Asymmetric Synthesis of Propargylic α-Chiral Tertiary Amines by Reductive Alkynylation of Tertiary Amides Using Ir/Cu Tandem Catalysis.

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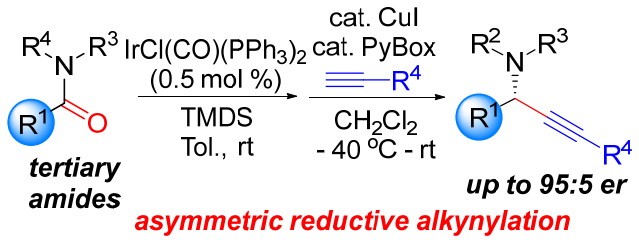
Supporting Information Placeholder



ABSTRACT: The development of an asymmetric protocol for the reductive alkynylation of amides to access important α-chiral tertiary propargylic amines is reported using tandem Ir-catalyzed hydrosilylation/enantioselective Cu-catalyzed alkynylation. The reaction utilizes a Cu/PyBox catalyst system in the alkynylation step to achieve asymmetry and affords excellent yields with moderate to good levels of enantiocontrol while employing low Ir-catalyst loadings (0.5 mol %).

α-Chiral amines are prevalent motifs found in organic compounds and drug molecules leading to important biological activity.[1] As a result, synthetic methods for the stereoselective preparation of α-chiral amines is an important endeavor in organic chemistry.[2] One powerful emerging strategy for the synthesis of α-chiral amines utilizes amides as building blocks through partial reduction[3] or activation[4,5] of the amide followed by reaction with nucleophiles (Figure 1A,B) in an overall deoxygenative process.[6] The value of this approach arguably lies in the reliable access to amide building blocks **3** from ubiquitous carboxylic acid (**1**) and amine (**2**) precursors[7] enabling a programmatic technique for the preparation of α-chiral amines **4**. Such protocols are enabled by the conversion of amide **3** to an electrophilic *N,O*-aminal derivative (**5**,**6**) that are subsequently functionalized with nucleophiles (Figure 1B).[3-6,8,9] Conversion of the amide into the requisite electrophilic species is achieved through either amide activation,[4,5] typically employing Tf_2O, followed by trapping with an organometallic reagent to afford **5**, or through partial reduction of the amide employing the Schwartz reagent (Cp_2ZrHCl),[3g] DIBAL,[3h] or by Ir-[3a-f] or Mo-catalyzed[3i,j] hydrosilylation giving **6**. Of these methods, reductive functionalization of tertiary amides through partial reduction by Ir-catalyzed hydrosilylation[8] followed by nucleophile trapping have proven to be an attractive technique for the synthesis of α-chiral tertiary amines due to the robustness of the Ir-catalyzed hydrosilylation reaction that occurs at very low Ir-catalyst loading.[6,8] However, the majority of these processes produce racemic α-chiral amines, and enantioselective variants are extremely rare.[9] As a result, our group became interested in developing catalytic asymmetric variants of these processes to

