

Enantioselective A³ Reactions of Secondary Amines with a Cu(I)/Acid–Thiourea Catalyst Combination

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S Supporting Information

ABSTRACT: Pyrrolidine and related amines undergo asymmetric A³ reactions in the presence of copper iodide and an easily accessible cocatalyst possessing both a carboxylic acid and a thiourea moiety. Propargylamines are obtained with up to 96% ee, and catalyst loadings can be as low as 1 mol %. Pyrrolidine-derived propargylamines, in the absence of directing groups, can be transformed to the corresponding allenes without loss of enantiopurity.

Propargylamines are compounds of substantial synthetic value and are most readily accessed by addition of terminal alkynes to imines or iminium ions (Scheme 1).¹ When the imine or iminium ion is prepared in situ from an aldehyde and an amine, these transformations are referred to as A³ coupling reactions.¹ The catalytic enantioselective synthesis of propargylamines derived from primary amines is a well-developed process, most commonly utilizing copper(I) catalysis and ligands such as pybox.² Copper and silver salts have also been used in combination with different organocatalysts.³ When secondary rather than primary amines are employed, the nature of the reaction changes dramatically as do the requirements for asymmetric catalysis. Rather than involving imines as intermediates (e.g., **1**), secondary amines by necessity require the intermediacy of iminium ions such as **4**. These species lack an available lone pair on nitrogen and thus are not readily amenable to activation/enantiocontrol via hydrogen bonding, protonation, or metal coordination. Presumably because of this added difficulty, relatively few reports have addressed the challenge of performing catalytic enantioselective A³ reactions with secondary amines.^{4–7} Without exception, these processes require the use of phosphine-based ligands. Trimethylsilylacetylene is used predominantly and is often required to achieve high enantioselectivities. Here we report the application of readily available carboxylic acid–thiourea compounds (e.g., **5**) as efficient cocatalysts in copper(I)-catalyzed asymmetric A³ reactions with pyrrolidine and related amines.

The first catalytic enantioselective A³ reaction with secondary amines was reported by Knochel and co-workers who employed copper(I) bromide in combination with QUINAP.⁴ Carreira et al. later introduced tunable PINAP ligands which were applied to asymmetric A³ coupling reactions with dibenzylamine and 4-piperidinone.⁵ Recently, the Aponick group developed an imidazole-based P,N ligand (**L1**) for enantioselective A³ reactions.^{6,7} As part of our ongoing efforts to develop new organocatalytic processes, we recently reported

Scheme 1. Synthesis of Enantioenriched Propargylamines

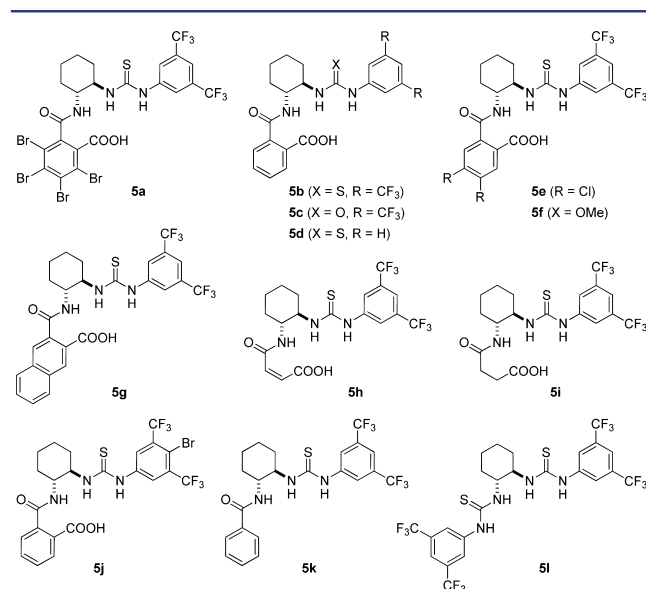
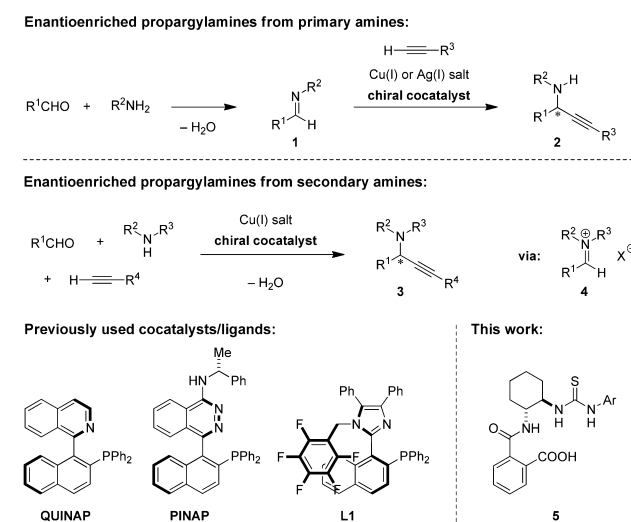


