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## Copper-Promoted and Catalyzed Intra/Intermolecular Diamination of Alkenes\*\*

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### Keywords

copper; catalysis; diamination; alkenes; nitrogen; heterocycles

Olefin diamination methods provide powerful access to vicinal diamines useful in drug discovery, materials and catalysis.[1] A number of impressive diastereoselective, enantioselective and catalytic olefin diamination methods have been recently reported.[2–7]

The *intramolecular* olefin diamination forms nitrogen heterocycles directly and has predominantly been accomplished by using tethered amine nucleophiles wherein both amine additions occur in intramolecular fashion (cf. Scheme 1). This olefin diamination strategy has been reduced to practice by using palladium,[4a] nickel[4b] and gold[4c] catalysts and stoichiometric copper reagents[3] and has resulted in the synthesis of a number of interesting compounds such as bicyclic sulfamides, ureas and guanidines. An intra/intermolecular alkene diamination would result in the convergent formation of one new nitrogen heterocycle along with the installation of a differently functionalized amine substituent. In a recent report, Michael and co-workers found that the use of a palladium catalyst, in combination with *N*-fluorobenzenesulfonimide led to the formation of nitrogen heterocycles with  $-\text{CH}_2\text{N}(\text{SO}_2\text{Ph})_2$  substitution.[5] Herein we report a new copper(II)-promoted and catalyzed intra/intermolecular diamination of alkenes that engages a wide range of internal and external amine sources for the formation of differently functionalized and various nitrogen heterocycles. Importantly, this communication reports the first intramolecular diamination protocol where catalyst-based asymmetric induction has been observed (*vide infra*). Impressive catalytic enantioselective intermolecular olefin diaminations have been reported,[2] but no enantioselective intramolecular variant has been reported.[8] Herein is reported our progress towards this elusive transformation.

The copper(II)-promoted and catalyzed intra/intermolecular alkene diamination protocols disclosed herein are an advance on earlier studies by our lab which involved the synthesis of bicyclic sulfamides and ureas via a tethered olefin diamination approach (Scheme 1).[3] We have recently found that we can expand this process to involve the participation of an external amine source in the second C-N bond-forming step (Table 1).

Thus, heating 1-allyl-1-benzyl-2-phenyl urea (**1a**) in the presence of copper(II) 2-ethylhexanoate,  $\text{Cu}(\text{EH})_2$  (3 equiv),  $\text{Cs}_2\text{CO}_3$  and aniline (1.5 equiv) in  $\text{PhCF}_3$  for 24 h

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provides imidazolidin-2-one **2a** in 92% yield (Table 1, Conditions **A**). Other copper-promoted processes such as intramolecular carboamination,[9] aminoacetoxylation[9e] and hydroamination[9b] can occur with the substrates used in this study (see Supporting Information), but the intra/intermolecular diamination process appears to be most favorable when the reaction is run in the presence of an external amine nucleophile.

A number of substituted anilines (substituents = Cl, CF<sub>3</sub>, Me, F, OMe, *i*-Pr, NO<sub>2</sub>) also participated as the external amine in this diamination process, providing **2b–2i** in good to excellent yield (Table 1). The amount of substituted aniline had to be increased to 3 equiv (Conditions **B**) in order to minimize competitive formation of **2a**, a product that can originate from the creation of PhNH<sub>2</sub> from partial decomposition of **1a** under the reaction conditions. In addition, at least 2 equiv of Cu(EH)<sub>2</sub> is necessary to minimize formation of a hydroamination side product (see Supporting Information for optimization tables). Sodium azide,[10] benzamide and *p*-toluene sulfonamide were also competent nucleophiles in this diamination reaction (entries 10–12, Table 1).

The 4,4-disubstituted imidazolidin-2-one **4** was formed efficiently from diamination/cyclization of the corresponding 1,1-disubstituted alkenyl urea **3** (Scheme 2). Gratifyingly, chiral imidazolidin-2-ones **6** were formed with high 4,5-*trans* selectivity from the corresponding alkenyl urea substrate **5** (Scheme 3). Formation of the *trans* diastereomer can be rationalized via cyclic transition state **A**, where the substituent adopts a pseudo-equatorial position.