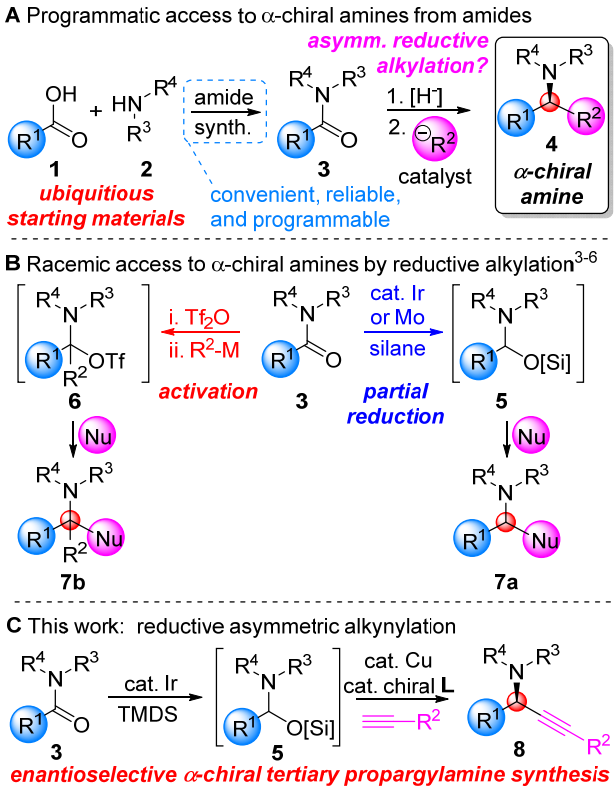
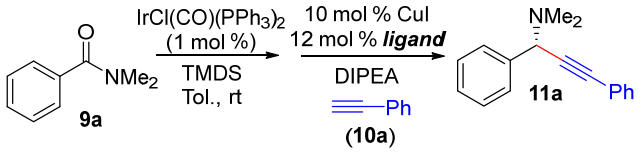


Figure 1. Preparation of α-Chiral Amines through Reductive Alkylation of Amides.

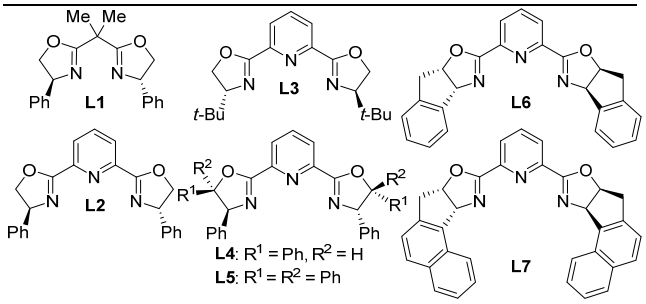
access α-chiral amines in enantioenriched form through coupling processes employing partially reduced amides from Ir-catalyzed hydrosilylation as electrophiles. Furthermore, due to the reliable nature at which the amide functional group can be prepared synthetically,[7] we reasoned such an asymmetric functionalization of amides would be a highly reliable technique to access α-chiral tertiary amines. Based on the elegant work of Huang[3c] where racemic α-chiral propargylic tertiary amines were prepared through tandem Ir-catalyzed amide hydrosilylation followed by Cu-catalyzed alkynylation under ligandless conditions, we chose this reaction as an initial starting point to study by investigating the addition of chiral ligands to the reaction to determine if enantioselective ligand-accelerated catalysis[10] could be achieved to afford the α-chiral propargylic tertiary amine products in high enantioselectivities (Figure 1C). During the course our investigations, Huang and Wang[9b] reported a Cu/bis(phosphine) catalyzed version of this reaction providing products with high levels of enantiocontrol. This report prompted us to disclose our investigations into the analogous reaction where we have focused on application of chiral

Table 1. Chiral Ligand Survey[a]



entry	ligand	conditions	% yield[b]	er [c]
1	none	d8-tol, rt, 6 h	90	50:50
2	**L1**	Tol, rt	91	50:50
3	**L2**	d8-Tol, rt, 1 h	95	42:58
4	**L3**	Tol, -40°C to rt	80	62:38
5	**L4**	Tol, rt	89	40:60
6	**L4**	Tol, -40°C to rt	94	16:84
7	**L5**	Tol, rt	82	45:55
8	**L6**	Tol, -40°C to rt	92	86:14
9	**L6**	DCM, -40°C to rt	92	88:12
10[d]	**L6**	DCM, -40°C to rt	81	92:8
11[d]	**L7**	DCM, -40°C to rt	81	89:13

[a]**9a** (0.100 mmol), $IrCl(CO)(PPh_3)_2$ (1 mol %), TMDS (0.20 mmol) in 0.25 mL of toluene, rt, 1 h; CuI (0.010 mmol), ligand (0.012 mmol), DIPEA (0.15 mmol), **10a** (0.15 mmol) in 0.50 mL of solvent. See the Supporting Information for further details. [b]Isolated yield. [c]Value determined by chiral HPLC analysis. [d]Reaction performed in the absence of DIPEA using 5 mol % CuI and 7 mol % ligand.

