Enantioselective Catalysis

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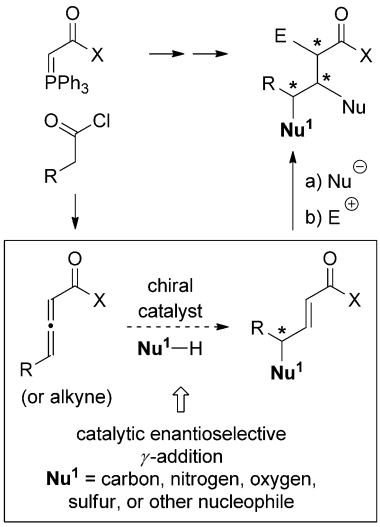
Catalytic Asymmetric C–N Bond Formation: Phosphine-Catalyzed Intra- and Intermolecular γ-Addition of Nitrogen Nucleophiles to Allenoates and Alkynoates**

*Rylan J. Lundgren, Ashraf Wilsily, Nicolas Marion, Cong Ma, Ying Kit Chung, and Gregory C. Fu**

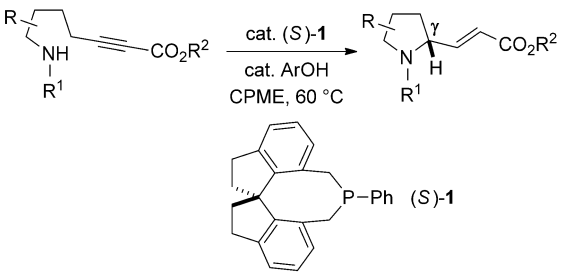
The use of chiral phosphines as nucleophilic catalysts represents an important second dimension of their utility in catalytic asymmetric synthesis,[1] in addition to their more familiar role as ligands for transition metals.[2] Cognizant of the paucity of general methods for the catalytic enantioselective γ-functionalization of carbonyl compounds,[3] we have recently pursued the development of phosphine-catalyzed processes that couple nucleophiles with allenoates and related compounds in the γ position (Scheme 1).[4–6] Given the ready availability of the starting allenes, along with the plethora of methods for stereoselective α- and β-functionalization of α,β-unsaturated carbonyl compounds,[7,8] this approach should provide straightforward access to highly functionalized, stereochemically rich, target molecules (Scheme 1).

To date, we have established the viability of this approach with oxygen (intramolecular additions to alkynes), as well as carbon and sulfur (intermolecular additions to allenes), nucleophiles.[4] In view of the biological significance of amines,[9,10] including γ-amino-α,β-unsaturated carbonyl compounds,[11–13] achieving catalytic enantioselective γ-additions with nitrogen nucleophiles is a particularly important objective.[14] However, attempts to effect phosphine-catalyzed γ-addition (even non-enantioselective) of nitrogen nucleophiles to γ-substituted 2,3-allenoates and 2-alkynoates (and related compounds) have been unsuccessful (≤30% yield),[15] owing in part to the propensity of such electrophiles to isomerize to 1,3-dienes.[16] Herein, we demonstrate that spirophosphine **1** not only can achieve γ C–N bond formation in good yield for the first time, but it can also provide good enantioselectivity, both for intra- and for intermolecular processes [Eq. (1) and Eq. (2); CPME = cyclopentyl methyl ether; TBME = *tert*-butyl methyl ether].



Scheme 1. Access to highly functionalized, stereochemically rich, carbonyl compounds through catalytic enantioselective γ-additions to allenes.

From the outset of our investigation of phosphine-catalyzed γ-additions of nitrogen nucleophiles, we decided to simultaneously address the two key challenges: accomplishing C–N bond formation and controlling the stereo-



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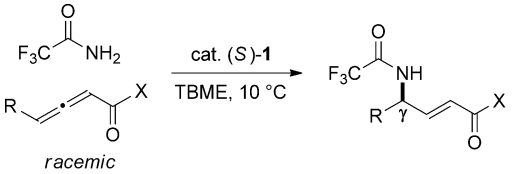

(2)

[*] Dr. R. J. Lundgren, Prof. G. C. Fu
Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, CA 91125 (USA)
E-mail: gcfu@caltech.edu
Dr. A. Wilsily, Dr. N. Marion, Dr. C. Ma, Dr. Y. K. Chung
Department of Chemistry, Massachusetts Institute of Technology
Cambridge, MA 02139 (USA)