*N*-aryl- $\gamma$ -pentenyl amides, and sulfonamides with different  $\gamma$ -alkenyl backbones, were also good substrates in this intra/intermolecular diamination reaction (Table 2). Both 2,5-*cis* and 2,5-*trans* pyrrolidines can be formed with high diastereoselectivity (Table 2, entries 10–12).

In general it appears that electron-deficient anilines are better coupling partners than electron-rich anilines in this reaction. For example, the electron-deficient *p*-trifluoromethylaniline provided the highest yield with **1a**, giving 97% of **2f** (Table 1, entry 6), while only the product of substrate decomposition, **2a**, was observed in the attempted diamination with *p*-methoxyaniline with **1a**. *p*-Methoxyaniline was marginally competent in the diamination reaction with *N*-tosyl-orthoallylaniline (which cannot undergo the same decomposition), giving **12d** in 42% yield (Table 2, entry 7). Electron-rich amines may bind too tightly to the copper promoter, thereby inhibiting either or both of the C-N bond forming steps.

To gain insight into the formation of the second C-N bond, we subjected the *trans*-deuterated alkene **d-13**[9b] to the diamination reaction (Scheme 4). Partial conversion led to isolation of a 1:1 ratio of diamination diastereomers **d-14a** (64%) and 25% of **d-13**, recovered without alkene isomerization. We interpret this to indicate the irreversible formation of a transient primary carbon radical (as in Scheme 5), the result of C-Cu(II) bond homolysis.[3,9b] The radical can then recombine with Cu(II) to generate a C-Cu(III) intermediate which may then undergo RNH<sub>2</sub> and reductive elimination to produce the observed diamine product (Scheme 5).

We interpret the 2,5-*cis*-pyrrolidine selectivity shown in products **16** and **18** to be the result of the first C-N bond formation occurring through either the chair-like or boat-like transition states in Scheme 5, where the dominant stereochemistry-determining interaction is avoidance of steric hindrance between the alpha-substituent and the *N*-substituent.[9] This diastereoselectivity can be switched to favor the 2,5-*trans*-pyrrolidine (cf. **20**) by connecting these two substituents directly to one another.[11]

Our initial attempts to render this diamination reaction catalytic in copper(II) using MnO<sub>2</sub> as stoichiometric oxidant with either *N*-allyl urea **1a** or *N*-sulfonyl ortho-allylaniline **11a** and aniline or NaN<sub>3</sub> as nucleophiles led to no reaction. MnO<sub>2</sub> is a competent oxidant in our previously reported copper-catalyzed carboamination reaction.[9c,e] Sulfamide and urea substrates such as those shown in Scheme 1 also failed to undergo copper-catalyzed doubly intramolecular alkene diamination. To our delight, however, when *p*-TolSO<sub>2</sub>NH<sub>2</sub> was used as the nucleophile with substrates **1a** and **11a**, the catalytic intra/intermolecular alkene diamination reactions occurred efficiently (Table 3). Superior yields (87% vs 72%, entry 1) were obtained when 2,6-di-*tert*-butyl-4-methyl pyridine was used as base instead of Cs<sub>2</sub>CO<sub>3</sub>.

We next challenged the reaction in the catalytic enantioselective manifold. When copper(II) triflate (30 mol%) complexed with (*R*)-Ph-bis(oxazoline) ligand (37.5 mol%) was used, diamination adduct **12e** was obtained in 51% yield and 71% ee (Scheme 6). The major enantiomer is tentatively assigned *S* by analogy.[9c] This is a promising lead for development of the elusive catalytic enantioselective intramolecular alkene diamination reaction. Mechanistically, this reaction clearly demonstrates copper is present in the C-N bond-forming step (as indicated in Schemes 3 and 5). Further optimization of the catalytic enantioselective process is underway in our labs.

