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Catalytic Direct Dehydrogenative Cross-Couplings of C−H (Pro)Nucleophiles and Allylic Alcohols without an Additional Oxidant

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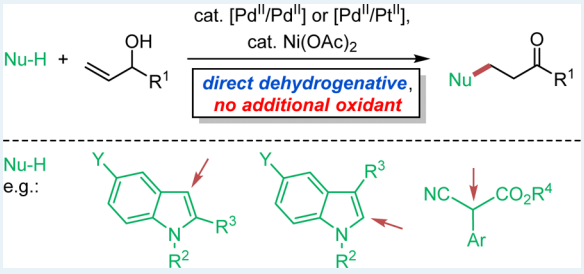
Supporting Information

ABSTRACT: Transition-metal-catalyzed cross-coupling reactions between sp^2-hybridized C atoms are of prime importance in both target and diversity oriented synthesis. Ideal cross-coupling reactions would neither require any leaving groups nor stoichiometric reagents. In this article, we report the first direct dehydrogenative cross-couplings between aromatic C−H bonds (in most cases using indole substrates) and allylic alcohols, which do not require an additional classical stoichiometric oxidizing agent and provide β-arylketones as value-added products. Ruthenocene- or ferrocene-based bismetallacycles, in which either Pd(II) or Pt(II) are the catalytically active centers, were found to be particularly efficient catalysts. Control experiments suggest that the bismetallacycles initially transform the allylic alcohols into vinylketones, which then alkylate the aromatic substrate in the presence of the catalyst. The fact that the dehydrogenative coupling does not require a classical stoichiometric oxidizing agent is explained either by protonolysis of a metallacyclic M(II)-H intermediate or by a mechanism in which an excess of the allylic alcohol substrate serves as a sacrificial hydrogen acceptor. The title reaction is supported by cocatalytic amounts of $Ni(OAc)_2$. In preliminary studies, it was observed that the title reaction can as well be applied to prochiral CH-acidic pronucleophiles such as α-cyanoacetates, representing the first examples for direct enantioselective β-ketoalkylations via allylic alcohols in the absence of an additional oxidant.



KEYWORDS: *bimetallic catalysts, bispalladacycles, α-cyanoacetate, dehydrogenative cross-coupling, direct cross-coupling, ferrocene, indole, β-ketoalkylations, oxidant-free, platinacycle, ruthenocene*

INTRODUCTION

Cross coupling reactions between aromatic substrates and olefins provide an indispensable tool to construct C−C bonds for both target- and diversity-oriented synthetic applications.[1] The most well-known reaction of this type is the classical Mizoroki−Heck reaction, which is widely utilized in organic synthesis because of its high level of generality.[2] Heck type reactions between arylhalides and allylic alcohols have been intensively investigated in the past to allow for a synthetic access of β-arylketones, avoiding highly electrophilic alkylating reagents such as alkyl halides or vinylketones, which may cause severe safety issues as a result of their toxicity and carcinogenicity.[3] The β-arylketone products are of high synthetic value because the versatile ketone moiety offers a number of possibilities for further functionalization.

A disadvantage of classical Heck type reactions is the need for aromatic halides Ar-X as coupling partners and the resulting generation of HX as a side product that needs to be trapped by stoichiometric amounts of a base. The atom economy is thus not ideal because large amounts of salt waste are generated.[4,5] Recently, an activation strategy has been reported in which leaving groups X on the aromatic rings could be omitted in the generation of β-arylketones.[6] Aromatic C−H bonds could be utilized for Rh-catalyzed dehydrogenative cross-couplings with allylic alcohols.[6a] A pyrimidin-2-yl substituent on the aromatic substrate was used as an ortho-directing group to allow for a sufficient reactivity. To turn over the catalytic cycle, an excess of $Cu(OAc)_2$ (2.1 equiv) was required as an oxidant.