Figure 1. Cocatalysts evaluated in this study.

a new type of chiral Brønsted acid catalyst containing both a carboxylic acid and a thiourea subunit (Figure 1).^{8–11} These

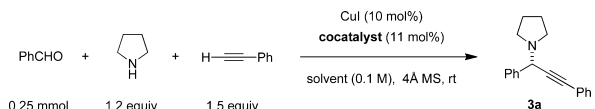
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catalysts were designed with the notion that the thiourea moiety would function as an anion receptor, serving to stabilize the catalyst's conjugate base and thus increasing its Brønsted acidity. Compound **5a** emerged as an effective catalyst for asymmetric Povarov reactions with secondary amines.^{8a} As these reactions likely proceed via intermediates related to **4** (with X⁻ representing the conjugate base of **5a**), we reasoned that carboxylic acid–thioureas **5** might serve as effective chiral cocatalysts in Cu(I)-catalyzed A³ reactions.¹²

Benzaldehyde, pyrrolidine, and phenylacetylene were selected as model substrates to evaluate the title reaction (Table 1). Catalyst **5a**, when used in combination with CuI, facilitated

Table 1. Optimization of Reaction Conditions



entry	cocatalyst	solvent	time [h]	yield (%)	ee (%)
1	5a	PhCH ₃	3	78	20
2	5b	PhCH ₃	6	91	60
3	5b	CH ₂ Cl ₂	2	90	73
4 ^a	5b	CH ₂ Cl ₂	2	92	64
5 ^b	5b	CH ₂ Cl ₂	3	82	25
6	5c	CH ₂ Cl ₂	3	92	0
7	5d	CH ₂ Cl ₂	4	89	14
8	5e	CH ₂ Cl ₂	2	92	64
9	5f	CH ₂ Cl ₂	2	92	73
10	5g	CH ₂ Cl ₂	2	94	70
11	5h	CH ₂ Cl ₂	4	96	42
12	5i	CH ₂ Cl ₂	4	94	-5
13	5j	CH ₂ Cl ₂	3	91	74
14	5k	CH ₂ Cl ₂	3	92	0
15	5l	CH ₂ Cl ₂	24	70	8
16 ^c	5j	CH ₂ Cl ₂	3	92	82
17 ^{c,d}	5j	CH ₂ Cl ₂	3	91	88
18 ^{c,d,e}	5j	CH ₂ Cl ₂	12	92	92

