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α-Aminoamides as ligands in Goldberg amidations

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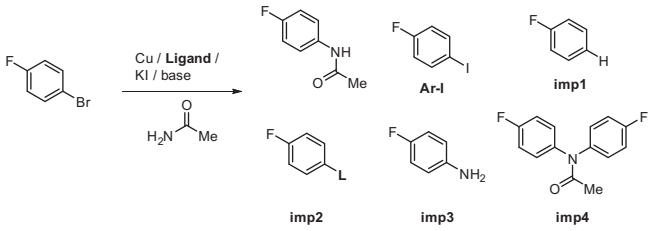
ABSTRACT

α-Aminoamides are shown to be useful as ligands in Goldberg amidations. A number of α-aminoamides are examined and the importance of substitution on the α-aminoamides is explored. Acetamide is focused on as the nucleophilic coupling partner due to its low cost, stability and convenience as a protecting group. The initial substrate scope for these catalysts is explored and includes electronically activated and deactivated aryl bromides, however *o*-substituted aryl bromides are problematic.

Buchwald–Hartwig C–N bond forming cross-coupling reactions are among the most powerful transformations utilized by organic chemists for the synthesis of pharmaceuticals and agrochemicals.[1] There are a number of versatile catalysts based on Pd or Cu that offer advantages for different substrate combinations. The complementariness of these two different systems has been outlined recently by Beletskaya,[2] and in general, the simplicity and affordability of Cu-based catalyst systems make them very attractive especially for amidation reactions, commonly referred to as the Goldberg coupling.[3]

Through the course of our process development, we became interested in the coupling of acetamide with various aryl bromides. We realized there were only scattered examples of this species in the cross-coupling literature.[4] This may be attributed, in part, to the apparent simplicity of acetamide as a substrate and in part to the known toxicity issues with acetamide.[5] In fact, acetamide can be a surprisingly problematic substrate due to the enolizable protons and the ease with which residual water can hydrolyze the acetanilide product to the aniline and acetic acid.[6] Despite these factors, the low cost, stability and convenience of the acetyl protecting group still make this a reaction of interest. As depicted in Scheme 1, our initial investigation into this coupling indicated several side products were forming in addition to our desired product. While **Imp1**, **Imp2**, **Imp3,** and **Imp4** all derive from undesired side reactions, the aryl iodide (**Ar–I**) is thought to be a critical and productive intermediate in this transformation as was shown by Buchwald and coworkers.[7]



Scheme 1. Cu-catalyzed cross-coupling of acetamide and 4-bromofluorobenzene.

Thus, we evaluated a large variety of ligands for the Cu-catalyzed coupling of acetamide and 4-bromofluorobenzene to minimize these side products. Through this study, summarized in Table 1, we found that α-aminoamides could serve as supporting ligands in these reactions. This was somewhat surprising, though α-aminoamides have been used as ligands in other transition metal catalyzed reactions,[8] to the best of our knowledge they have not been used as ligands in Cu-catalyzed coupling reactions.

Upon examination of Table 1, several themes begin to emerge. First, it is immediately obvious that a surprisingly few number of the ligands tested work for this seemingly simple transformation. In fact, of the more popular ligands for Cu (**1**–**3**,[9a,9b] **4**,[9a] **6**, **11**,[9c] **13**,[9d] and **15**–**17**), only **1** and **2** provide full conversion and high yield and this is by far the best result. This is not surprising given the high utility of these ligands demonstrated by Buchwald and coworkers.[10] It is noteworthy that the three phenanthroline derivatives tested (**15**[11a], **16**[11b], and **17**[11c]), although great for other Cu-catalyzed reactions,[11] did not provide very active catalysts for this transformation. Similarly, the diketones tested (**5** and **6**) did not