Ideally, dehydrogenative cross-couplings would allow for the direct construction of C−C bonds without the need for stoichiometric reagents, generating H_2 as the only side product.[7] Currently, the number of examples for oxidant-free dehydrogenative C−C coupling reactions via H_2 evolution is, in general, still very much limited, which has been explained by a thermodynamically unfavorable situation.[7] In this context, independent studies by the groups of Wu and Wang, who used Ru or Co and Mn catalysts, respectively, need to be particularly mentioned.[8,9]

Herein, we report the first direct dehydrogenative cross coupling reactions of aromatic substrates Ar−H with allylic substrates, in which there is no need for an additional classical stoichiometric oxidizing agent. In addition ortho-directing groups are also not needed for a sufficient reactivity. The title reaction using allylic alcohol substrates has been accomplished by trimetallic catalytic systems, which make use of the group 10 metals {either [Pt(II)/Pd(II)/(Ni(II)] or $[Pd(II)_2/Ni(II)]$}.[10] The precatalysts studied are either the metallocene-based bisimidazoline[11] bispalladacycles[12] $[FBIP\text{-}Cl]_2$ (**1**)[13,14] and

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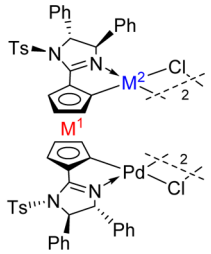
[RuBIP-Cl]$_2$[15] (**2**) (Figure 1) or the related ferrocene-based heterobimetallic pallada-/platinacycle [FBIPP-Cl]$_2$ (**3**).[16] Ni-



M^1 = Fe; M^2 = Pd: **[FBIP-Cl]$_2$ (1)**
M^1 = Ru; M^2 = Pd: **[RuBIP-Cl]$_2$ (2)**
M^1 = Fe; M^2 = Pt: **[FBIPP-Cl]$_2$ (3)**

Figure 1. Metallocene-based bis-metallacycle precatalysts relevant for this study.

$(OAc)_2$ acts as a cocatalyst. Preliminary studies showcase that the discovered reactivity can also be applied to CH-acidic pronucleophiles in enantioselective alkylations.

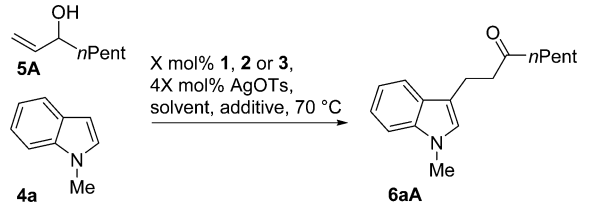
RESULTS

Development of the Title Reaction. Because the dimeric metallocene-based bismetallacycles **1**−**3** usually show nearly no activity in catalytic applications as a result of the quite inert chloride bridges, which hamper an efficient coordination of neutral substrates, typically, these complexes need to be activated by chloride removal, which results in the formation of monomeric complexes.[13b,14f,16] This is readily achieved in quantitative yields by treatment with various different silver salts according to our previously published protocols.[13a,b,14−16]

Because of the prominent role of indoles[17] as bioactive compounds, in our exploratory trials, we investigated the coupling of 1-octen-3-ol (**5A**) with *N*-methylindole (**4a**, Table 1). With 2.5 mol % of **1** (activated by AgOTs/MeCN)[13] in 1,2-dichloroethane (DCE) at 70 °C, the *β*-heteroarylketone **6aA** was formed with promising efficiency in the absence of an additional stoichiometric oxidant (entry 1).[18]

In 2,2,2-trifluoroethanol (TFE) the reaction outcome was similar but with a slightly increased conversion (entry 2). Different Brønsted basic acetate salts, such as NaOAc or [*n*Bu$_4$N]OAc decreased the productivity of the indole alkylation (entries 3−4). Lewis acidic acetate salts usually also did not improve the reaction outcome, with the exception of $Ni(OAc)_2$. In the presence of 20 mol % of $Ni(OAc)_2$, full conversion was observed, and the product was obtained in a yield of 86% (entry 5). In contrast, the homologous $Pd(OAc)_2$ decreased the reaction efficiency (entry 6). $Ni(OAc)_2$ (20 mol %) gave only traces of product in the absence of the bispalladacycle (entry 7).[19] Reducing the $Ni(OAc)_2$ quantity from 20 to 10 mol % in the presence of the bispalladacycle still allowed for a good product yield (entry 8). Reducing the amount of the bispalladacycle precatalyst [FBIP-Cl]$_2$ **1** by a factor of 2 (1.25 mol %) gave a similar result (79% yield, entry 9), whereas with 0.5 mol % of precatalyst, the reaction was found to be less effective (61% yield, entry 10). A comparison of the ferrocene bispalladacycle **1** with the ruthenocene bispalladacycle **2** (entry 11) and the mixed ferrocene pallada-/platinacycle **3** (entry 12) exhibited quite similar productivities in the model reaction.