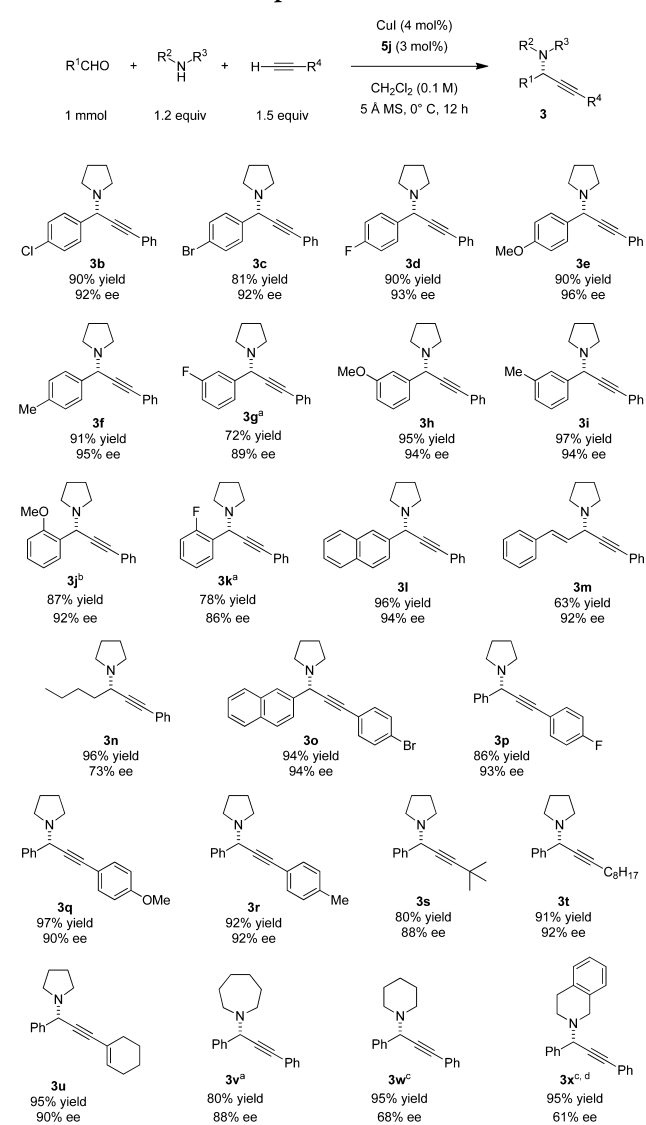
^aWith CuBr. ^bWith CuCl. ^cWith 5 Å MS. ^dReaction was run at a 1 mmol scale with 4 mol % CuI and 3 mol % cocatalyst. ^eReaction was run at 0 °C.

the formation of product **3a** in good yield albeit with only 20% ee (entry 1). Surprisingly, acid–thiourea **5b**, a poor catalyst for Povarov and Pictet–Spengler reactions,⁸ provided a marked increase in enantioselectivity (entry 2). Subsequent evaluation of various solvents led to further improvements with dichloromethane providing the best results (entry 3).¹³ Replacement of CuI for either CuBr or CuCl led to inferior results (entries 4 and 5). Remarkably, and in stark contrast to our previous studies, urea catalyst **5c** was equally active as thiourea **5a**. However, product **3a** was obtained in racemic form (entry 6). Removal of the two trifluoromethyl groups on the catalyst's thiourea moiety was also detrimental (entry 7). Other modifications targeting the carboxylic acid moiety were tolerated to varying degrees but failed to provide any improvements (entries 8–12). A slightly more selective catalyst, compound **5j**, was obtained through introduction of a bromine substituent between the two flanking trifluoromethyl groups (entry 13). The poor results obtained with catalyst **5k** and the Nagasawa catalyst¹⁴ (**5l**) clearly demonstrate that a carboxylic acid substituent is essential for effective catalysis (entries 14 and 15).

Further optimizations were conducted with catalyst **5j**.¹³ Replacement of 4 Å with 5 Å molecular sieves provided a slight boost in enantioselectivity (74% vs 82% ee).¹⁵ Reactions performed in the absence of molecular sieves or with other dehydrating agents (3 Å MS, Drierite, Na₂SO₄, MgSO₄) gave inferior results (not shown).¹³ Evaluation of various ratios of CuI and cocatalyst **5j** led to the observation that higher selectivities are obtained when CuI is used in slight excess.¹⁶ Furthermore, the catalyst loading could be reduced and optimal results were obtained with 4 mol % of CuI and 3 mol % of **5j**. Finally, product **3a** was obtained with 92% ee in a reaction conducted at 0 °C (entry 18).

The scope of the catalytic enantioselective A³ reaction with pyrrolidine was found to be relatively broad (Scheme 2). Aromatic aldehydes and terminal arylalkynes with diverse substituents in different ring positions were well tolerated. More challenging terminal alkynes with alkyl and alkenyl substituents were also viable substrates. Lower selectivities were obtained with aliphatic aldehydes. Whereas azepane performed

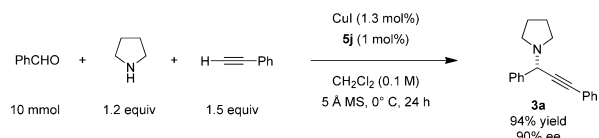
Scheme 2. Substrate Scope



^aRun at -30 °C for 48 h. ^bThe ee was determined after demethylation. ^cRun at rt for 24 h. ^dCuBr was used instead of CuI.

