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Title: Tunable Triazole-Phosphine-Copper Catalysts for the Synthesis of 2-Aryl-1H-benzo[d]imidazoles from Benzyl Alcohols and Diamines by Acceptorless Dehydrogenation and Borrowing Hydrogen Reactions

Authors: Zhaojun Xu, Duo-Sheng Wang, Xiaoli Yu, Yongchun Yang, and Dawei Wang

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Tunable Triazole-Phosphine-Copper Catalysts for the Synthesis of 2-Aryl-1*H*-benzo[d]imidazoles from Benzyl Alcohols and Diamines by Acceptorless Dehydrogenation and Borrowing Hydrogen Reactions

Zhaojun Xu,[a] Duo-Sheng Wang,[b] Xiaoli Yu,[a] Yongchun Yang,[a] Dawei Wang*[a]

[a] Key Laboratory of Synthetic and Biological Colloids, Ministry of Education, School of Chemical and Material Engineering, Jiangnan University, Wuxi 214122, Jiangsu Province, China. E-mail: wangdw@jiangnan.edu.cn
[b] Department of Chemistry, University of Chicago, 5735 S. Ellis Avenue, Chicago, IL 60637, USA.

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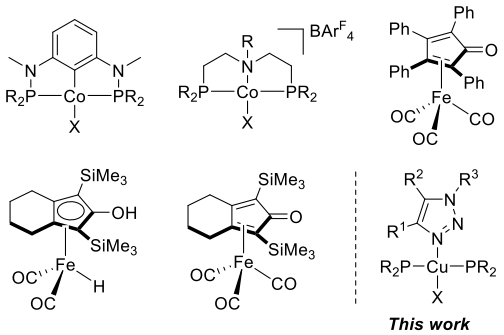
Abstract. Triazole-phosphine-copper complexes (TAP-Cu) have been synthesized and applied as tunable and efficient catalysts for the selective synthesis of fluoro-substituted 2-aryl-1*H*-benzo[d]imidazole and 1-benzyl-2-aryl-1*H*-benzo[d]imidazole derivatives from simple alcohols in only one step. TAP-Cu exhibited excellent and tunable catalytic activity for both dehydrogenation and borrowing hydrogen reactions with more than 80 examples being demonstrated for the first time. It was observed that the ligand played a critical role in catalyst activity. Mechanistic studies and deuterium labeling experiments indicated that the reactions proceeded by an initial and reversible alcohol dehydrogenation resulting in a copper hydride intermediate. This was also supported by the direct observation of a diagnostic copper hydride signal by solid-state infrared spectroscopy. The TAP-Cu-H complex showed absorptions at 912 cm^{-1} that could be assigned to copper–hydride stretches. Furthermore, the direct trapping of an intermediate bisimine was also successfully performed.

Keywords: triazole; copper; alcohols; dehydrogenation; borrowing hydrogen

Borrowing hydrogen and dehydrogenation reactions have become an effective tool in organic synthesis and medicinal chemistry. Moreover, this strategy can provide an easy and convenient route to an abundance of natural compounds and pharmaceuticals from simple alcohols and amines.[1] It has been demonstrated that catalysts such as palladium, ruthenium, iridium and rhodium can perform a host of dehydrogenation and borrowing hydrogen reactions. Beller,[2] Milstein,[3] Williams,[4] Krische,[5] Li,[6] Zhang,[7] Xu,[8] Yu[9] and Shi[10] *et al.* have greatly expanded and advanced this area of research.[11,12] Recently, Kirchner and co-workers[13] concluded that inexpensive metals, such as Fe, Co, Cu, Mn (Figure 1), which are highly economic and promising catalysts, were much less developed.[14] In 2015, Kempe and co-workers described the alkylation of aromatic amines through a borrowing hydrogen reaction with a new Co-catalyst containing a PNP pincer ligand.[15a] Hanson,[16] Zhang[17] and Kirchner also proved that cobalt could catalyze borrowing hydrogen reactions. Meanwhile, Saito,[18] Feringa and Barta,[19] Wills[20] and Zhao[21] reported that iron is effective for the classical borrowing hydrogen strategy. In 2009, Beller and Shi successfully performed the copper-catalyzed alkylation of sulfonamides with alcohols in excellent yields. They revealed that bis-sulfonylated amidines served as novel and highly influential ligands.[22] Li, Xu, Yus and Ramón have also disclosed some important results in this area.[23] Recently, Liu and Huang revealed that potassium *tert*-butoxide is necessary for the generation of the active catalyst using $Cu(OAc)_2$, which suggested that ligand or additive plays an important role in copper-catalyzed borrowing hydrogen reactions.[24]