Table 1. Preliminary Investigations[a]

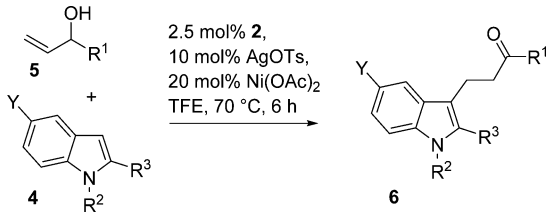


no.	precat.	X	additive (equiv)	solvent	conv. (%)[b]	yield (%)[c]
1	**1**	2.5		DCE	92	65
2	**1**	2.5		TFE	97	66
3	**1**	2.5	NaOAc (0.2)	TFE	54	44
4	**1**	2.5	[nBu$_4$N]OAc (0.2)	TFE	36	33
5	**1**	2.5	$Ni(OAc)_2$ (0.2)	TFE	100	86
6	**1**	2.5	$Pd(OAc)_2$ (0.2)	TFE	100	50
7	**1**	0	$Ni(OAc)_2$ (0.2)	TFE	9	5
8	**1**	2.5	$Ni(OAc)_2$ (0.1)	TFE	100	78
9	**1**	1.25	$Ni(OAc)_2$ (0.2)	TFE	99	79
10	**1**	0.5	$Ni(OAc)_2$ (0.2)	TFE	96	61
11	**2**	2.5	$Ni(OAc)_2$ (0.2)	TFE	87	83
12	**3**	2.5	$Ni(OAc)_2$ (0.2)	TFE	93	85

[a]Ratio **4a**/**5A** = 1:3. [b]Conversion of **4a** determined by ^{1}H NMR using an internal standard. [c]Yield of **6aA** determined by ^{1}H NMR using an internal standard.

Substrate Scope. The reaction conditions shown in Table 1/entry 11 were subsequently applied to different indoles and allylic alcohols (Table 2). The ruthenocene-based bispalladacycle **2** was selected to prepare different *β*-arylketones **6** because it is the most robust of the three investigated precatalysts. The yields of the purified products **6** were usually close to the yields determined by ^{1}H NMR via an internal

Table 2. Application of the Optimized Conditions to Various Indole and Allylic Alcohol Substrates[a]



no.	6	R^1	R^2	R^3	Y	yield (%)[b]
1	**6aA**	*n*Pent	Me	H	H	83 (83)
2	**6bA**	*n*Pent	Et	H	H	71 (69)
3	**6cA**	*n*Pent	Bn	H	H	81 (75)
4	**6dA**	*n*Pent	3-F$_3$CC$_6$H$_4$−CH$_2$	H	H	66 (58)
5	**6eA**	*n*Pent	4-BrC$_6$H$_4$−CH$_2$	H	H	33 (32)
6	**6fA**	*n*Pent	H	H	H	60 (57)
7	**6gA**	*n*Pent	Me	H	OBn	54 (50)
8	**6hA**	*n*Pent	Me	Me	H	90 (90)
9	**6aB**	(CH$_2$)$_2$Ph	Me	H	H	61 (60)
10	**6aC**	*n*Pr	Me	H	H	72 (65)
11	**6aD**	Et	Me	H	H	78 (73)
12	**6aE**	cyclo-Hex	Me	H	H	89 (89)

[a]Ratio **4**/**5** = 1:3. [b]Yield of **6** determined by ^{1}H NMR using an internal standard (in parentheses: yield of isolated **6** after column chromatography).