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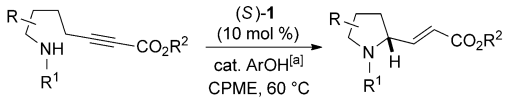
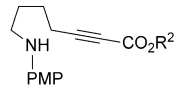
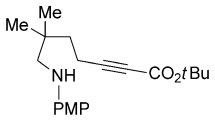
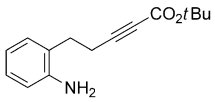
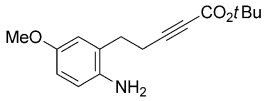
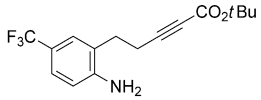
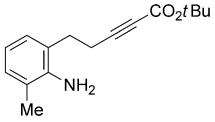
chemistry of the γ-carbon. Upon examining an array of conditions for the enantioselective cyclization of the aminoalkyne illustrated in entry 1 of Table 1, we developed a method whereby spirophosphine **1**[17–19] catalyzes the desired intramolecular γ-addition to generate the target pyrrolidine[20,21] with very good enantioselectivity (91% *ee*) and acceptable yield (68%).

Table 1: Catalytic enantioselective synthesis of pyrrolidines and indolines by intramolecular γ-additions of nitrogen nucleophiles to alkynoates.



Entry	Substrate		*ee* [%]	Yield [%][b]
1		$R^2 = tBu$	91	68
2		Bn	95	70
3		Me	94	78
4			94	60
5			90	55
6			89	44
7			88	44
8			88	67

All data are the average of two experiments. [a] For entries 1–4, cat. ArOH = 2,4-dimethoxyphenol (50%). For entries 5–8, cat. ArOH = 2-fluoro-6-methoxyphenol (20%). [b] Yield of purified product. Bn = benzyl, PMP = *p*-methoxyphenyl.

Spirophosphine **1** serves as an effective catalyst for the asymmetric cyclization of an array of aminoalkynes (Table 1; > 95:5 *E*/*Z* for all reactions).[22] The choice of ester attached to the alkyne has only a modest impact on the efficiency of the catalytic enantioselective γ-addition process (entries 1–3). Furthermore, substitution on the alkyl chain between the nucleophilic aniline and the electrophilic alkyne is tolerated (entry 4).

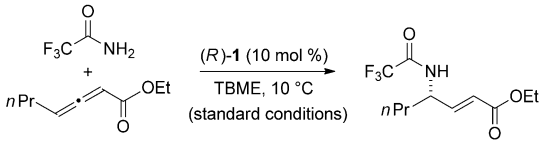
If the aromatic ring of the aniline lies between the amine and the alkyne, then spirophosphine-catalyzed asymmetric intramolecular γ-addition of the amine furnishes enantioenriched indolines[23] (Table 1, entries 5–8). Relative to the parent substrate (entry 5), incorporation of an electron-donating or an electron-withdrawing group on the aromatic ring leads to cyclization with similar enantioselectivity, but with somewhat lower yield (entries 6 and 7). On the other hand, the presence of a methyl substituent *ortho* to nitrogen results in improved cyclization (entry 8).

Next, we turned our attention to the challenge of also achieving the first effective phosphine-catalyzed *inter*molecular γ-additions of nitrogen nucleophiles to alkynes and allenes. Unfortunately, our standard conditions for intramolecular reactions of anilines (Table 1) were not useful for intermolecular additions of anilines to alkynes and allenes (< 10% yield).

2,2,2-Trifluoroacetamide is a particularly attractive nitrogen nucleophile, as it can be hydrolyzed under mild conditions to liberate a free amine. Employing our published methods for enantioselective phosphine-catalyzed γ-additions of other families of nucleophiles,[4] we obtained either poor *ee* (< 35%) or poor yield (< 10%) for the catalytic asymmetric γ-addition of 2,2,2-trifluoroacetamide to ethyl 2,3-heptadienoate.

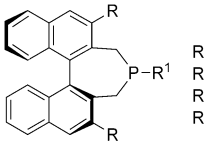
Nevertheless, upon surveying a range of parameters, we developed a new method wherein spirophosphine **1** catalyzes the desired γ-amination process with good enantioselectivity and yield, as well as excellent *E*/*Z* selectivity (≥ 95:5) (Table 2, entry 1); interestingly, although we have found this spirophosphine to be the catalyst of choice for intramolecular catalytic asymmetric γ-additions, it had not previously emerged as the optimal phosphine for intermolecular reactions.[4] An array of other chiral phosphine catalysts that we have found useful in other contexts furnish significantly lower *ee*, yield, or *E*/*Z* selectivity in this enantioselective γ-amination (entries 2–6). The amount of γ-addition product

Table 2: The effect of reaction parameters on the catalytic enantioselective intermolecular γ-addition of a nitrogen nucleophile to an allene.