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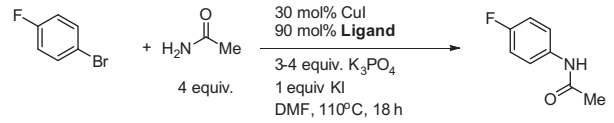
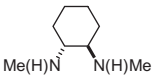
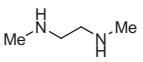
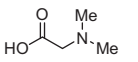
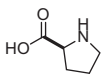
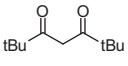
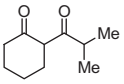
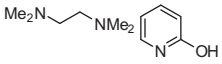
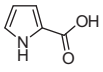
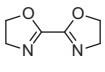
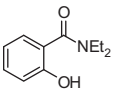
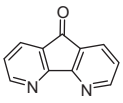
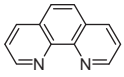
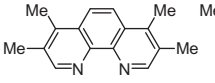
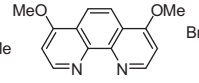
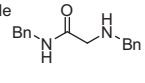
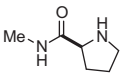
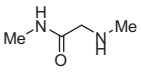
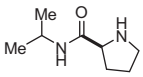
Table 1
General ligand screen for the coupling of acetamide and 4-bromofluorobenzene[a]



				
Ligand (%)	**1**	**2**	**3**	**4**
Conv. (%)	>99	>99	69	97
Ar–I (%)	0	<1	<1	<1
Yield (%)	95	99	11	50
				
Ligand (%)	**5**	**6**	**7**	**8**
Conv. (%)	47	65	39	49
Ar–I (%)	<1	<1	0	<1
Yield (%)	9	43	1	1
				
Ligand (%)	**9**	**10**	**11**	**12**
Conv. (%)	38	62	43	75
Ar–I (%)	<1	<1	<1	<1
Yield (%)	<1	12	3	18
				
Ligand (%)	**13**	**14**	**15**	
Conv. (%)	46	45	89	
Ar–I (%)	<1	0	<1	
Yield (%)	2	7	<1	
				
Ligand (%)	**16**	**17**	**18 (oxalate)**	
Conv. (%)	33	61	64	
Ar–I (%)	<14	<1	7	
Yield (%)	17	27	38	
				
Ligand (%)	**19 (HCl)**	**20**	**21 (oxalate)**	
Conv. (%)	97	84	64	
Ar–I (%)	<1	<1	10	
Yield (%)	17	24	47	

[a] Reaction and conditions: 30 mol % CuI, 90 mol % ligand, 240 mg (1.36 mmol) 4-bromofluorobenzene, 4 equiv acetamide, 1 equiv KI, 3–4 equiv K_3PO_4 (4 equiv base with oxalate salts, 3 equiv in all other cases) 7.5 vols (mL/g ArBr) DMF. Conversion, Ar–I and yield were determined by HPLC, average of two runs.

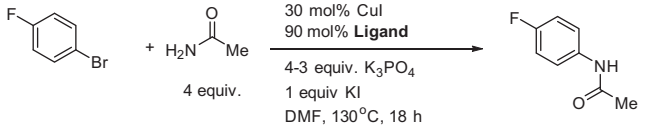
provide very active catalysts despite their excellent utility for other Cu-catalyzed transformations.[12] Other ligands included in this study were added to provide structural diversity. Although the activities were not the highest of the ligands examined, the catalysts resulting from use of α-aminoamides **18**– and **21** provided productive catalysts for this transformation. While **19** and **20** suffered from significant side product formation, it is noteworthy that **18** and **21** both provided relatively good yields of product relative to the conversion of the starting material to either product or the intermediate aryl iodide (Scheme 1, **Ar–I**).[7]