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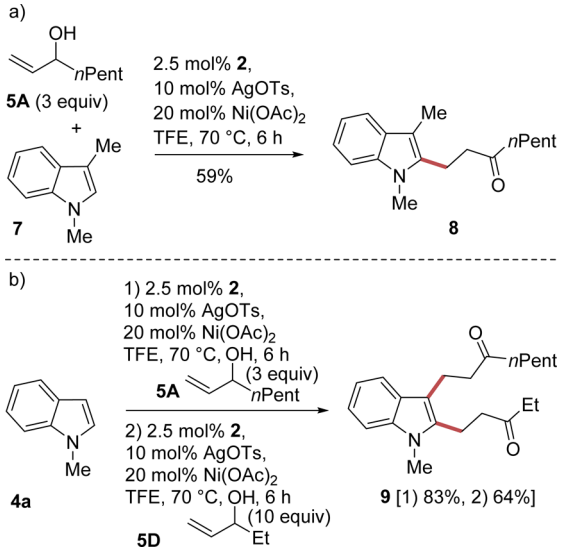
standard, mainly depending on the sometimes limited product stabilities under air atmosphere or on silica gel. In terms of the indoles' N-substituents R^2, different alkyl moieties, such as methyl (entry 1), ethyl (entry 2), benzyl (entry 3),[20] or *m*-(trifluoromethyl)benzyl (entry 4), were well tolerated. Notably, a bromide substituent also was possible on a 4-Br-benzyl residue to afford product **6eA** in moderate yield (entry 5).

This latter result indicates that substrates prone to oxidative addition pathways do not need to be categorically excluded with the bispalladacycle **2**. Noteworthy also is the observation that a N-protecting group on the indole substrate is not strictly required because useful yields were also obtained with the parent indole (entry 6).

With an alkoxy group Y on the indole core, which is a prominent substituent for indoles of pharmaceutical relevance,[17,21] the targeted cross coupling product was also formed in useful yield (entry 7). Substituents R^3 at the indole 2-position were also accepted as displayed in entry 8. Product **6hA** with R^3 = Me was formed in high yield, showing that polysubstituted indoles are accessible via the title reaction. Regarding the allylic alcohol substrates **5**, various α,β-unbranched alkyl substituents R^1 were investigated, and all allowed for similar results (entries 9−11),[22] but an α-branched cyclohexyl residue R^1 was also well tolerated (entry 12). If the indole 3-position is blocked by a substituent, the methodology can also be applied to functionalize the 2-position by a dehydrogenative cross-coupling (Scheme 1a).

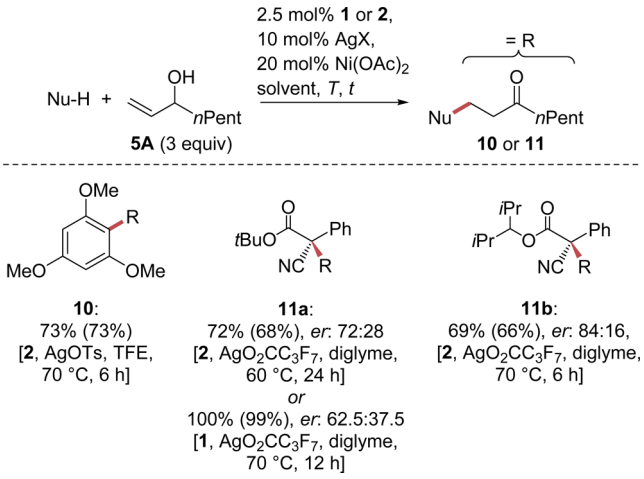
Scheme 1. (a) C−C Bond Formation Using the Indole 2-Position and (b) Sequential Functionalization of the 3- and 2-Positions



It was also found that this latent reactivity of the indole 2-position causes the formation of small amounts of side products during the above-described syntheses of products **6** by formation of the corresponding double alkylation products (typically up to 4%). This reactivity can also be of preparative use for sequential double dehydrogenative cross-couplings (Scheme 1b). In the first step, product **6aA** was prepared from model substrate **4a** and **5A** under standard conditions. The second step made use of a different allylic alcohol (**5D**) in larger excess and formed diketone **9** in a yield of 64%.