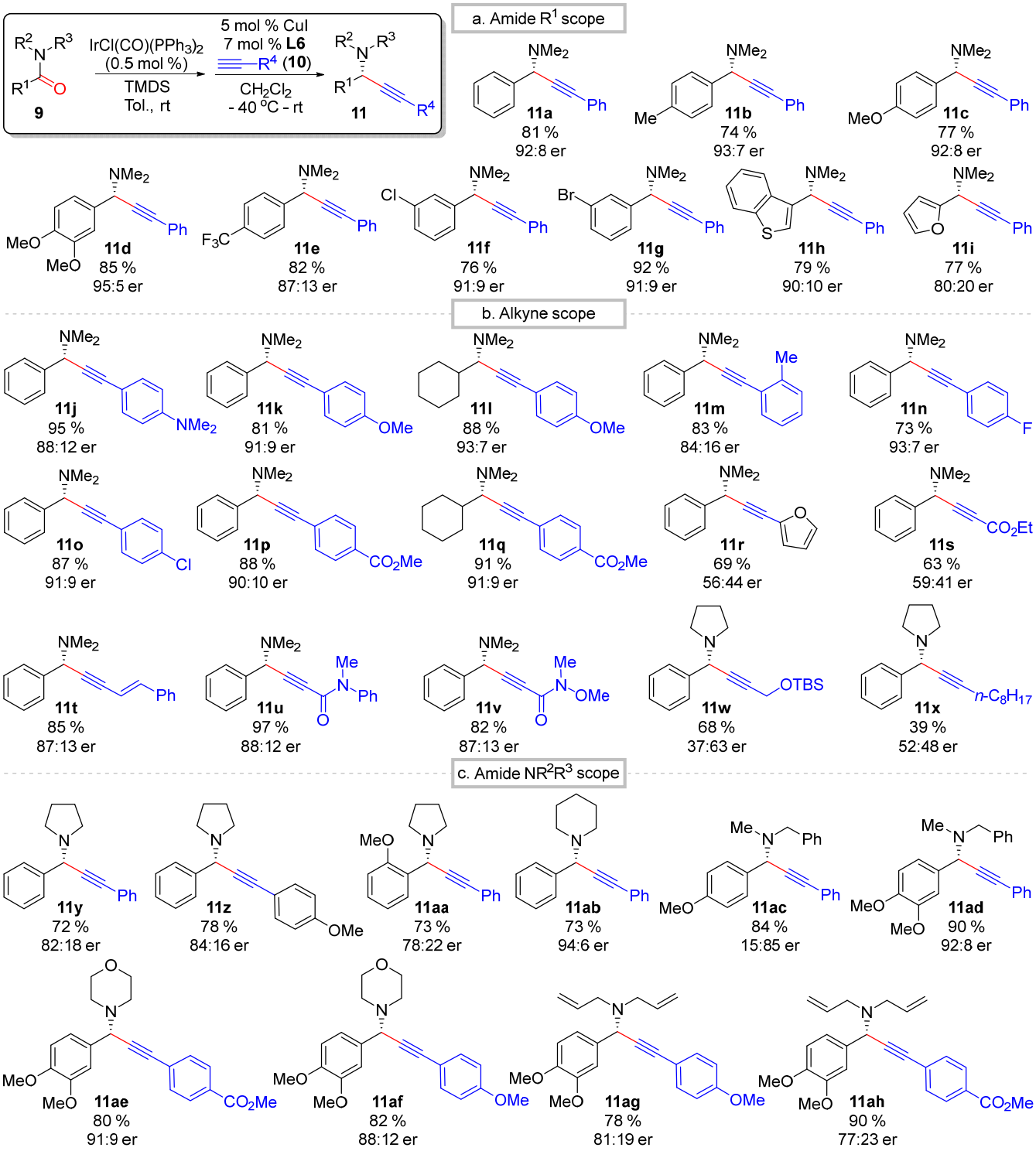


PyBox ligands to achieve enantiocontrol. Herein we report our findings on the development of an enantioselective α-chiral propargylic amine synthesis through tandem partial amide reduction by Ir-catalyzed hydrosilylation followed by asymmetric Cu/PyBox catalyzed alkynylation.

Initial investigation into the feasibility of an asymmetric tandem reductive amide alkynylation reaction was carried out utilized *N,N*-dimethylbenzamide (**9a**) in an Ir-catalyzed hydrosilylation reaction followed immediately by Cu-catalyzed coupling with phenylacetylene (**10a**) to afford α-chiral propargylic amine **11a** (Table 1). Use of chiral Ph-Box ligand **L1** discouragingly afforded product **11a** as a racemate (entry 2). As a result, a series of PyBox ligands (**L2** – **L7**) were next investigated under the hypothesis that the added chelation available with these ligands may enable a more selective catalyst (entries 3 – 11). Indeed, use of PyBox **L2** afforded non-racemic **11a**, albeit with poor enantioselectivity, and ligand accelerated catalysis was observed relative to the reaction in the absence of ligand by monitoring reaction progress throughout the alkynylation step using ^{1}HNMR spectroscopic analysis while performing the reactions in d8-toluene (entry 3 *vs* 1). The reaction employing ligand **L2** (entry 3) was complete in 1 h whereas the ligandless reaction (entry 1) required > 4 h to reach completion. Increasing the steric size of the substituents at the stereogenic centers of the PyBox ligand (*i.e.* **L3**), and reducing the reaction temperature, did not afford significant improvements in enantioinduction (entry 4). However, it was found that substitution on the *C*-atom of the C–O group of the oxazoline ring of the PyBox ligand (*i.e.* **L4** – **L7** *vs* **L2** – **L3**) allowed for significant improvements in enantiocontrol (entries 3 and 4 *vs* entries 5 – 11).