Phosphine Catalysis

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Phosphine-Catalyzed Enantioselective γ-Addition of 3-Substituted Oxindoles to 2,3-Butadienoates and 2-Butynoates: Use of Prochiral Nucleophiles**

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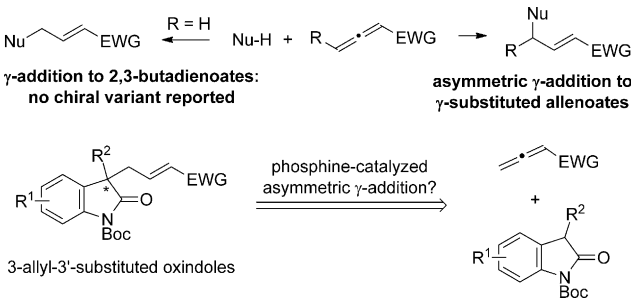
Abstract: *The first phosphine-catalyzed enantioselective γ-addition with prochiral nucleophiles and 2,3-butadienoates as the reaction partners has been developed. Both 3-alkyl- and 3-aryl-substituted oxindoles could be employed in this process, which is catalyzed by a chiral phosphine that is derived from an amino acid, thus affording oxindoles that bear an all-carbon quaternary center at the 3-position in high yields and excellent enantioselectivity. The synthetic value of these γ-addition products was demonstrated by the formal total synthesis of two natural products and by the preparation of biologically relevant molecules and structural scaffolds.*

Nucleophilic catalysis with chiral phosphines has captured considerable attention in recent years.[1] In the most common mode of activation, a phosphine activates an alkene, allene, or alkyne by forming a phosphonium enolate intermediate, which reacts with a suitable electrophile. Reactions in this category include phosphine-catalyzed (aza)-Morita–Baylis–Hillman (MBH) reactions[2] and various cycloadditions.[3] The high nucleophilicity of the phosphorus atom is also well utilized for chiral phosphine promoted kinetic resolution,[4] and a number of catalytic processes that employ MBH-type adducts.[5] On the other hand, the phosphonium enolate intermediate that is generated upon phosphine addition is basic in nature and could thus be utilized for the activation of pronucleophiles. In this context, we recently developed the first chiral phosphine catalyzed asymmetric Michael addition reaction.[6] Phosphine-mediated γ-addition reactions are mechanistically similar, and a few examples of their applications in organic synthesis have been reported. Pioneering studies on phosphine-mediated γ-addition reactions of pronucleophiles to allenoates or alkynoates were first disclosed by the groups of Trost[7a–c] and Lu[7d] in the 1990s. However, asymmetric variants of the γ-addition reaction were not reported until more than a decade later.

Recently, Fu and co-workers described enantioselective γ-addition reactions of oxygen,[8a] carbon,[8b,c] sulfur,[8d] and nitrogen[8e] pronucleophiles to γ-substituted allenoates and/or alkynoates by utilizing C_2-symmetric chiral phosphine catalysts. To date, γ-substituted allenes have been employed in a vast majority of the reported phosphine-mediated γ-additions, and only the enantioselective formation of stereocenters at the γ-position was successfully demonstrated. In sharp contrast, there is virtually no progress on the use of prochiral nucleophiles for phosphine-triggered γ-addition reactions (Scheme 1), despite the fact that this type of



Scheme 1. Phosphine-catalyzed γ-addition of oxindoles.

addition reaction can be synthetically highly valuable. To the best of our knowledge, there has been only one report by Zhang and co-workers that describes the γ-addition of β-ketoesters to allenoates.[9] However, the enantioselectivity and the scope of that reaction were disappointing. The difficulty in achieving an adequate level of stereochemical control in γ-addition reactions with prochiral nucleophiles may be attributed to the fact that the newly formed stereogenic center is rather distant from the allene/alkyne reaction partner. It thus became our goal to demonstrate that excellent stereochemical control can be realized in a phosphine-catalyzed γ-addition of pronucleophiles to an allene.

Optically active 3,3′-disubstituted oxindole frameworks are a prominent substructure in bioactive molecules. In particular, oxindoles that bear an allyl-substituted quaternary stereogenic center at the 3-position[10] have attracted considerable attention owing to their biological significance and great synthetic value. In their pioneering studies, Trost and co-workers developed palladium-[11a,b] and molybdenum-catalyzed[11c–f] asymmetric allylic alkylation (AAA) reactions of 3-substituted oxindoles to synthesize chiral 3-allyl-3′-substituted oxindoles. Kozlowski and Taylor utilized Pd-catalyzed processes for the synthesis of allyl-substituted oxindoles.[12] Krische et al. developed the iridium-catalyzed enantioselective allylation, crotylation, and reverse prenylation of sub-

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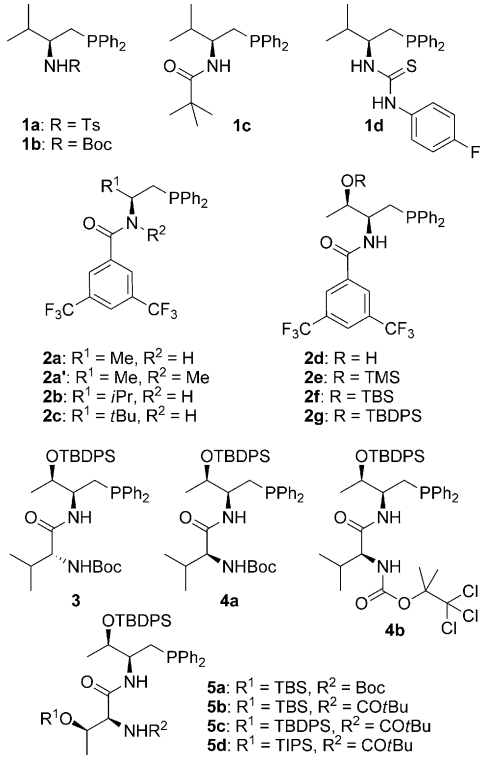
stituted isatins.[13] The only reported organocatalytic variant entails the utilization of MBH carbonates in an AAA reaction of 3-substituted oxindoles, which was described by Chen and co-workers.[14] There clearly exists a need for an effective non-metal-based approach to access enantioenriched 3-allyl-3′-substituted oxindoles. Herein, we describe a highly enantioselective allyl-type functionalization of 3-substituted prochiral oxindoles by a chiral phosphine mediated γ-addition reaction that employs simple 2,3-butadienoates (Scheme 1).