To learn more about the possible utility of oxidant-free direct dehydrogenative couplings with allylic alcohols, a few non-indole C-nucleophiles were studied (Scheme 2). The reaction

Scheme 2. Application of the β-Ketoalkylation to Other (Pro)Nucleophiles[a]



[a]Yields were determined by ^{1}H NMR using an internal standard (in parentheses: yield of isolated products after column chromatography).

can also be used for electron-rich aromatic substrates other than indoles, such as 1,3,5-trimethoxybenzene, which provided the isolated product **10** in a yield of 73%.[23] An overalkylation was again largely avoided.

Gratifyingly, the tandem reaction could also be applied to CH-acidic α-cyanoacetate pronucleophiles. In that case, diglyme is a superior solvent, and catalyst activation with silver heptafluorobutyrate resulted in an enhanced reactivity and allowed for a quantitative formation of **11a** within 12 h at 70 °C. These preliminary studies show for the first time that enantiocontrol is, in principle, also possible for oxidant-free dehydrogenative couplings. Compound **11b** with a sterically demanding ester group was formed in good yield and with a promising enantiomeric ratio of 84:16, making use of a dynamic kinetic resolution of racemic starting material.

The precatalysts **1** and **2** (identified by ^{1}H NMR and ESI-MS; the activated palladacycles often act as a trap for chloride traces upon reisolation, see e.g. ref 14i) could both be reisolated in good yields (~80%) by a simple filtration of the reaction mixture over silica gel. This shows that the catalyst is relatively stable under the reaction conditions. In addition, the enantioselectivity obtained for **11** indicates that the palladacycles used do not lose their structural identity in the catalytic cycle and keep their coordination shell bearing the chiral ligand at the metal centers. Optimization of the enantioselectivity and the investigation of the scope of applicable substrates for catalytic asymmetric reactions are currently ongoing in our group.

Control Experiments. A direct dehydrogenative cross-coupling employing an allylic alcohol substrate should involve the generation of a metal hydride species at one point of the catalytic cycle, either by a Heck-type reaction pathway[6] or by oxidation of the allylic alcohol to the corresponding enone via a β-H-elimination.[24,4,5] To investigate the fate of the allylic alcohol **5A**, the standard reaction conditions were applied to the allylic alcohol in the absence of the nucleophile (Table 3). Using 2.5 mol % of **1** activated by 10 mol % of AgOTs,

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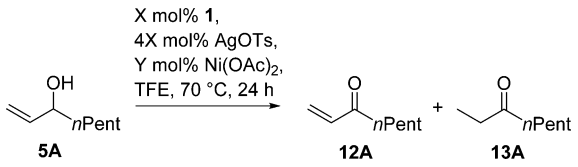
Table 3. Control Experiment in the Absence of a Nucleophile



5A 12A 13A

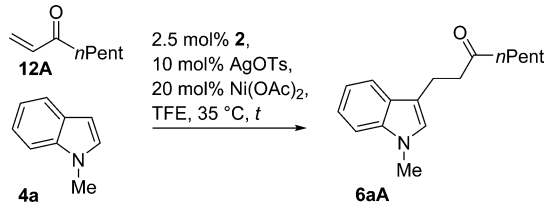
no.	X	Y	yield **12A** (%)[a]	yield **13A** (%)[a]
1	2.5	10	12	55
2	2.5	0	6	40
3	0	10	0	0

[a]Yield determined by ^{1}H NMR using an internal standard.

vinylketone **12A** and ethylketone **13A** had been formed in yields of 12% and 55%, respectively, after a reaction time of 24 h (entry 1). Repetition of this experiment in the absence of $Ni(OAc)_2$ provided similar results (entry 2). In contrast, using 10 mol % of $Ni(OAc)_2$ in the absence of the bismetallacycle, the formation of neither **12A** nor **13A** was observed (entry 3). The major catalyst for an oxidation of the allylic alcohol is thus the bismetallacycle, and $Ni(OAc)_2$ should support this event.