Figure 1. Inexpensive metal catalysts for the borrowing hydrogen reaction



During the past several years, we found that triazole oxazole and thiazole are effective ligands to adjust reaction activity at a metal center.[25,26] It was observed that the reactivity and chemoselectivity of catalysts were dramatically changed and often enhanced through the use of azole ligands. Recently, we developed several iridium complexes based on benzoxazoles and benzothiazoles, which were effective catalysts for the borrowing hydrogen reaction.[26] However, for the synthesis of biologically active benzimidazole derivatives,[27,28] we found that these iridium catalysts couldn't be used for a dehydrogenative approach. Furthermore, benzimidazole derivatives exhibit excellent biological activity (Figure 2), such as antifungal, antiallergenic, insecticidal, herbicidal, anti-inflammatory,

anti-histaminic and potential anthelmintic activities.[28] Therefore, we turned our focus to searching for an effective approach to realize their synthesis through the implementation of triazole ligands within economic metal-complexes.

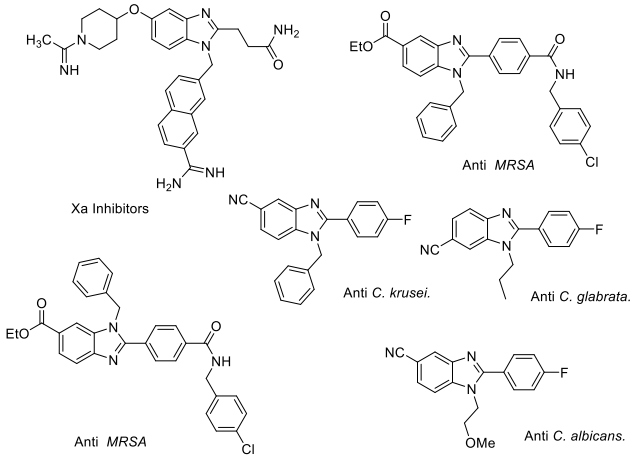
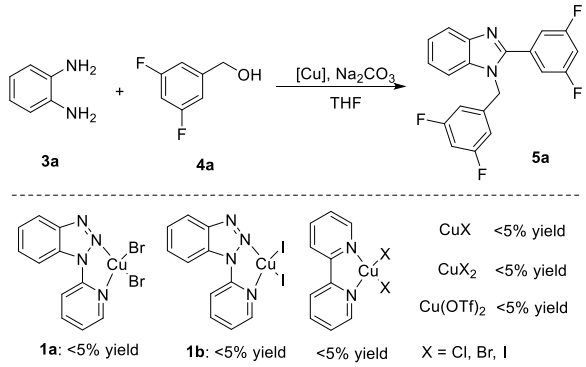


Figure 2. The biological benzoimidazole derivatives.

In the outset, several triazole copper complexes were synthesized in good yields from triazole and simple copper salts. When these triazole-copper complexes were used to catalyze the synthesis of 1-benzyl-2-aryl-1*H*-benzo[d]imidazole, no desired product was achieved, which might be caused by the strong coordinating ability and strong electron withdrawing properties of the triazole. Meanwhile, control reactions revealed that the simple copper salts couldn't catalyze this reaction (Scheme 1).



Scheme 1. Cu-catalyzed borrowing hydrogen reaction.

As described in a plethora of reports,[22-24] ancillary ligands can play an important role in copper-catalyzed dehydrogenation and borrowing hydrogen reactions. With this in mind, phosphines were assessed as ancillary ligands to further adjust the reactivity of the Cu. It was pleasing to see that triazole-phosphine-copper complexes (TAP-Cu) could be synthesized in good yields. To better define and validate the structure of TAP-Cu, single crystal X-ray diffraction analysis was conducted (Figure 3). As depicted, the structure of **2a** was unambiguously confirmed by single-crystal analysis.[29]

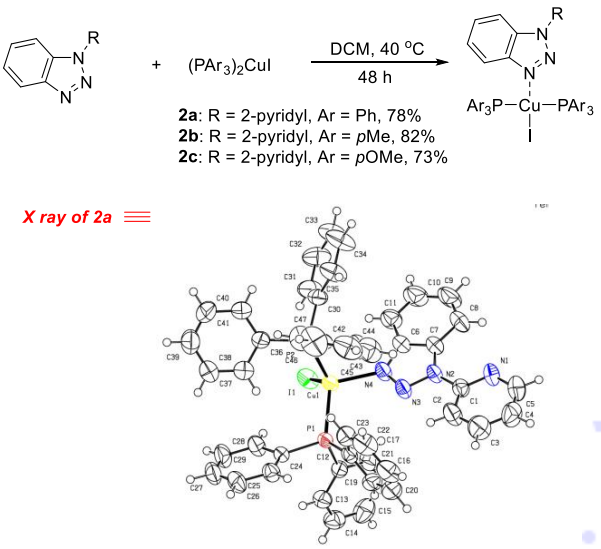
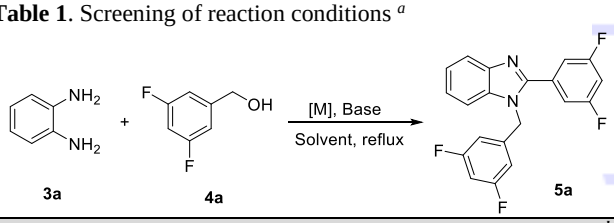


Figure 3. Synthesis of phosphine-triazole-copper complexes **2**.