## Experimental Section

Typical procedure for the copper 2-ethylhexanoate promoted diamination (conditions **B**): **1a** (40 mg, 0.15 mmol) was placed in a glass pressure tube equipped with a magnetic stir bar and was treated with Cs<sub>2</sub>CO<sub>3</sub> (48.8 mg, 0.15 mmol) and Cu(EH)<sub>2</sub> (105 mg, 0.30 mmol, 2 equiv). PhCF<sub>3</sub> (0.75 mL) and 4-chloroaniline (41 μL, 0.45 mmol) were added via syringe. The tube was capped and the reaction mixture was placed in a 120 °C oil bath and stirred. After 24 h, the reaction mixture was cooled to 23 °C, diluted with EtOAc (10 mL) and placed in a separatory funnel and was washed with sat. aq. EDTANa<sub>2</sub> (2×10 mL) and 2M NaOH (2×10 mL). The aqueous layers were each washed once with EtOAc and the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The resulting oil was purified by flash chromatography on SiO<sub>2</sub> (0–40% EtOAc/hexanes gradient) providing 50.3 mg (86%) of **2b** (yellow oil).

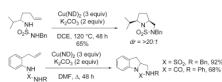
## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

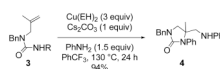
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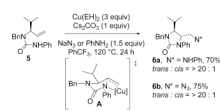
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10. These reactions were run using no more than 15 mg of  $\text{NaN}_3$ . Care should be taken with this reaction as  $\text{NaN}_3$  is potentially explosive when heated or exposed to metals and their salts.
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**Scheme 1.**

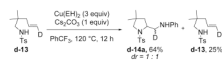
Previous work: Copper-promoted doubly intramolecular alkene diamination. ND = neodecanoate.



**Scheme 2.**  
Diaminations of a 1,1-disubstituted alkenyl urea.

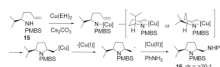


**Scheme 3.**  
High diastereoselectivity for allylic substituted ureas.

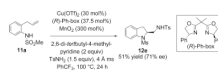


**Scheme 4.**  
Isotopic labeling experiment.





**Scheme 5.**  
Origin of 2,5-cis-pyrrolidine diastereoselectivity.

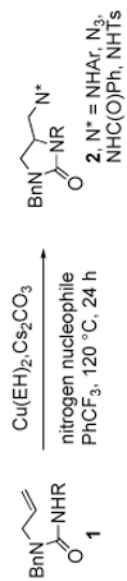


**Scheme 6.**  
Enantioselective copper(II)-catalyzed intra/intermolecular alkene diamination (%ee determined by chiral HPLC).

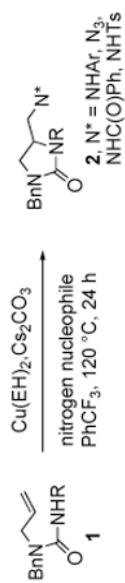
Table 1

Copper(II)-promoted intra/intermolecular diamination of *N*-allyl ureas.

Entry	1 (R)	Nitrogen nucleophile	Product	Yield (%)
1[a]	1a (Ph)	PhNH <sub>2</sub>		92
2[b]	1a	<i>p</i> -Cl-C <sub>6</sub> H <sub>4</sub> NH <sub>2</sub>		86
3[b]	1a	<i>p</i> -F-C <sub>6</sub> H <sub>4</sub> NH <sub>2</sub>		76
4[b]	1a	<i>p</i> -Me-C <sub>6</sub> H <sub>4</sub> NH <sub>2</sub>		72
5[a,c]	1a	<i>p</i> -( <i>i</i> -Pr)-C <sub>6</sub> H <sub>4</sub> NH <sub>2</sub>		85
6[b]	1a	<i>p</i> -CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> NH <sub>2</sub>		97
7[b]	1a	<i>o</i> -Cl-C <sub>6</sub> H <sub>4</sub> NH <sub>2</sub>		72



Entry	<b>1 (R)</b>	Nitrogen nucleophile	Product	Yield (%)
8[b]	<b>1a</b>	<i>m</i> -NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> NH <sub>2</sub>		82
9[b]	<b>1a</b>	<i>m</i> -MeO-C <sub>6</sub> H <sub>4</sub> NH <sub>2</sub>		70
10[a]	<b>1a</b>	NaN <sub>3</sub>		85
11[b]	<b>1a</b>	TsNH <sub>2</sub>		86
12[b]	<b>1a</b>	BzNH <sub>2</sub>		65
13[b]	<b>1b</b> , (Ts)	PhNH <sub>2</sub>		60