These results suggest that the allylic alcohol **5** is first oxidized into a vinylketone **12**, which is the active electrophile in the coupling with a nucleophilic indole. Oxidation of the allylic alcohol **5** to the vinylketone **12** via a β-hydride elimination and a subsequent hydrogenation of the vinylketone to an ethylketone **13** by insertion of the C=C double bond into a Pd−H species, followed by protonolysis, would also be an explanation why an excess of allylic alcohol (3 equiv) was usually required for high reaction yields. To confirm the assumption that vinylketones **12** are involved as the electrophilic component, indole **4a** was directly treated with vinylketone **12A** at a reaction temperature of only 35 °C under otherwise unchanged reaction conditions (Table 4).

Table 4. Control Experiment Using a Vinylketone Substrate[a]



12A 4a 6aA

no.	t (min)	yield **6aA** (%)[b]
1	1	24
2	5	48
3	10	64
4	180	87[c]

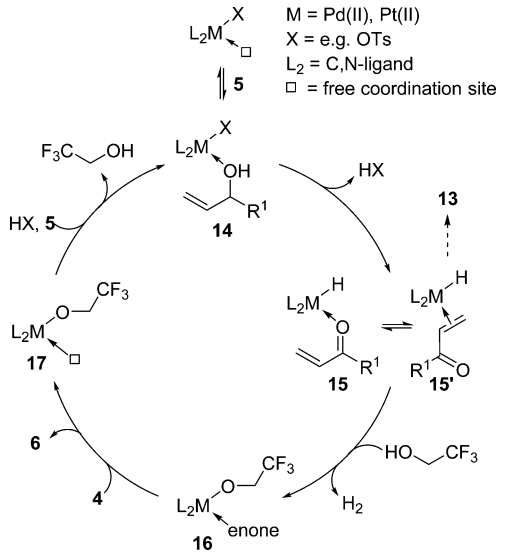
[a]Ratio **4**:**5** = 1:3. [b]Yield determined by ^{1}H NMR using an internal standard. [c]In addition, the corresponding double alkylation product was formed in 13% yield.

Despite the much lower reaction temperature the reaction product **6aA** was formed very rapidly.[25] After 1 and 10 min, 24% and 64%, respectively, of **6aA** were already detected (entries 1 and 3).[26]

DISCUSSION

A Pd−H species such as **15** or **15′**, which is assumed to be formed by oxidation of the allylic alcohol substrate **5** via β-hydride elimination, might be trapped by protonolysis with trifluoroethanol (or the allylic alcohol in an aprotic solvent) to form the corresponding Pd(II)-alkoxide intermediate, such as **16** (Scheme 3).[27−29] Nucleophilic attack of the indole **4** at the

Scheme 3. Possible Simplified Mechanism with Release of H_2



activated enone could then form the coupling product. Release of TFE and coordination of another allylic alcohol substrate molecule would close the catalytic cycle.

Analysis of the crude product mixtures by GC-MS and ^{1}H NMR revealed the generation of saturated alcohols **20** in yields ranging from 0 to 78%, based on 1 equiv of the indole substrates **4** for the reactions shown in Table 2 (yields of 0−26% based on allylic alcohols **5**). Compound **20** should be formed by hydrogenation of the allylic alcohol substrates **5**. A possible catalytic cycle to rationalize this result is depicted in Scheme 4. This alternative scenario might be an additional explanation why a relatively large excess of the allylic alcohol is required for high reaction efficiency.

The bismetallacycles were also compared with structurally related monopallada-[30] or -platinacycles[11c] **21** and **22**, respectively (Scheme 5). With increased catalyst loadings to achieve the same amount of a noble metal present as with **1**−**3**, only poor to low activity was noticed under the standard reaction conditions.