With these TAP-Cu complexes in hand, the reaction of *o*-phenylenediamine (**3a**) and (3,5-difluorophenyl)methanol (**4a**) was first explored. To our pleasure, the desired product was smoothly obtained in 81% yield (Table 1, entry 11). Other simple copper salts were also tested and could not catalyze this reaction (Table 1, entries 4-8). The effects of catalysts on the reactivity can be seen in the results shown in Table 1. Several solvents were screened including CH_3CN, DCE, DMF, EtOAc, DCM, THF, toluene and xylene (Table 1), with toluene producing the best result (Table 1, entry 11). As expected, no desired product was achieved in the absence of TAP-Cu catalyst (Table 1, entry 25).

Table 1. Screening of reaction conditions [a]



Entry	Catalyst	Base	Solvent	Yield[%][b]
1	-	-	Toluene	<5
2	-	*t*BuOK	Toluene	<5
3	CuCl	*t*BuOK	Toluene	23
4	CuBr	*t*BuOK	Toluene	<5
5	CuI	*t*BuOK	Toluene	<5
6	$Cu(OTf)_2$	*t*BuOK	Toluene	<5
7	$CuCl_2$	*t*BuOK	Toluene	<5
8	$Cu(PPh_3)_2I$	*t*BuOK	Toluene	<5
9	**1a**	*t*BuOK	Toluene	<5
10	**1b**	*t*BuOK	Toluene	<5
11	**2a**	*t*BuOK	Toluene	81
12	**2b**	*t*BuOK	Toluene	64
13	**2c**	*t*BuOK	Toluene	73
14	**2a**	K_2CO_3	Toluene	32
15	**2a**	NEt_3	Toluene	<5
16	**2a**	Cs_2CO_3	Toluene	48
17	**2a**	*t*BuOK	THF	68
18	**2a**	*t*BuOK	Xylene	65
19	**2a**	*t*BuOK	Dioxane	32
20	**2a**	*t*BuOK	DMF	<5
21	**2a**	*t*BuOK	DCM	<5
22	**2a**	*t*BuOK	DCE	<5

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23	**2a**	*t*BuOK	EtOAc	<5
24	**2a**	*t*BuOK	CH_3CN	21
25	-	*t*BuOK	Toluene	<5

[a]Reagents and conditions: **3a** (0.5 mmol), **4a** (1.5 mmol), [Cu] loading (2 mol%, 0.02 mmol), base (0.75 mmol), solvent (3 mL), reflux, 24 h. [b] Isolated yield.

To better explain this transformation, the reaction profiles were also studied. As illustrated in Figure 4, 75% yield of desired product was obtained when the reaction was run for 8 hours.

