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Transition Metal and Hydrogen Bond Donor Hybrids: Catalysts for the Activation of Alkylidene Malonates

David M. Nickerson and Anita E. Mattson*[a]

Advances within synthetic organic chemistry have largely led to the development of transition metal catalysis and organic catalysis into two distinct catalyst systems.[1,2] The combination of these two catalyst systems is a relatively recent, new direction enabling access to useful bond-forming processes that are inaccessible with either catalyst system alone.[3,4] Driven by the advantageous prospect of combined catalyst systems, we anticipated the design of hybrid catalysts: single molecules containing both transition metal *and* organocatalytic sites. More specifically, we reasoned that the strategic merger of transition metals and hydrogen bond donor (HBD) catalysts would present opportunities for the development of single catalyst systems benefitting from enhanced activity and unprecedented reactivity. This account describes the successful and strategic incorporation of palladium into a urea scaffold to generate urea palladacycle catalysts (**1**) for the activation of alkylidene malonates.

The inspiration for the development of urea palladacycle catalysis grew from the separate and exceptional successes in the catalytic development of the two key components: palladium and the hydrogen bonding functionality of the urea. Individually, the fields of palladium catalysis and urea catalysis have allowed significant advances in synthetic chemistry, and we reasoned a hybrid palladium–urea catalyst might offer an opportunity to coalesce the best of both fields. Our urea palladacycle design (**1**) was inspired by boronate ureas (Figure 1), a recently disclosed family of tunable urea catalysts that exhibit enhanced activity when compared with conventional urea catalysts.[5–7] This improvement in activity is proposed to arise from the increased polarization of the urea functionality as a result of internal Lewis acid coordination. We speculated that similarly placed transition metals on the urea scaffold would give rise to hybrid catalysts with interesting reactive properties. We were particularly excited to explore several specific features of our new hybrid catalysts including: 1) enhanced hydrogen bond donor catalyst activity; 2) tunable ligands and their effect on catalyst reactivity; 3) ease of preparation; 4) stability, and 5) the promising nature of future, bifunctional catalysis involving the enhanced hydrogen bonding site *and* the transition metal center. To explore the promise of urea palladacycles as a new family of hybrid catalysts, we set out to probe their ability to catalyze the conjugate addition of indole to alkylidene malonates.

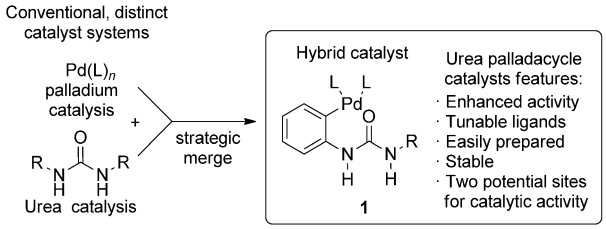

Figure 1. Urea palladacycles as hybrid transition metal and hydrogen bond donor catalysts.

The activation of alkylidene and arylidene malonates for nucleophilic attack is a useful synthesis technique typically achieved with traditional Lewis acid catalysts like $Cu(OTf)_2$.[8] Conventional ureas and thioureas, although easily able to activate nitroalkenes[9] (**2**) and α,β-unsaturated imides[10] (**3**) through proposed hydrogen bonding interactions, have rarely been reported as catalysts for alkylidene malonate (**4**) activation (Figure 2).[11] These few reports rely on bifunctional urea or thiourea catalysts that may operate to activate both the nucleophile and electrophile; no simple ureas have been reported in the activation of alkylidene malonates. Prompted by this lack of reactivity, we considered this process an ideal testing ground to study urea palla-

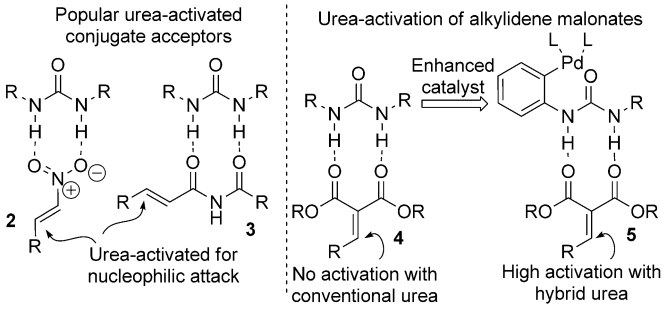

Figure 2. Urea palladacycle hybrid catalysts for the activation of alkylidene malonates.