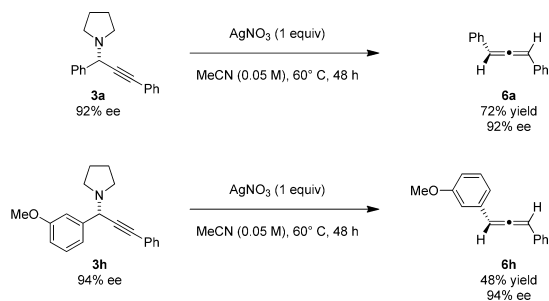
similarly to pyrrolidine with regard to selectivity and reactivity, piperidine proved to be less reactive and provided product with reduced selectivity. Interestingly, 1,2,3,4-tetrahydroisoquinoline (THIQ) afforded mixtures of the expected product **3x** and the corresponding redox- A^3 product (not shown).^{17,18} The use of CuBr in place of CuI allowed for the exclusive formation of **3x**, albeit with moderate enantioselectivity. To illustrate the utility of this process, a reaction was performed on a 10 mmol scale with only 1 mol % of **5j** (Scheme 3). A high level of efficiency was maintained, and product **3a** was obtained in 94% yield and 90% ee.

Scheme 3. Scale-up Reaction at Lower Catalyst Loading



Nonracemic propargylamines derived from cyclic amines have been used extensively as starting materials for enantioenriched allenes.^{19,20} These reactions proceed via activation of the alkyne by a metal ion, triggering a 1,5-hydride transfer and subsequent elimination of an imine byproduct. In all cases known to us, the presence of a stereogenic center on the amine moiety or a directing group on the amine or alkyne is required for an efficient transfer of point-to-axial chirality. In preliminary experiments, we have accomplished an efficient transfer of chirality in the absence of such control elements (Scheme 4).

Scheme 4. Transformation of A^3 Products to Enantioenriched Allenes



To obtain insights into potential catalyst aggregation phenomena that might affect the catalytic process, we evaluated A^3 reactions catalyzed by **5b** possessing varying levels of enantiopurity (Figure 2). However, no nonlinear effects were observed. The available data seem to suggest that cocatalyst **5j** acts as a ligand for copper(I),²¹ forming a highly reactive copper acetylide complex that serves to attack a transient iminium ion. Supporting this notion is the complete lack of selectivity observed for the corresponding urea catalyst **5c**, making it highly likely that coordination of copper to the thiourea sulfur atom is crucial for efficient catalysis.²² Also, the strong dependence on the counteranion of the copper salt speaks against one alternative scenario, namely that a neutral copper acetylide reacts with an ion pair such as **4** where X^- represents the conjugate base of **5j**. While the carboxylic acid moiety of **5j** is undoubtedly involved in the formation of the active iminium ion, the role of the corresponding carboxylate in

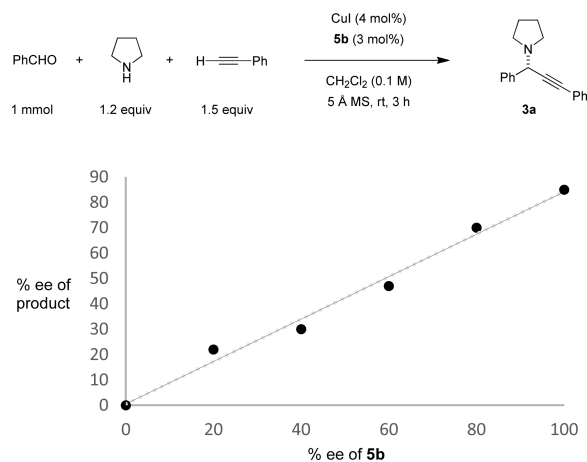


Figure 2. Nonlinear effects study.

the enantiodetermining step remains unclear at present. Carboxylate could conceivably interact with copper to form a cuprate complex or serve as the counterion to an intermediate iminium species. Either of these roles could alternatively be fulfilled by iodide which also appears to be involved in the enantiodetermining step.

In summary, we have developed an efficient method for the synthesis of enantioenriched propargylamines, using CuI in combination with a readily available Brønsted acid cocatalyst. Pyrrolidine-based propargylamines lacking directing groups can be transformed to allenes without loss of enantiopurity. The present approach features the lowest catalyst loadings reported to date for catalytic enantioselective A^3 reactions with secondary amines.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data, including an X-ray crystal structure of product **3o** (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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