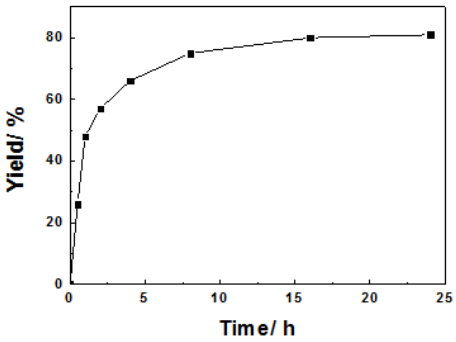
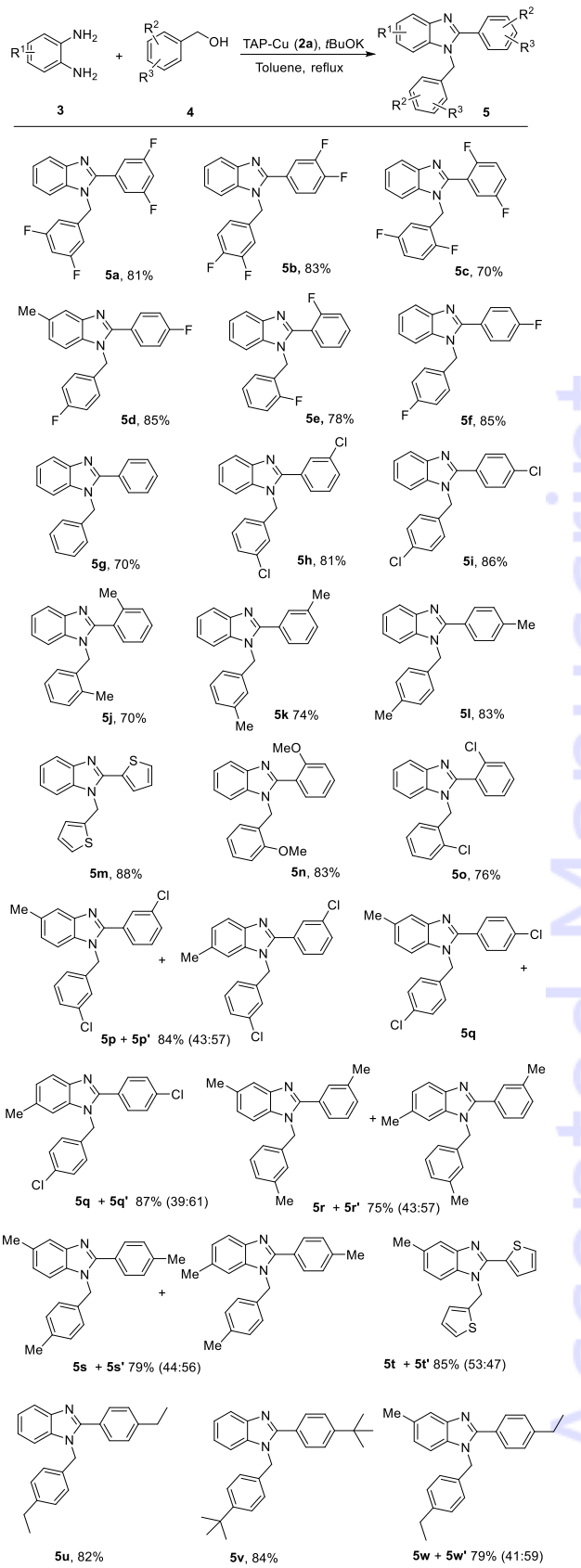


Figure 4. Reaction process profile.

Table 2. Substrate expansion of 1-benzyl-2-aryl-1H-benzo[d]imidazole derivatives [a,b]



[a]Conditions: **3** (0.5 mmol), **4** (1.5 mmol), TAP-Cu (**2a**) (2 mol%), *t*BuOK (0.75 mmol), toluene (3 mL), 24 h, reflux. [b]Isolated yields based on **3**.

Following optimization, we then explored the substrate tolerance by utilizing other diamines and alcohols. As shown in Table 2, a wide range of diamines and alcohols were smoothly transformed into the corresponding 1-

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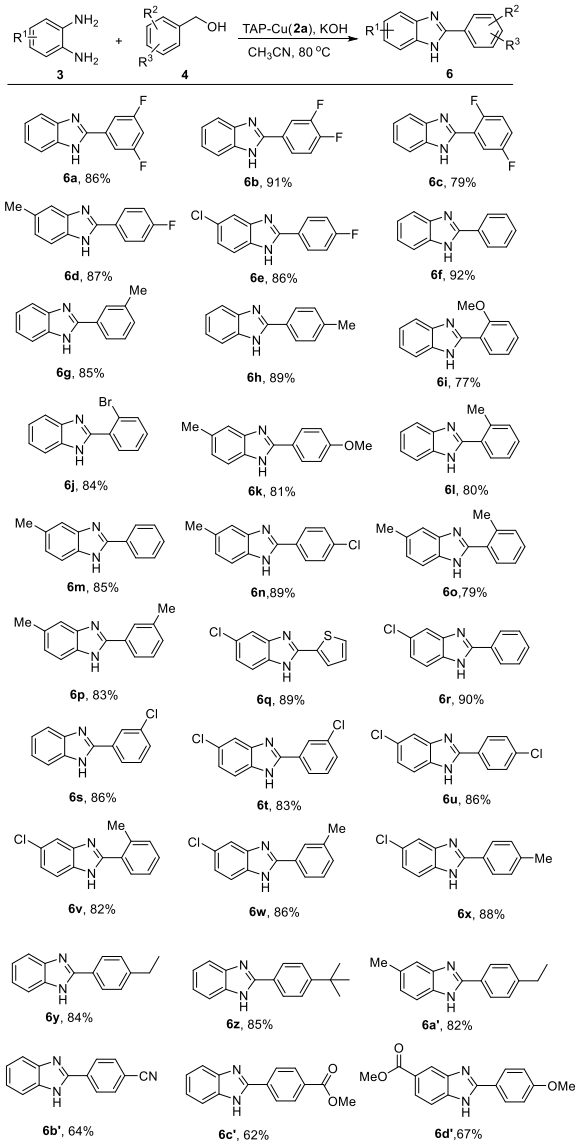
benzyl-2-aryl-1*H*-benzo[d]imidazole products in moderate to good yields. For thiophen-2-ylmethanol, the desired 2-(thiophen-2-yl)-1-(thiophen-2-ylmethyl)-1*H*-benzo[d]imidazole was isolated in 88% yield. It was observed that fluoro-substituted benzyl alcohols were converted into tetrafluoro and difluoro substituted-1*H*-benzo[d]imidazole in good yields.