[a] D. M. Nickerson, Dr. A. E. Mattson
Department of Chemistry, The Ohio State University
100 W. 18th Ave., Columbus, OH 43210 (USA)
Fax: (+1) 614-292-1685
E-mail: mattson@chemistry.ohio-state.edu

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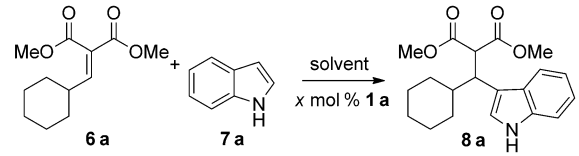
dacycle catalysis. If our hypothesis that urea palladacycles would have enhanced activity compared to conventional ureas held true, then we would be able to effect a transformation that is difficult to achieve with traditional urea and thiourea catalysts, such as the activation of alkylidene malonates (**5**). With this in mind, investigations were initiated by using urea palladacycles (**1**) as enhanced HBDs to catalyze the addition of indoles (**7**) to alkylidene malonates (**6**).

Our early studies focused on the addition of indole (**7a**) to dimethyl 2-(cyclohexylmethylene)malonate (**6a**) in the presence of 15 mol% urea palladacycle (**1a**, Table 1). The palladacycle (**1a**) was rapidly synthesized in gram quantities by using procedures adapted from the literature.[12,13] Initial results confirmed the formation of the desired bonds and after optimization of the reaction conditions, a 69% yield of desired product **8a** was observed after 24 h at 50°C in toluene (entry 1). The proposed mode by which **1a** activates **6a** is through hydrogen bonding to the 1,3-dicarbonyl functionality, perhaps through a species similar to that depicted as **9**.

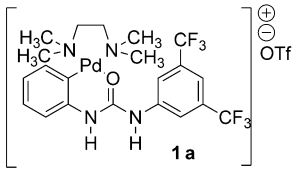
Solvent effects were substantial in this process. After achieving only modest yields with chloroform and dioxane (47 and 72%, respectively, entries 2 and 3), methanol was found to provide nearly quantitative yields of **8a** (99%, entry 4). At this time we propose that the dramatic solvent effects are linked to catalyst solubility: the catalyst is sparingly soluble in aprotic solvents, such as chloroform, 1,4-dioxane and toluene, whereas the urea palladacycle is easily dissolved in methanol. With an excellent solvent identified, a control experiment to determine the background reaction rate in optimized conditions showed no observable reactivity of the alkylidene malonate with indole nucleophile in the absence of **1a** (entry 9). Convinced that our palladacycle urea was indeed catalyzing the reaction, we proceeded to investigate the limits of the reaction with respect to catalyst loading. Reducing the loading of **1a** by half to 7.5 mol% afforded a 91% yield of **8a** after 24 h (entry 5). Even just 2.5 mol% of **1a** gave rise to a 70% yield of **8a** after 72 h (entry 8). Given adequate time for completion, reactions at room temperature also proceeded in high yield with higher catalyst loadings serving to decrease reaction times. For example, at 20 mol%, a reaction at 23°C gave a 98% isolated yield after 96 h (entry 11).

A survey of several catalysts revealed that ligands play an important role in the reactivity of urea palladacycle catalysts

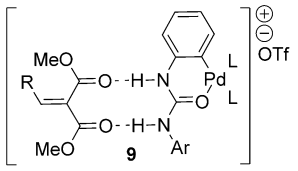
Table 1. Optimization of reaction conditions for the addition of indole to alkylidene malonates catalyzed by urea palladacycle **1a**.[a]



Urea palladacycle catalyst:



