (6.2 mg, 0.015 mmol) and $AgBF_4$ (5.8 mg, 0.03 mmol) were dissolved in 1 mL of DCM and the mixture was stirred at room temperature for 30 min in the dark under nitrogen. To this solution, epoxide **2** (0.3 mmol) in 2 mL of DCM was added. The resulting mixture was continually stirred at room temperature in the dark until the epoxide was consumed completely as determined by TLC analysis. After that the solvent was removed and the crude product was purified *via* column chromatography on silica gel (petroleum ether/ethyl acetate, 50:1) to afford 3-formylfurans in good yields.

2,5-Diphenylfuran-3-carbaldehyde (3a):[5a] Yield: 82%; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=10.17$ (s, 1H), 7.83 (d, 2H, $J=7.7$ Hz), 7.76 (d, 2H, $J=7.7$ Hz), 7.58–7.51 (m, 3H), 7.47–7.41 (m, 2H), 7.38–7.33 (m, 1H), 7.14 (s, 1H).

Acknowledgements

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[16] TLC (thin-layer chromatography) intuitively shows the differences between two cases (with or without ligands), for TLC traces and the ^{31}P NMR spectrum, see the Supporting Information, S80 and S82.