Table 3. Substrate expansion of 2-aryl-1*H*-benzo[d]imidazole derivatives [a,b]

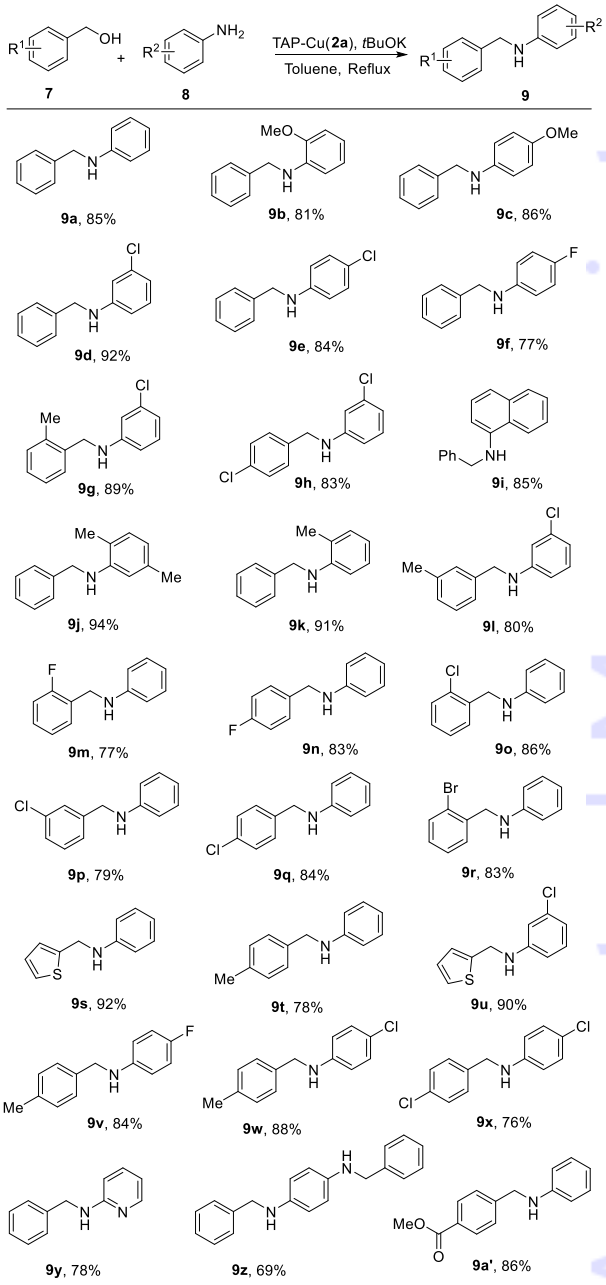


[a]Conditions: **3** (0.5 mmol), **4** (0.6 mmol), TAP-Cu(**2a**) (2 mol%), KOH (0.75 mmol), CH_3CN (3 mL), 24 h, 80 °C. [b]Isolated yields based on **3**.

Interestingly, 2-aryl-1*H*-benzo[d]imidazole derivatives could also be reached in excellent yields by tuning reaction conditions. TAP-Cu (**2a**) was then investigated as the catalyst, for the synthesis of 2-aryl-1*H*-benzo[d]imidazole derivatives. The results of those investigations are summarized in Table 3. It can be seen that diamines were reacted with alcohols smoothly and 2-aryl-1*H*-benzo[d]imidazole derivatives were achieved with good to excellent yields in most cases (Table 3).

Given these interesting results, we further employed this method to the borrowing hydrogen reaction of amines and alcohols. We were pleased that the *N*-alkylated amine was obtained in toluene with TAP-Cu (**2a**) as the catalyst. The results are summarized in Table 4. The experiments showed that different N-alkylated anilines could be obtained with good to excellent yields. Additionally, the effect of substituents on the aromatic ring of amine was explored (Table 4).

Table 4. Substrate expansion of the borrowing hydrogen reaction of alcohols with amines [a,b]



[a]Conditions: **7** (0.75 mmol), **8** (0.5 mmol), TAP-Cu(**2a**) (2 mol%), base (0.75 mmol), Toluene (3 mL), 24 h, reflux. [b]Isolated yields based on **8**.