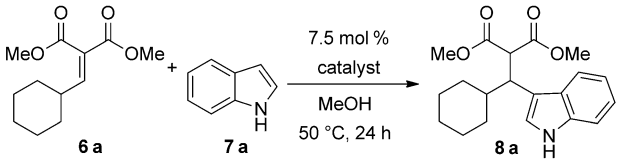
Proposed mode of action:

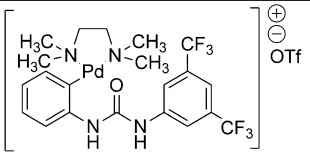
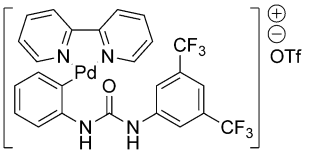
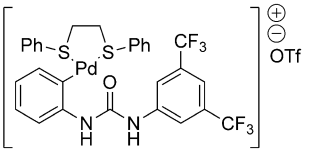
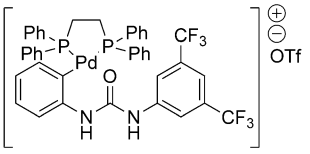
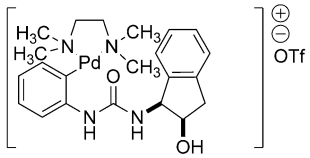


Entry	**1a** [mol%]	Solvent	*T* [°C]	*t* [h]	Yield [%][b]	
1	15	toluene	50	24	69	
2	15	$CHCl_3$	50	24	47	solvent screen
3	15	1,4-dioxane	50	24	72	
4	15	MeOH	50	24	99	
5	7.5	MeOH	50	24	91	
6	5	MeOH	50	24	82	
7	5	MeOH	50	48	92	catalyst loading study
8	2.5	MeOH	50	72	70	
9	0	MeOH	50	24	0	
10	20	MeOH	23	48	63	
11	20	MeOH	23	96	98	RT example

[a] Reactions were performed by using 1.5 equiv indole at a concentration of 2 M; see the Supporting Information for detailed experimental procedures. [b] Isolated yield.

Table 2. Optimization of reaction conditions for the addition of indole to **6a** catalyzed by urea palladacycles (**1**).[a]



Entry	Catalyst		Yield [%][b]
1		**1a**	91
2		**1b**	6[c]
3		**1c**	NR
4		**1d**	24
5		**1e**	15[c]

[a] Reactions were performed by using 1.5 equiv indole at a concentration of 2 M; see the Supporting Information for detailed experimental procedures. [b] Isolated yield unless otherwise noted. [c] Yield obtained by ^{1}H NMR spectroscopy analysis.

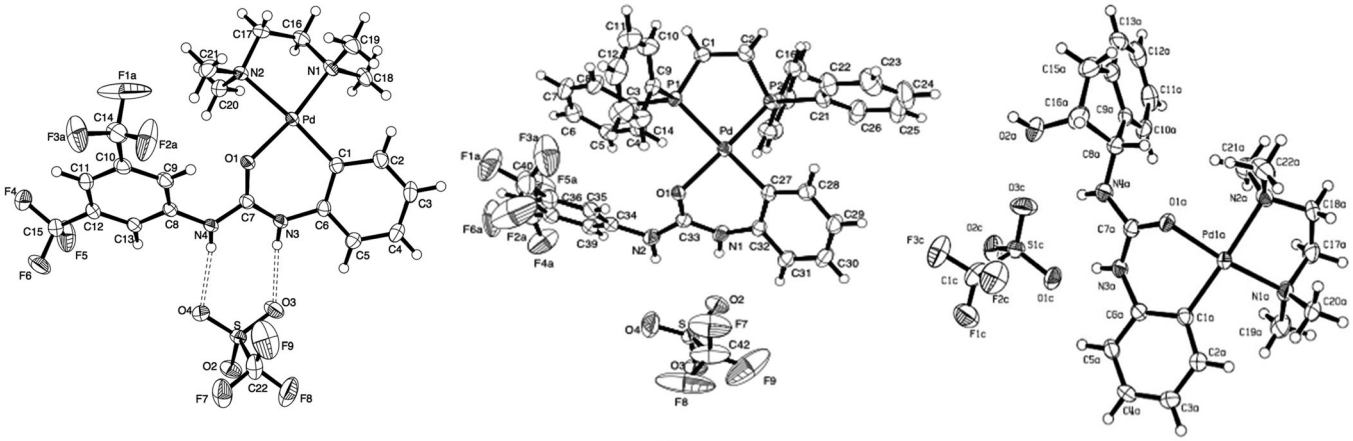
in the addition of indole to **6a** (Table 2). A series of urea palladacycles containing various ligands including 2,2,-bipyridine (**1b**), 1,2-bis(phenylthio)ethane (**1c**), and 1,2-bis(diphenylphosphino)ethane (DPPE, **1d**) were prepared and compared as catalysts (entries 2–4). Ureas **1b** and **1d** gave rise to low yields of product **8a**, 6 and 24% yields, respectively, whereas **1c** resulted in no reaction after 24 h in methanol at 50°C. A chiral urea palladacycle derived from *cis*-aminoindanol was also examined and found to afford low yields of **8a** after 24 h at 50°C; this suggests that the bistrifluoromethylphenyl substituent on the urea working along with the internal palladium coordination is critical for optimal catalyst activity (15%, entry 5).[13] Initial attempts to promote enantioselective reactions by using chiral **1e** were not successful.