[11] Performing the reaction at – 40 °C was found to be optimal[12] and led to improved stereocontrol relative to reactions performed at rt (entry 5 *vs* 6). Ultimately, aminoindanol-derived PyBox ligand **L6** afforded the highest levels of enantiocontrol (entries 8 – 10). Dichloromethane (entry 9,10) was identified as the optimal reaction solvent,[12] which may be due to the fact that **L6** was found to have poor solubility in most organic solvents except for CH_2Cl_2. Additionally, no exogenous amine base was needed in the alkynylation reaction and the Cu-catalyst loading could be reduced to 5 mol % with a slight reduction in yield, but with improved stereoselectivity (entry 10). Finally, extending the π-system of the PyBox ligand as in **L7** did not lead to any further improvements.

After having identified optimal conditions for the tandem reductive amide alkynylation reaction (Table 1, entry 10), the substrate scope of this process was next investigated (Scheme 1). Varying the R^1-substituent of amide **9** employing phenylacetylene (**10a**) generally afforded similar results (**11a-h**). A small electronic effect may be observed where electron-rich aromatic R^1-groups afforded slightly higher levels of enantiocontrol relative to electron-poor aromatics (**11b,d** *vs* **11e-h**). Reduction in the steric size of the R^1-group led to a decrease in enantioselectivity (**11i**). Varying the R^4-group of the alkyne nucleophile (**10**) showed a dramatic effect on enantioselectivity (**11j-x**). Alkynes bearing aromatic R^4-groups (**10j-q**) generally gave similar levels of enantiocontrol, and amides bearing aliphatic R^1-groups could also be used (**11l,q**). However, when the R^4-group of the alkyne was a smaller aromatic ring (**10r**), an ester moiety (**10s**), or an aliphatic group (**10w,x**) very low levels of enantioinduction were obtained. Interestingly, when using a conjugated aromatic group on the alkyne (**10t**) or amide groups (**10u,v**), similar levels of enantiocontrol to that obtained with aromatic