Following the studies on functional group tolerance, a preliminary mechanistic investigation was performed. The key intermediate for this borrowing hydrogen reaction is a copper hydride species, which we wanted to intercept or verify in some way. First, the transfer hydrogenation control experiment between imine and alcohol was set up. As described in Scheme 2, the result showed that benzyl alcohol could serve as the hydrogen donor for this

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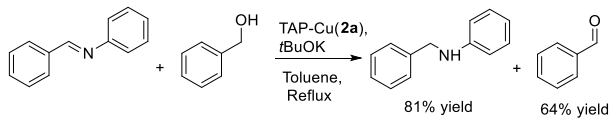
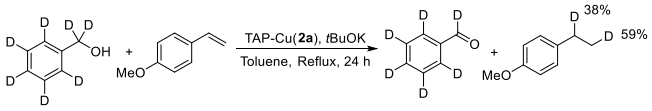
transformation and the corresponding amine and aldehyde were all obtained in moderate or good yields.



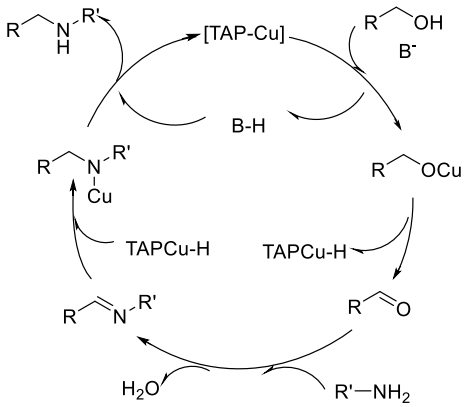
Scheme 2. Control experiment.

For a better mechanistic understanding of this method, a deuterium labeling experiment using 1-methoxy-4-vinylbenzene and d_7-benzyl alcohol was set up and the corresponding 1-ethyl-4-methoxybenzene and aldehyde were all obtained with full conversion of starting material. The results showed a mixture of H/D products was obtained in the reduced styrene product. This further indicated that a copper hydride species was formed and served as a catalytic intermediate (Scheme 3).



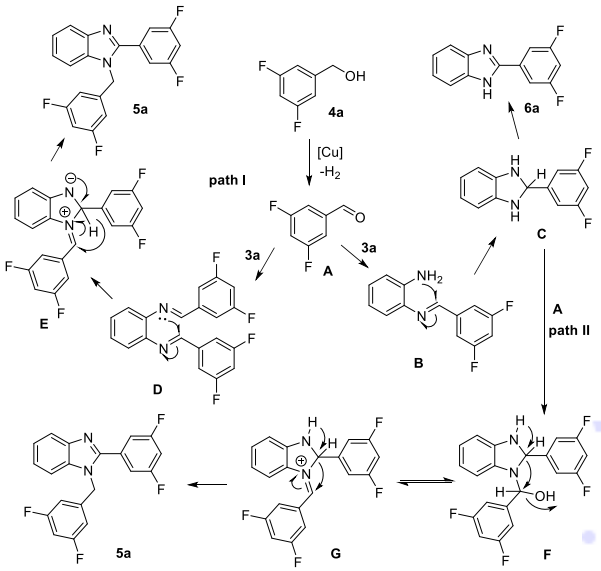
Scheme 3. Deuterium labeling experiment.

Spectroscopic analysis of a copper hydride intermediate was then performed to further confirm its intermediacy in this copper-catalyzed borrowing hydrogen reaction. TAP-Cu (**2a**) was reacted with sodium *tert*-butoxide and then treated with benzyl alcohol. The solid-state infrared spectra of **2a** showed absorptions at 912 cm^{-1}, which could be assigned to copper-hydride stretches based on previously reported absorption profiles for other Cu-H intermediates.[30]



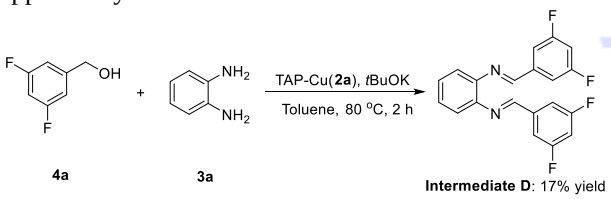
Scheme 4. The proposed possible mechanism for TAP-Cu catalyzed borrowing hydrogen reaction.

With data obtained through mechanistic studies, a possible reaction pathway for the present transformation was proposed (Scheme 4). Initially, the hydrido-copper species would be formed by the reaction of alcohol at the cationic Cu(I). The copper hydride intermediate is produced by a β-hydrogen elimination of a Cu-alkoxy moiety to form the aldehyde. After the condensation of aldehyde and amine, the intermediate imine was reduced using the borrowed H_2 from one molecule of alcohol while water was produced as the only byproduct.