The comparison of crystal structures of **1a** and **1d** helped us gain a better understanding of the properties of the newly designed urea palladacycle catalysts (Figure 3).[14] Of particular interest is the length of the urea carbonyl as it can be correlated to the urea polarization due to internal Lewis acid coordination. The urea carbonyl length is slightly longer in TMEDA catalyst **1a** (1.258 Å) versus that of DPPE catalyst **1d** (1.255 Å). Interestingly, these lengths fall between those of a conventional urea (about 1.23 Å)[15] and a boronate urea (about 1.28 Å).[6] A more significant difference between **1a** and **1d** exists when comparing the Pd–O bond lengths (2.023 vs. 2.108 Å, respectively). Chiral urea palladacycle **1e** crystallized as two unique palladacycle complexes within the asymmetric unit. Its carbonyl bond lengths were close to that of **1a** (1.259 and 1.257 Å) and its Pd–O bond lengths were in between those of **1a** and **1d** (2.029 and 2.037 Å).[14]

Studies to probe the role of the palladium Lewis acid and its effect on urea activity in the conjugate addition reaction were initiated next (Scheme 1). An experiment directly comparing palladacycle **1a** with traditional HBD urea catalysts (**10** and **11**) revealed that no reaction occurred with 20 mol% of **10** or **11** in otherwise identical reaction conditions. Clearly, palladium was playing a major role in catalyst reactivity.

In order to support our proposed HBD mode of action (**9**), we synthesized methylated control ureas **1f** and **1g** (Scheme 1). We were surprised to see that **1f**, with only a single available hydrogen-bonding site, still promoted the reaction, albeit with reduced reactivity. This result initially suggested the possibility that palladium could be playing a role as a Lewis acid in its own right; however, testing **1g**, a homologous control urea with no hydrogen bond capabilities resulted in no observable reaction. These results suggest that N–H urea components are necessary for catalysis and that the reactive intermediate, though benefitting from a dual hydrogen bond interaction, is also viable with a single hydrogen bond event.[16] Alternative explanations for the variations in observed catalytic activity of **1a**, **1f** and **1g**, such as conformational constraints present in dimethylated **1g** but not **1a** and **1f**, have not been explicitly ruled out at this time and are the source of ongoing studies in our laboratory. All of our attempts to catalyze the reaction with various Pd^{II} sources or triflic acid resulted in no observed addition products.[14]

With new urea palladacycle **1a** operating catalytically under the optimized reaction conditions, we set out to determine how tolerant the process would be with respect to different alkylidene and arylidene malonates (Table 3). A substrate scope of various conjugated diesters derived from dimethyl malonate were prepared and tested. Substrates derived from aliphatic aldehydes (i.e., cyclohexanecarboxaldehyde, hexanal and hydrocinnamaldehyde) provided excellent yields of desired product (>90%) after 24 h with 10 mol% of **1a** (entries 1–3). Diesters derived from aromat-