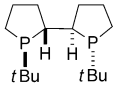


Entry	Change from standard conditions	*ee* [%]	Yield [%] (*E*/*Z* ratio)[a]
1	none	87	90 (≥ 95:5)
2	**2** instead of **1**	80	88 (65:35)
3	**3** instead of **1**	9	52 (≥ 95:5)
4	**4** instead of **1**	64	89 (90:10)
5	**5** instead of **1**	84	64 (60:40)
6	**6** instead of **1**	27	96 (85:15)
7	1.0 equiv, instead of 2.0 equiv, of allene	88	52 (≥ 95:5)
8	**1** (5 mol%), instead of **1** (10 mol%)	88	39 (≥ 95:5)
9	room temperature instead of 10°C	82	90 (≥ 95:5)

All data are the average of two experiments. [a] The yield was determined by ^{1}H NMR spectroscopy with the aid of an internal standard.



R = H, $R^1 = NEt_2$ (**2**)
R = H, $R^1 = tBu$ (**3**)
R = H, $R^1 = Ph$ (**4**)
R = Ph, $R^1 = Ph$ (**5**)

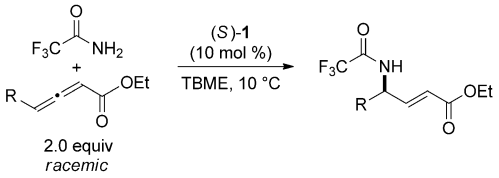


TangPhos (**6**)

diminishes when a smaller quantity of allene (entry 7) or catalyst (entry 8) is employed, and a small erosion in *ee* is observed when the catalytic asymmetric γ-addition is conducted at room temperature, rather than at 10 °C (entry 9).

Under the standard conditions, spirophosphine **1** catalyzes the intermolecular γ-amination of an array of allenoates by 2,2,2-trifluoroacetamide in generally excellent yield, thereby furnishing ready access to γ-amino-α,β-unsaturated esters; at the same time, good enantioselectivities are obtained (Table 3).[24] As might be anticipated on the basis of the simplicity of the method and the mild reaction temperature, a variety of functional groups are compatible with the asymmetric γ-addition process, including a terminal alkyne, a (*Z*)-alkene, an ester, and a sulfur heterocycle. The method is not particularly air- or moisture-sensitive: for example, the addition of water (0.5 equiv) did not erode enantioselectivity or yield, and running the reaction in a capped vial under air had no effect on *ee* and only a modest impact on yield. On a gram scale, the γ-amination in entry 4 of Table 3 proceeds with comparable results (87% *ee*, 95% yield, ≥95:5 *E*/*Z*). The 2,2,2-trifluoroacetyl group can be removed by hydrolysis under mild conditions.[25]

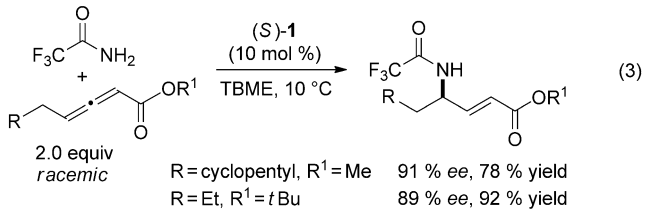
Table 3: Scope of the catalytic enantioselective intermolecular γ-addition of 2,2,2-trifluoroacetamide to allenoates.



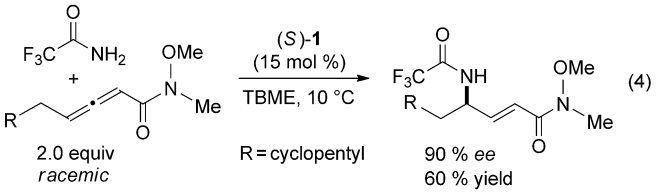
Entry	R	*ee* [%]	Yield [%][a]
1	Me	86	89
2	*n*Pr	87	90
3	*i*Bu	88	92
4	$(CH_2)_2Ph$	88	94
5	$(CH_2)_4OBn$	89	87
6	$(CH_2)_3$–≡	89	86
7	$(CH_2)_6$–CH=CH–*n*Oct	87	88
8	$(CH_2)_2CO_2Me$	82	68
9	$(CH_2)_2$–thienyl	86	87

All data are the average of two experiments. [a] Yield of purified product (*E*/*Z* ≥ 95:5).

A preliminary mechanistic investigation revealed that product *ee* correlates linearly with catalyst *ee* and that the rate law is positive order in allene and catalyst, but negative order in nucleophile. Although ^{31}P NMR spectroscopy did not provide clear evidence for a catalyst–nucleophile adduct, several phosphorus-containing species (potentially, phosphonium intermediates) and free spirophosphine **1** were observed during the course of the γ-addition process.