In addition, the use of $Pd(OAc)_2$ and $(MeCN)_2PdCl_2$ was examined. Under typical reaction conditions (in the presence of 20 mol % of $Ni(OAc)_2$) using 5 and 10 mol % of $(MeCN)_2PdCl_2$, **6aA** was again formed in poor yields (10 and 25%, respectively). Reactions with $Pd(OAc)_2$ instead resulted in low reproducibility and, in most cases, provided varying product yields in a range of 30−40%. Addition of 10 mol % of AgOTs as a cocatalyst did not change this outcome. These data indicate that bismetallacycles with M = Pd(II) or Pt(II) offer a distinct reactivity advantage in the title reaction as compared with simple Pd(II) salts. A bimetallic precoordination of the allylic alcohol substrate might, for example, facilitate the vinylketone formation. Similar reactivity differences have already been noticed for rearrangements of allylic imidates and were explained by an increased binding affinity of the substrates due to bimetallic precoordination.[16]

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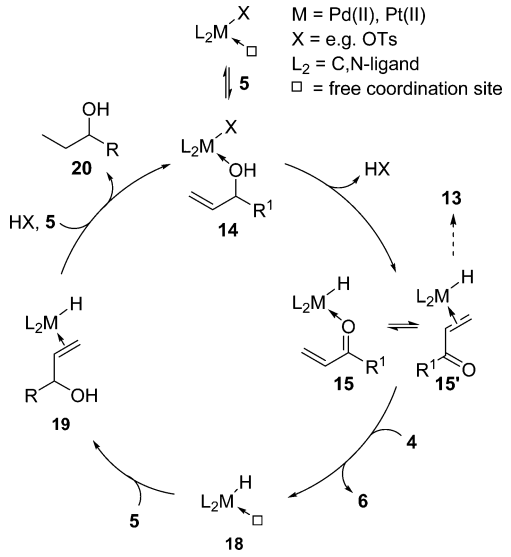
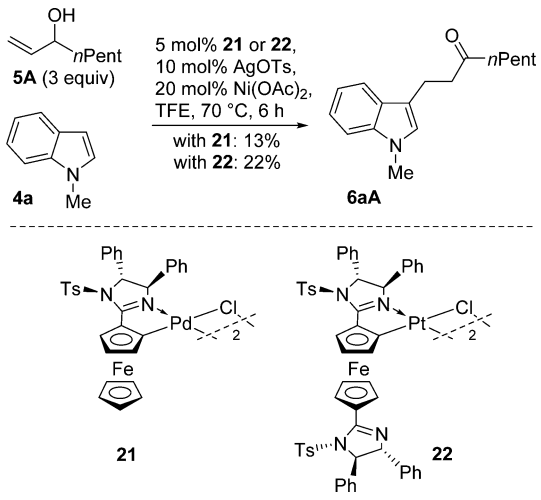
Scheme 4. Alternative Simplified Mechanism in Which Allylic Alcohol 5 Also Serves As a Sacrificial Hydrogen Acceptor



Scheme 5. Control Experiments with Ferrocene Monopalladacycle 21 and Monoplatinacycle 22



The observation that $Ni(OAc)_2$ improves the reaction efficiency might have various reasons, and the precise role of Ni(II) is not yet clear. In the catalytic cycle shown in Scheme 3, protonolysis of the M-H species is assumed to be a critical event. We hypothesize that $Ni(OAc)_2$ might facilitate the protonolysis step, for example, via an acetate-bridged M/Ni−H complex.[28] Such a Ni−H species might also be responsible for hydrogenation of the allylic alcohol.

CONCLUSION

In conclusion, we have reported the first direct dehydrogenative cross-couplings of aromatic substrates with allylic alcohols to form β-arylketones without the need for an additional classical oxidant. These reactions do not require an ortho-directing group. Metallocene-based bispalladacycles or mixed pallada-/platinacycles were identified as competent catalysts and are significantly more active than related monopallada- or -platinacycles. Control experiments suggest that the coupling initially proceeds via conversion of the allylic alcohols into vinylketone intermediates. The latter subsequently rapidly react with an indole substrate in the presence of the catalyst. The fact that there is no need for an additional stoichiometric oxidizing agent might be explained by protonolysis of a M(II)−H intermediate by either a protic solvent or the substrate OH groups. Because significant amounts of fully saturated alcohols are also formed, the allylic alcohol substrates might probably also act as sacrificial H_2 acceptors. The reactions are supported by cocatalytic amounts of $Ni(OAc)_2$, but the precise role of the Ni salt is not clear yet. Preliminary studies have also shown that the reactivity of the catalytic system can be transferred to prochiral racemic CH-acidic pronucleophiles, such as α-cyanoacetates, providing the tandem reaction products in enantioenriched form. These are the first catalytic asymmetric examples for enantioselective direct dehydrogenative couplings via allylic alcohol electrophiles without the need for an additional classical oxidant. These findings pave the way for future investigations in asymmetric catalysis.