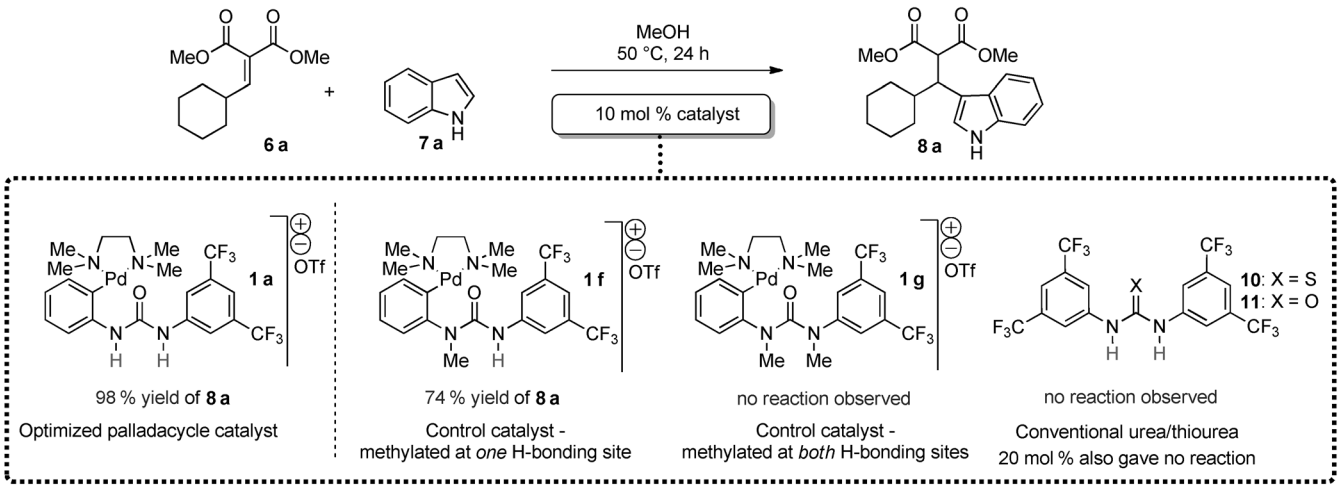


1a
Key bond lengths:
C=O: 1.258(2) Å
Pd–O: 2.023(1) Å

1d
Key bond lengths:
C=O: 1.255(3) Å
Pd–O: 2.108(2) Å

1e
Key bond lengths:
C=O: 1.259(4); 1.257(4) Å
Pd–O: 2.029(2); 2.037(2) Å

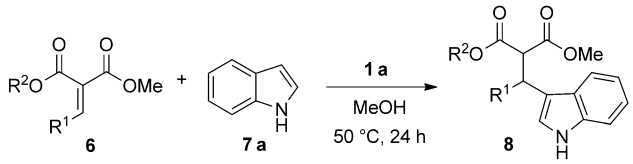
Figure 3. ORTEP representations of **1a**, **1d** and **1e**. Ellipsoids are displayed at 50% probability. For **1e**, only one complex from the asymmetric unit is shown.[13]

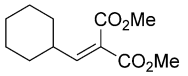
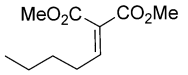
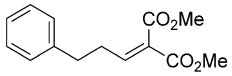
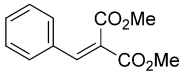
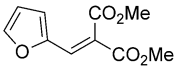
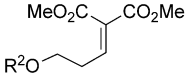
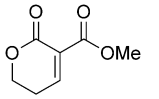
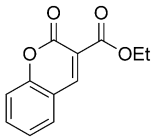


Scheme 1. Control experiments support the enhanced HBD activity of catalyst **1a**.

ic aldehydes were more sluggish in the reactions. A benzaldehyde-derived diester gave rise to 46% of **8d** after 24 h at a 20 mol% loading, whereas the 2-furfural derivative provided a 42% yield of product **8e** at 20 mol% loading (entries 4 and 5). Alkylidene malonates containing alcohols protected with *p*-methoxybenzyl (PMB) or *tert*-butyldimethylsilyl (TBS) were successfully incorporated into the process giving rise to the desired adducts **8f** and **8g** in excellent yields (entry 6). The addition of indole to lactones **6h** and **6i** occurred in excellent yield affording product **8i** and **8j** as >20:1 mixture of diastereomers favoring a *trans* relationship between the two stereocenters (entries 7 and 8).