(3)



(4)

In summary, we have provided the first examples of catalyzed γ-additions of nitrogen nucleophiles to γ-substituted alkynoates or allenoates that proceed with good efficiency, specifically, intra- and intermolecular processes that employ distinct and useful families of nitrogen nucleophiles (anilines and 2,2,2-trifluoroacetamide), catalyzed by spirophosphine **1**. Furthermore, we have furnished the first demonstration of asymmetric reactions, affording interesting classes of target molecules, such as enantioenriched pyrrolidines, indolines, and γ-amino-α,β-unsaturated carbonyl compounds. This investigation thus adds an important new family of nucleophiles (nitrogen) to those (carbon, oxygen, and sulfur) that have previously been shown to engage in phosphine-catalyzed asymmetric γ-additions. Ongoing studies are directed at further expanding this strategy for the rapid generation of functionalized carbonyl compounds.

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Keywords: amination · asymmetric catalysis · heterocycles · organocatalysis · phosphanes

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[7] For a review and leading references on catalytic asymmetric β functionalizations of carbonyl compounds, see: *Catalytic Asymmetric Conjugate Reactions* (Ed.: A. Cordova), Wiley-VCH, Weinheim, **2011**.

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[12] γ-Aminobutyric acid (GABA), γ-amino-β-hydroxybutyric acid (GABOB), carnitine, statine, and pregabalin (Lyrica) are examples of bioactive γ-aminocarboxylic acids.

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[14] For complementary methods for catalytic asymmetric γ-aminations that employ a nitrogen electrophile, see: a) T. B. Poulsen, C. Alemparte, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 11614 – 11615; b) S. Bertelsen, M. Marigo, S. Brandes, P. Dinér, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 12973 – 12980; c) J. Wang, J. Chen, C. W. Kee, C.-H. Tan, *Angew. Chem.* **2012**, *124*, 2432 – 2436; *Angew. Chem. Int. Ed.* **2012**, *51*, 2382 – 2386.

[15] We are not aware of any reports of phosphine-catalyzed intramolecular γ-additions of nitrogen nucleophiles to γ-substituted 2,3-allenoates or 2-alkynoates, or of any enantioselective intra- or intermolecular processes. For reports of non-asymmetric intermolecular additions to γ-substituted electrophiles, all of which proceed in $\leq 30\%$ yield, see: a) B. M. Trost, G. R. Dake, *J. Am. Chem. Soc.* **1997**, *119*, 7595 – 7596 (9% yield); b) B. Liu, R. Davis, B. Joshi, D. W. Reynolds, *J. Org. Chem.* **2002**, *67*, 4595 – 4598 (17% and 28% yield); c) D. Virieux, A.-F. Guillouzic, H.-J. Cristau, *Tetrahedron* **2006**, *62*, 3710 – 3720 (30% yield).

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[17] For the development of spirophosphine **1** as a chiral ligand for metal-catalyzed enantioselective processes, see: a) S.-F. Zhu, Y. Yang, L.-X. Wang, B. Liu, Q.-L. Zhou, *Org. Lett.* **2005**, *7*, 2333 – 2335; b) J.-H. Xie, Q.-L. Zhou, *Acc. Chem. Res.* **2008**, *41*, 581 – 593.

[18] For the first use of spirophosphine **1** as a chiral nucleophilic catalyst, see Ref. [4a]. Spirophosphine **1** is not highly susceptible to oxidation: after exposure of the solid to air for three days at room temperature, no phosphine oxide is observed by NMR spectroscopy.

[19] Spirophosphine **1** is commercially available.

[20] For leading references on the enantioselective synthesis of pyrrolidines, see: *Asymmetric Synthesis of Nitrogen Heterocycles* (Ed.: J. Royer), Wiley-VCH, Weinheim, **2009**.

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[22] Under our standard conditions: 1) the *ee* of the product was constant during the course of a γ-addition process; 2) in the absence of spirophosphine **1**, no reaction was observed; 3) the phosphine oxide of **1** does not serve as a catalyst for γ-addition; 4) six-membered ring formation was less effective; 5) γ-addition to an alkyne substituted with a Weinreb amide proceeded in excellent *ee* but modest yield; 6) 2,4-dimethoxyphenol enhances the yield, not the enantioselectivity.

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[24] a) Under our standard conditions: 1) the *ee* was constant during the course of a γ-addition; 2) the carboxylic acid and the phenol additives that we examined were deleterious with respect to *ee*, yield, or *E*/*Z* selectivity; 3) in the absence of spirophosphine **1**, no reaction was observed; 4) the phosphine oxide of **1** does not serve as a catalyst for γ-addition; 5) an allenoate with a γ-isopropyl substituent, a 2-alkynoate, an allenyl phosphonate, and an allenyl nitrile were not suitable electrophiles; 6) 1,3-diene is a side product. b) In a preliminary study, we determined that spirophosphine **1** can catalyze the γ-addition of $TsNH_2$ to an allenoate in 68% *ee* and 75% yield (unoptimized); further exploration revealed that phosphepine **2** can achieve an array of γ-additions of $TsNH_2$ with ca. 85% *ee* and ca. 85% yield (ca. 85:15 *E*/*Z*; toluene, RT).

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