Entry	<b>1</b> (R)	Nitrogen nucleophile	Product	Yield (%)
14[b]	<b>1c</b> (1-nap-ethyl)	$\text{PhNH}_2$	<b>2n</b>	76
15[b]	<b>1d</b> (Bz)	$\text{PhNH}_2$	<b>2o</b>	60

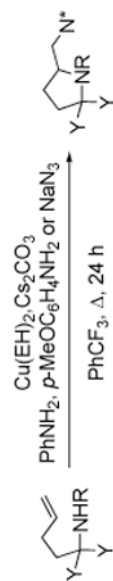
[a] Conditions **A**: *N*-allylurea **1** (0.15 mmol),  $\text{Cu}(\text{EH})_2$  (3 equiv), nitrogen nucleophile (1.5 equiv),  $\text{Cs}_2\text{CO}_3$  (1 equiv),  $\text{PhCF}_3$  (0.2 M w/r to **1**),  $120^\circ\text{C}$ , 24 h, pressure tube.

[b] Conditions **B**: Same as **A** except 3 equiv nitrogen nucleophile and 2 equiv  $\text{Cu}(\text{EH})_2$  were used.

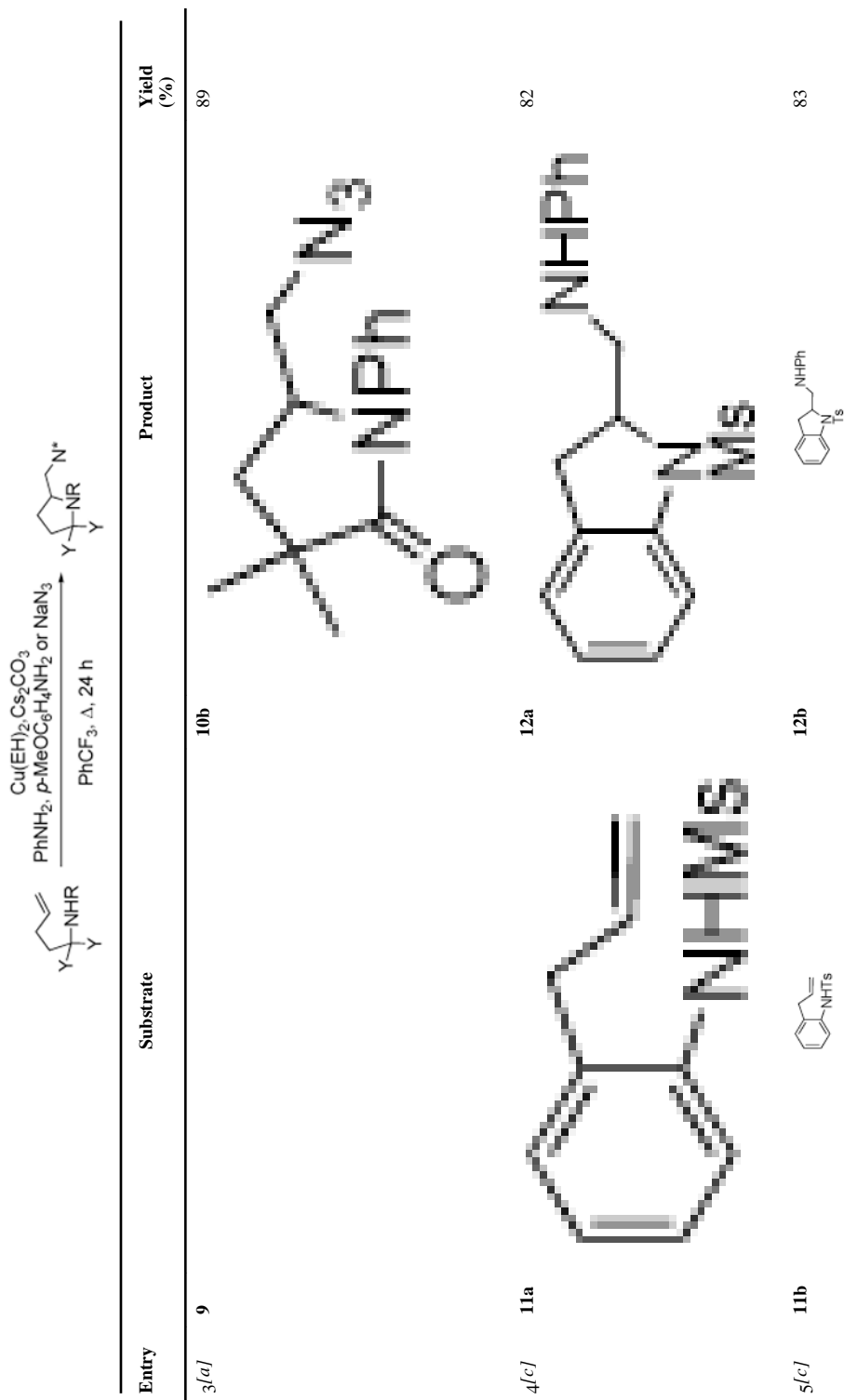
[c] Reaction run with 1 equiv nitrogen nucleophile.