Scheme 1. Scope of the Tandem Reductive Amide Asymmetric Alkynylation Reaction[a]



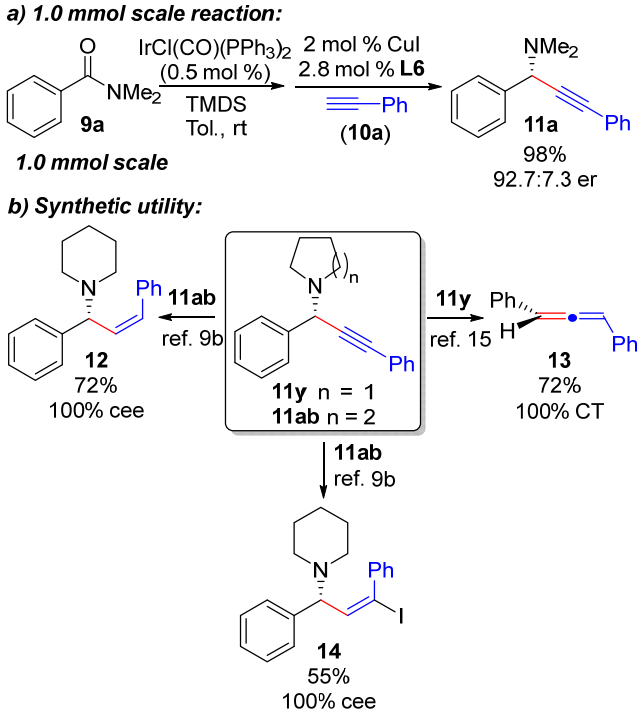
[a]Reaction utilizes 0.400 mmol of amide **9**; see the Supporting Information.

alkynes was restored. Finally, analysis of the NR^2R^3 group of amide **9** demonstrated that cyclic (**11y-ab**, **11ae**, **11af**) and acyclic (**11ac**, **11ad**, **11ag**, **11ah**) amino-groups were tolerated with similar levels of enantiocontrol. Six-membered carbocyclic amines (**11ab**) afforded improved stereoselectivity relative to smaller five-membered versions (**11y**). Acyclic amino-groups larger than CH_3 generally afforded reduced levels of enantiocontrol (**11ac**, **11ad**, **11ag**, **11ah**).

The tandem Ir-catalyzed amide reduction/enantioselective Cu-catalyzed alkynylation reaction could easily be performed on a 1.0 mmol scale with reduction in the Cu catalyst loading to 2 mol % providing near quantitative yield of **11a** in 92.7:7.3 er (Scheme 2a). Furthermore, the synthetic utility of chiral propargylic amines in organic synthesis has already been extensively demonstrated.[13] For example, conversion of **11y** to axially chiral internal allene **13** with complete chirality transfer (CT) has already been reported using $AgNO_3$ (Scheme 2b).[14]

Additionally, **11ab** was previously shown[9b] to be converted into *cis*-alkene **12** or stereodefined vinyl iodide **14** with complete conservation of enantiomeric excess (cee) in both cases.

Scheme 2. Practicality of the Amide Reductive Alkynylation Method.



In conclusion, an asymmetric reductive alkynylation of amides using tandem Ir- and Cu-catalysis for the synthesis of α-chiral tertiary propargylic amines was described. Moderate to good enantioselectivities were observed using an aminoindanol-derived PyBox ligand when employing alkynamides or aromatic-substituted alkynes as the coupling partner in the alkynylation step.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Detailed experimental procedures, compound characterization data, chiral HPLC traces, and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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