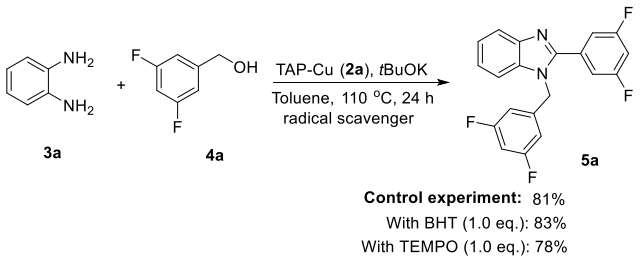
Scheme 5. The proposed possible mechanism for the synthesis of 1*H*-benzo[d]imidazoles.

Additionally, a possible reaction mechanism for the synthesis of 1*H*-benzo[d]imidazoles is also proposed, although the exact mechanism for this reaction is not clear at this moment (Scheme 5). Initially, the formation of the aldehyde should occur under the assistance of TAP-Cu. After the condensation of aldehyde with amine, the product **6a** was easily formed from ring closure and dehydrogenation. However, there are two possible pathways for the formation of **6a**. In this methodology, we believe pathway **I** might be possible (bisimine formation from condensation, cyclization and rearrangement), as intermediate **D** was detected via MS analysis, while intermediate **F** was not observed during this transformation. In addition, the bisimine could also be isolated and confirmed (Scheme 6). Therefore, pathway **I** may take place through a bisimine intermediate, which has been supported by related reactions.[26d]



Scheme 6. The capture of intermediate D.

To exclude the possibility of a radical pathway based on a single electron transfer (SET),[31] we carried out several control experiments (Scheme 7). Control reactions revealed that the yield of the desired product remained almost unchanged when using BHT (1.0 eq) and TEMPO (1.0 eq) with TAP-Cu (**2a**) as the catalyst. As expected, the reaction is not based on a single electron transfer (SET).



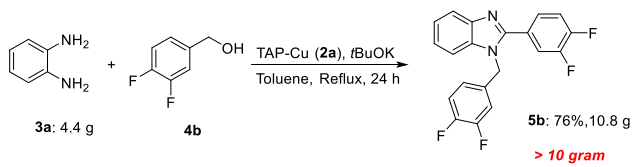
Scheme 7. Control experiments with radical scavengers.

Importantly, the fungicidal activity of the 1-benzyl-2-aryl-1*H*-benzo[d]imidazole and 2-aryl-1*H*-benzo[d]imid-azole derivatives was tested against *Fusaium graminearum*, *Magnaporthe grisea*, *Penicillium digitatum*, *Penicillium italicum* and *Rhizoctonia solani* at 100 mg/L concentration (Table 5).[32] The initial results show that compounds **5a**, **5b** and **5c** exhibited quite good inhibitory activities on *Penicillium digitatum* and *Penicillium italicum*. The compound **5b** had 83% inhibition rate on *Penicillium digitatum*, which is superior to that of the agricultural fungicide triadimefon.

Table 5. Fungicidal activities of compounds against five kinds of funguses.

Compd.	P. digitatum (%)	P. italicum (%)	F. graminearum (%)	M. grisea (%	R. solani (%)
5a	74	63	31	28	33
5b	83	71	32	37	31
5c	69	62	27	34	19
5g	24	31	0	0	21
5i	31	26	0	19	0
5i	44	17	0	14	33
6a	46	25	0	22	20
6b	53	0	24	0	38
6e	42	38	33	0	26
6m	34	20	0	0	0
Triadimefon	76	78	45	49	63
Diniconazole	100	100	93	98	100

Finally, to further extend the application of this new methodology and the TAP-Cu catalyst, the gram scale synthesis of 1-(3,5-difluorobenzyl)-2-(3,5-difluorophenyl)-1*H*-benzo[d]imidazole, which had better anti *P. digitatum* activity, was performed. Good yield and good selectivity were achieved for a reaction scale exceeding 10 grams (Scheme 8).



Scheme 8. The synthesis of 1-(3,5-difluorobenzyl)-2-(3,5-difluorophenyl)-1*H*-benzo[d]imidazole in large scale.