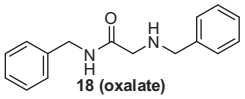
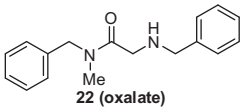
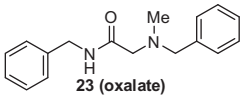
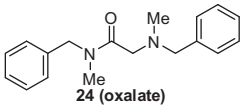
We wanted to further understand the use of α-aminoamides in Cu-catalyzed C–N bond forming reactions so we explored the importance of substitution. The importance of having the appropriate substitution pattern has been previously demonstrated for other ligands.[4a] In this case, we also wanted to understand if N–Hs were beneficial. Thus, several derivatives of an easily tunable α-aminoamide that provided moderate results (**18**) were used in our test reaction to determine the effect of different methyl group substitution patterns. As shown in Table 2, replacing either one (**22** and **23**), or both (**24**), of the N–H groups with a methyl group severely hampers the reactivity of the catalyst system. In these cases, the conversion is reduced from 98% to ~10% and the yield of the product drops correspondingly. In fact, the reactivity of either mono-methyl derivative or the per-methylated derivative is about the same as the background reaction with no ligand present (Table 2, entries 2–4 vs entry 6). Since several ligands are used as their oxalate salts, the background reactivity of oxalic acid was also tested and found to be inadequate for this transformation (Table 2, entry 5).

Once it was clear that both the amide and amine needed to be secondary vs. tertiary, several derivatives of **18** and **21** were synthesized and these derivatives were tested in the coupling of acetamide and 4-bromofluorobenzene. As shown in Table 3, several interesting reactivity trends were observed in this screen. The poor reactivity of tertiary amides was conserved in the proline scaffold, as illustrated by the use of **29**. It was observed that secondary proline amides were generally very reactive but their use resulted in the formation of high amounts of reduced product or ligand coupling (Scheme 1, **imp1** and **imp2**). In an effort to minimize the formation of these byproducts, more hindered derivatives were synthesized. The *m*-xylyl derivative **30** did not provide any improvement in reaction profile. The *i*-propyl derivative **21**, however, did provide a much more selective reaction (Table 3), albeit at a reduced reaction rate. Ligand **28** was synthesized from *o*-methoxybenzylamine in the hope that a slightly more electron rich and potentially chelating amide group might help corral the side product formation, however it did not provide any major selectivity improvements. Perhaps not surprisingly, making the *i*-propyl or *t*-butyl amide analogs of **18** (Table 3, ligands **26** and **27**) resulted in drastically reduced reaction rates. Thus, given the balance achieved between selectivity and reaction rate, we decided to explore the substrate scope of the catalyst derived from the use of **21**.

A small group of substrates were tested to gain some initial insight into the scope of this catalyst system.[13] As previously stated, the use of acetamide was one of our initial goals so we evaluated

Table 2
Examining the importance α-aminoamide substitution[a]

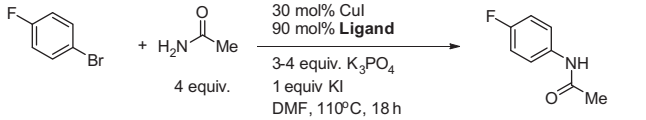


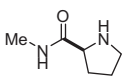
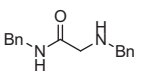
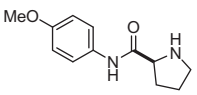
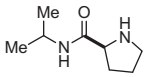
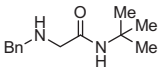
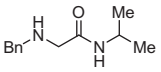
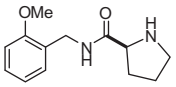
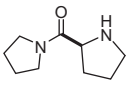
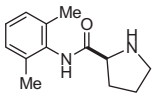
Entry	Ligand	Conv.[b] (%)	Yield[b] (%)
1	 **18 (oxalate)**	97	74
2	 **22 (oxalate)**	6	3
3	 **23 (oxalate)**	12	8
4	 **24 (oxalate)**	5	2
5	Oxalic acid	5	3
6	No ligand	10	3

[a] Reaction and conditions: 30 mol % CuI, 90 mol % ligand, 240 mg (1.36 mmol) 4-bromofluorobenze, 4 equiv acetamide, 1 equiv KI, 3–4 equiv K_3PO_4 (4 equiv base with oxalate salts, 3 equiv in all other cases), 7.5 vols (mL/g ArBr) DMF.
[b] Conversion and yields are determined by HPLC, average of two runs.

the use of acetamide with various *p*-substituted aryl bromides. These initial reactions illustrated that electron poor and rich substrates are tolerated (Table 4, entries 1, 3 and 5). Two examples of a very simple secondary amide, 2-pyrrolidinone, were also evaluated in this cross-coupling. We were surprised to learn the use of **18** with this as the secondary amide was very sluggish, <25% conversion after 48 h. These substrates were then tested with **25,** which generally provided very rapid conversion of aryl bromide,