Table 3. Survey of reaction scope with respect to electrophile **6**.[a]



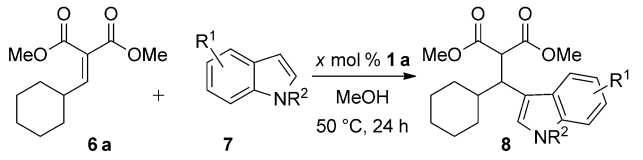
Entry		Substrate	Product	**1a** [mol%]	Yield [%][b]
1	**6a**		**8a**	10	98
2	**6b**		**8b**	10	94
3	**6c**		**8c**	10	98
4	**6d**		**8d**	20	46
5	**6e**		**8e**	20	42
6	**6f**, R^2 = PMB **6g**, R^2 = TBS		**8f** **8g**	10 10	94 96
7	**6h**		**8h**	10	94[c]
8	**6i**		**8i**	20	87[c]

[a] Reactions were performed by using 1.5 equiv indole at a concentration of 2 M; see the Supporting Information for detailed experimental procedures. [b] Isolated yield unless otherwise noted. [c] 20:1 diastereoselectivity.

Reaction scope screening was continued with a survey of nucleophilic heterocycles by assessing a variety of substituted indoles for reactivity in the new urea catalyzed process (Table 4). Excellent yields of product were obtained with most substituted indoles. *N*-Methylindole operated well as a nucleophile, requiring just 5 mol% of **1a** to yield 82% of **8j** after 24 h in methanol (entry 2). Electron-rich 5-methoxyindole gave rise to 90% of **8k** after 24 h in methanol (entry 3). As expected, less electron-rich species, such as 5-chloroindole and methyl indole-4-carboxylate, required either longer reaction times or higher catalyst loadings to perform similarly to more electron-rich species (entries 4 and 5).

In summary, urea palladacycles have been disclosed as a hybrid class of organometallic hydrogen bond donors benefitting from enhanced activity. The improved activity of urea palladacycles over conventional urea and thiourea hydrogen bond donor catalysts has enabled the activation of alkylidene malonates for nucleophilic attack by indoles. The activation of alkylidene malonates has not previously been achieved with conventional urea catalysts. We are excited about the promise of metallic–hydrogen bond donor hybrid catalysts and we look forward to reporting results from our ongoing efforts dedicated toward exploring their potential as bifunctional catalysts.

Table 4. Survey of reaction scope with respect to indoles **7**.[a]



Entry	7	Product	**1a** [mol %]	Yield [%][b]
1	indole	**8a**	10	98
2	*N*-methylindole	**8j**	5	82
3	5-methoxyindole	**8k**	10	90
4	5-chloroindole	**8l**	15	87
5	methyl indole-4-carboxylate	**8m**	20	58[c]

[a] Reactions were performed by using 1.5 equiv indole **7** at a concentration of 2 M; see the Supporting Information for detailed experimental procedures. [b] Isolated yield. [c] 48 h reaction time.

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Keywords: alkylidene malonate · catalysis · hydrogen bond donor · organocatalysis · palladacycles

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[3] For recent reviews see: a) C. Zhong, X. Shi, *Eur. J. Org. Chem.* **2010**, 2999; b) H. Zhang, Z. Shao, *Chem. Soc. Rev.* **2009**, *38*, 2745.

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[5] Difluoroboronate ureas as enhanced urea catalysts have been previously reported, see: a) S. S. So, T. J. Auvil, V. J. Garza, A. E. Mattson, *Org. Lett.* **2012**, *14*, 444; b) S. S. So, J. A. Burkett, A. E. Mattson, *Org. Lett.* **2011**, *13*, 716.

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