EXPERIMENTAL SECTION

General Considerations. All reactions were performed in oven-dried (150 °C) glassware under a positive pressure of nitrogen (about 0.2 bar). For all reactions, liquids and solutions were added via syringes and septa. For catalysis, all glassware used (also for catalyst activation and preparation of stock solutions) was washed intensively with demineralized water to remove traces of chloride. *N*,*N*-Dimethylformamide was stored in crown-capped bottles under argon over 4 Å molecular sieves. Acetonitrile and dichloromethane were purified by distillation and subsequently by a solvent purification system. 2,2,2-Trifluoroethanol was dried and degassed prior to use. For workup procedures and column chromatography, technical grade solvents (petrol ether and ethyl acetate) were purified by distillation prior to use. Solvents were mostly removed at a heating bath temperature of 40 °C and 600−10 mbar pressure by rotary evaporation. Nonvolatile compounds were dried in vacuo at 0.1 mbar.

If not stated otherwise, yields refer to chromatographically purified compounds and are calculated in mole percent of the used starting material. Catalytic reactions were carried out in a parallel synthesizer at 400 rpm. For thin layer chromatography, silica gel plates were used. Visualization occurred by fluorescence quenching under UV light, by staining with $KMnO_4$/NaOH followed by heating (230 °C), or both. Purification by flash chromatography was performed on silica gel 0.040−0.063 mm using a forced flow of eluent at 0.2−0.4 bar pressure.

General Procedure for the Catalytic Direct Dehydrogenative Cross-Couplings. The respective chloride-bridged precatalyst dimer **1-3** (1.00 equiv) and silver tosylate (4.00 equiv) were dissolved in MeCN (0.2 mL/mg) under nitrogen atmosphere. The mixture was stirred overnight at room temperature and subsequently filtered through Celite. The filtercake was extracted with MeCN until the organic solution was colorless. The solvent was removed by a steady stream of nitrogen and, finally, by high vacuum. A stock solution of the activated catalyst was prepared by dissolving the solid in dry, degassed TFE (40 mmol/L).

This stock solution was then used to add the activated catalyst (prepared from 2.5 mol % of precatalyst) to the nucleophile (0.16 mmol, 1.00 equiv), the allylic alcohol **5** (0.48 mmol, 3.00 equiv), and $Ni(OAc)_2$ (0.03 mmol 20 mol %) under a nitrogen atmosphere. The reaction tube was sealed and

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the reaction mixture was shaken at 400 rpm for 6 h at 70 °C. The reaction mixture was afterward suspended in petrol ether/ethyl acetate (10:1) and subsequently purified by filtration over silica gel.

■ ASSOCIATED CONTENT

Supporting Information

The following files are available free of charge on the ACS Publications website at DOI: 10.1021/cs501495g.

Experimental procedures, characterization data for all new products (PDF)
Crystallographic information file for $C_{23}H_{27}NO$ (CIF)
Crystallographic information file for $C_{27}H_{26}O_4$ (CIF)

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Notes

The authors declare no competing financial interest.

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(20) The constitution of **6cA** was confirmed by X-ray crystal structure analysis. Supplementary crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as deposition 1016528. This material is available free of charge via the Internet at http://www.ccdc.cam.ac.uk/products/csd/request/.
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(27) Protonolysis of metal hydride species has also been suggested for the oxidant-free dehydrogenative couplings reported by Wang (Mn-H, ref 8c) and Yang (Cu-H, ref 9).
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