Table 3
Screening α-aminoamides for the coupling of acetamide and 4-bromofluorobenzene[a]

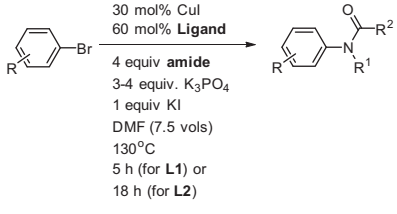


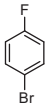
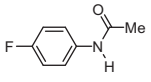
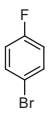
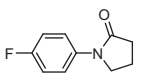
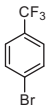
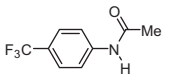
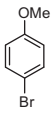
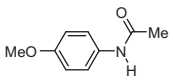
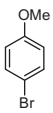
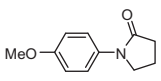
			
Ligand	**19 (HCl)**	**18 (oxalate)**	**25 (HCl)**
Conv. (%)	97	64	100
Ar–I (%)	<1	7	<1
Yield (%)	26	38	42
			
Ligand (%)	**21 (oxalate)**	**26 (oxalate)**	**27 (oxalate)**
Conv. (%)	64	10	6
Ar–I (%)	10	<1	1
Yield (%)	47	<1	2
			
Ligand (%)	**28 (HCl)**	**29 (oxalate)**	**30 (HCl)**
Conv. (%)	100	7	93
Ar–I (%)	<1	<1	10
Yield (%)	39	3	26

[a] Reaction and conditions: 30 mol % CuI, 90 mol % ligand, 240 mg (1.36 mmol) 4-bromofluorobenzene, 4 equiv acetamide, 1 equiv KI, 3–4 equiv K_3PO_4 (4 equiv base with oxalate salts, 3 equiv. in all other cases), 7.5 vols (mL/g ArBr) DMF. Conversion, Ar–I and yield were determined by HPLC, average of two runs.

and we found that the reaction proceeded to completion within 5 h using this ligand. Presumably, the steric demands of **18** are too great for use with secondary amides but the increased reactivity of **25** enables a productive coupling reaction. One limitation

Table 4
Substrate scope for Goldberg couplings utilizing α-aminoamide ligands[a]



Entry	Ar–Br	Amide	Product	Ligand	Conv.[b] (%)	Yield[c] (%)
1				**21**	>99	75
2				**25**	>99	61
3				**21**	>99	63
4				**21**	>99	83
5				**25**	>99	70

[a] Reaction and conditions: 30 mol % CuI, 60 mol % ligand, 1g Ar–Br, 4 equiv amide, 1 equiv KI, 3–4 equiv K_3PO_4 (4 equiv base with oxalate salts, 3 equiv in all other cases), 7.5 vols (mL/g ArBr) DMF.
[b] Determined by HPLC, average of two runs.
[c] Isolated yield, average of two runs.

worth noting is that a few *o*-substituted aryl bromides (2-bromobenzotrifluoride, 2-bromotoluene and 2-bromofluorobenzene) were tested using **18** or **25,** and these reactions were very poor with either acetamide or 2-pyrrolidinone.

In conclusion, we have shown that α-aminoamides can be used as ligands in Goldberg amidations. Our initial findings have shown that the substitution of the α-aminoamides is critical for maintaining a good level of reactivity. The catalysts based on α-aminoamides are not the most active for these reactions, however their use as ligands is Goldberg reactions is unusual and expands the scope of available ligand motifs. In particular, α-aminoamide ligand **18** was shown to be superior to most common ligands (with the exceptions of diamines **1** and **2**) used for the coupling of acetamide and 4-bromofluorobenzene. The initial substrate scope for these catalysts includes primary and secondary amide coupling partners and electronically activated and deactivated aryl bromides, however *o*-substituted aryl bromides appear to be problematic.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.09.099.

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