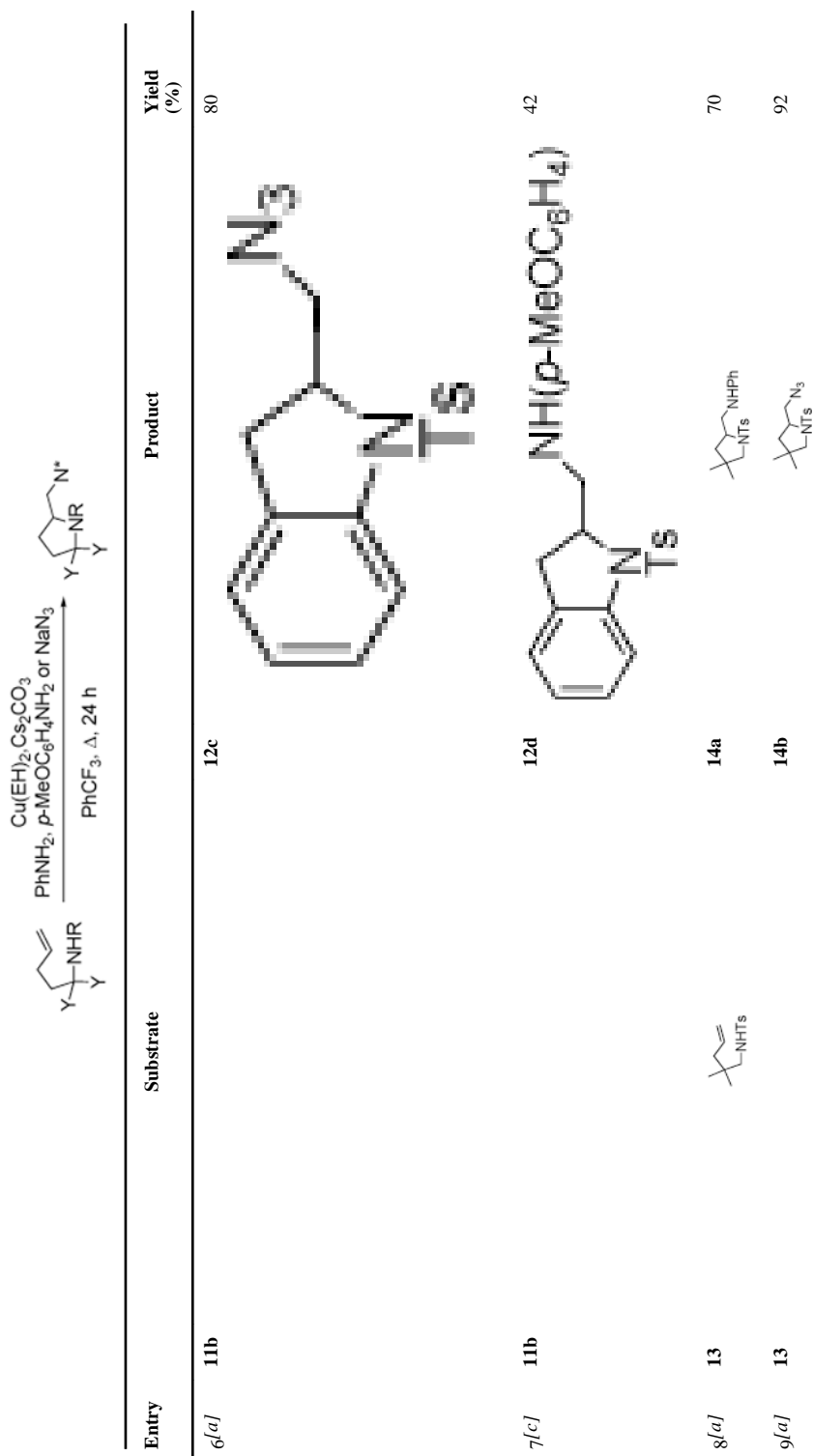
[d] Reaction run at  $130^\circ\text{C}$ .  $\text{Cu}(\text{EH})_2$  = Copper(II) 2-ethylhexanoate.