In conclusion, we reported the synthesis and unambiguous characterization of TAP-Cu through X-ray crystallography. TAP-Cu was demonstrated to be an effective and tunable catalyst for the synthesis of fluoro-substituted 2-aryl-1*H*-benzo[d] imidazole and fluoro-substituted 1-benzyl-2-aryl-1*H*-benzo[d] imidazole derivatives with more than 80 examples being successfully performed. It was observed that ligands played a key role in promoting copper-catalyzed dehydrogenation and borrowing hydrogen reactions. In addition, mechanism studies and deuterium labeling experiments revealed that this transformation proceeds by an initial reversible alcohol dehydrogenation step involving a copper hydride intermediate, which provided concrete evidence for a copper-catalyzed dehydrogenation reaction. Importantly, biological activity tests revealed that fluoro-substituted 2-aryl-1*H*-benzo[d] imidazole and fluoro-substituted 1-benzyl-2-aryl-1*H*-benzo[d]imidazole derivatives are potent compounds against *Penicillium digitatum* and *Penicillium italicum.*

Experimental Section

Typical experimental procedure for 2a

The triazole-phosphine-copper complexes (TAP-Cu) were synthesized from the reaction of $[Cu(PAr_3)_2I]$(1.0 mmol) with triazole ligand (1.1 mmol) in a dry CH_2Cl_2 solution (10 mL) at 40 °C for 48 h. The precipitate was isolated by vacuum filtration and washed with CH_2Cl_2 and diethyl ether 3 times. The solvent was removed under a reduced pressure, and the yellow solid was obtained with 78% yield of TAP-Cu (**2a**) through recrystallization.

Representative procedure for the preparation of 5a

To 20 mL colorimetric tube was added TAP-Cu (2 mol%), dry toluene (3 mL), alcohol (1.5 mmol), amine (0.5 mmol) and potassium *tert*-butoxide (0.75 mmol) was added. The mixture was heated under 120 °C for 24 h and then cooled to room temperature. After removing the solvent, the resulting mixture was directly purified by column chromatography with petroleum ether/ethyl acetate as eluent to give the desired product (**5a**).

Representative procedure for the preparation of 6a

To 20 mL colorimetric tube was added TAP-Cu (2 mol%), MeCN (3 mL), alcohol (0.6 mmol), amine (0.5 mmol) and KOH (0.75 mmol) was added. The mixture was heated under 80 °C for 24 h and then cooled to room temperature. fter removing the solvent, the resulting mixture was directly purified by column chromatography with petroleum ether/ethyl acetate as eluent to give the desired product (**6a**).

Representative procedure for the preparation of 9a

To 20 mL colorimetric tube was added TAP-Cu (2 mol%), dry toluene (3 mL), alcohol (0.75 mmol), amine (0.5 mmol) and potassium *tert*-butoxide (0.75 mmol) was added. The mixture was heated under 120 °C for 24 h and then cooled to room temperature. After removing the solvent, the resulting mixture was directly purified by column chromatography with petroleum ether/ethyl acetate as eluent to give the desired product (**9a**).

Acknowledgements

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COMMUNICATION

Tunable Triazole-Phosphine-Copper Catalysts for the Synthesis of 2-Aryl-1H-benzo[d]imidazoles from Benzyl Alcohols and Diamines by Acceptorless Dehydrogenation and Borrowing Hydrogen Reactions

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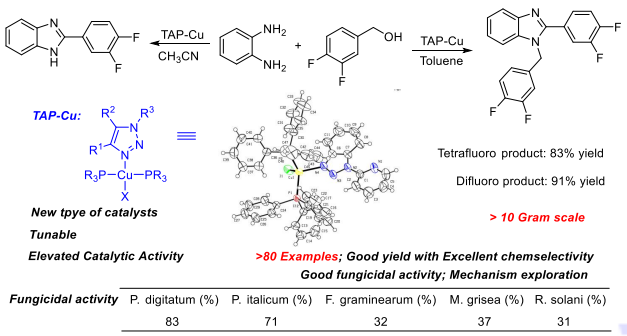
Zhaojun Xu,[a] Duo-Sheng Wang,[b] Xiaoli Yu,[a] Yongchun Yang,[a] Dawei Wang*[a]



Triazole-phosphine-copper complexes (TAP-Cu) have been synthesized and applied as tunable and efficient catalysts for the selective synthesis of fluoro-substituted 2-aryl-1*H*-benzo[d] imidazole and 1-benzyl-2-aryl-1*H*-benzo[d]imidazole derivatives from simple alcohols in only one step. TAP-Cu exhibited excellent and tunable catalytic activity for both dehydrogenation and borrowing hydrogen reactions with more than 80 examples being demonstrated for the first time. It was observed that the ligand played a critical role in catalyst activity. Mechanistic studies and deuterium labeling experiments indicated that the reactions proceeded by an initial and reversible alcohol dehydrogenation resulting in a copper hydride intermediate. This was also supported by the direct observation of a diagnostic copper hydride signal by solid-state infrared spectroscopy. The TAP-Cu-H showed absorptions at 912 cm^{-1} that could be assigned to copper-hydride stretches. Furthermore, the direct trapping of an intermediate bisimine was also successfully performed.