Table 2

Copper(II)-promoted intra/intermolecular diamination of  $\gamma$ -alkenyl amides and sulfonamides.<sup>[a]</sup>

Entry	Substrate	Product	Yield (%)
1 <sup>[a,b]</sup> 7			87
2 <sup>[a]</sup> 9			83







Entry	Substrate	Product	Yield (%)
10 <sup>[a,d]</sup>			78 dr >20:1
17 <sup>[a,d]</sup>			82 dr >20:1
19 <sup>[a,d]</sup>			63 dr >20:1

[a] Conditions **A** (see Table 1).

[b] Reaction run at 150 °C for 48 h.

[c] Conditions **B** (see Table 1).

*d*] Reaction run at 130 °C.

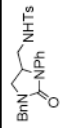
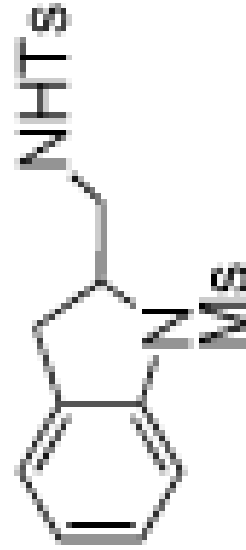
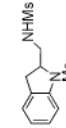
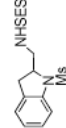
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Table 3

Copper(II)-catalyzed intra/intermolecular diamination of alkenes.<sup>[a]</sup>

Entry	Substrate	Nucleophile	Product	Yield (%)
1 <sup>[a, b]</sup>	<b>1a</b>	TsNH <sub>2</sub>		87 (72)
2 <sup>[a]</sup>	<b>11a</b>	TsNH <sub>2</sub>		83
3 <sup>[a]</sup>	<b>11a</b>	MeSO <sub>2</sub> NH <sub>2</sub>		64
4 <sup>[a, c]</sup>	<b>11a</b>	SESNH <sub>2</sub>		80

<sup>[a]</sup> Substrate **1a** or **11a** (0.24 mmol) was treated with Cu(EH)<sub>2</sub> (20 mol %), 2,6-di-*tert*-butyl-4-methyl pyridine (1 equiv), MnO<sub>2</sub> (300 mol %), and amine nucleophile (2.2 equiv), dissolved in PhCF<sub>3</sub> (0.2 M w/r to **1a** or **11a**), treated with activated 4 Å mol. sieves and heated at 100 °C in a pressure tube for 24 h. SES = trimethylsilylethylsulfonyl.

<sup>[b]</sup> Entry 1, yield in parentheses is when Cs<sub>2</sub>CO<sub>3</sub> (1 equiv) was used as base.

<sup>[c]</sup> Reaction run at 110 °C.