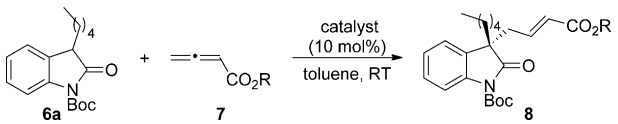
To begin our investigations, we first wanted to establish that phosphine catalysts may effectively promote the γ-addition of 3-pentyloxindole to an allenoate. A range of amino acid based chiral phosphines[15] were used in this study (Scheme 2). It was very encouraging to see that all of the



Scheme 2. Phosphine catalysts employed in this study.

bifunctional phosphines that were tested effectively catalyzed the reaction. L-Valine-derived phosphines led to the formation of the desired γ-addition product in good yields, but the stereoselectivity was poor (Table 1, entries 1–4). However, by changing the substituent on the nitrogen atom, efficient phosphine catalysts were obtained, which furnished the desired products with good enantioselectivities (entries 5–11). Alanine-derived phosphine **2a** turned out to be the most suitable catalyst, affording the γ-addition product in 93% yield and with 86% *ee*. Dipeptide phosphines only led to poor stereoselectivity (entries 12–13). Subsequently, we further optimized the reaction conditions by varying the ester moiety of the allenoate (entries 14–16). Among all of the allenoates examined, the *tert*-butyl ester was found to provide the corresponding product with the highest enantioselectivity

Table 1: Screening and optimization for the asymmetric γ-addition of 3-alkyl-substituted oxindoles to allenoates.[a]

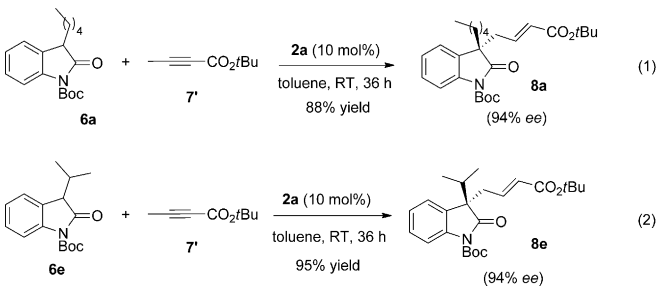


Entry	Catalyst	*t* [h]	R	8	Yield[b] [%]	*ee*[c] [%]
1	**1a**	15	$CHPh_2$	**8a-4**	67	20
2	**1b**	15	$CHPh_2$	**8a-4**	78	27
3	**1c**	15	$CHPh_2$	**8a-4**	62	21
4	**1d**	18	$CHPh_2$	**8a-4**	82	53
5	**2a**	15	$CHPh_2$	**8a-4**	93	86
6	**2b**	15	$CHPh_2$	**8a-4**	90	79
7	**2c**	24	$CHPh_2$	**8a-4**	79	60
8	**2d**	24	$CHPh_2$	**8a-4**	79	60
9	**2e**	15	$CHPh_2$	**8a-4**	90	80
10	**2f**	15	$CHPh_2$	**8a-4**	85	79
11	**2g**	15	$CHPh_2$	**8a-4**	83	78
12	**3**	24	$CHPh_2$	**8a-4**	90	5
13	**4a**	24	$CHPh_2$	**8a-4**	86	11
14	**2a**	15	Et	**8a-1**	96	90
15	**2a**	**15**	***t*Bu**	**8a-2**	**95**	**94**
16	**2a**	15	Bn	**8a-3**	94	75

[a] Reactions were performed with **6a** (0.1 mmol), **7** (0.15 mmol), and catalyst (0.01 mmol) in toluene (1.0 mL) at room temperature. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl, TMS = trimethylsilyl, Ts = 4-toluenesulfonyl.

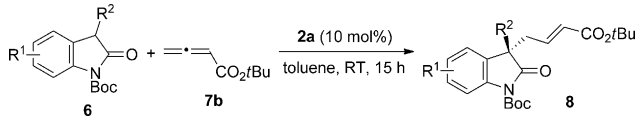
(94% *ee*; entry 15). A solvent screen and varying the reaction temperature did not lead to further improvements.[16]

With the optimized reaction conditions in hand, the scope of this reaction was evaluated. Different 3-alkyl-substituted oxindoles were smoothly transformed into the corresponding products; the reaction was insensitive to the length of the alkyl chain, and both linear and branched alkyl groups were tolerated (Table 2, entries 1–10). Furthermore, substituents on the oxindole core had only small effects on both the reactivity and the enantioselectivity (entries 11 and 12). 2-Butynoate (**7′**) could also be employed instead of the allenoate. Although the reactions proceeded more slowly, the enantioselectivity remained the same [Eq. (1) and Eq. (2)]. The absolute configuration of the γ-addition products was determined by comparing the optical rotation of derivative **14** (Scheme 3) with a previously reported value.[11c]



Our next goal was to extend the scope of this transformation to 3-aryl-substituted oxindoles. This seems to be

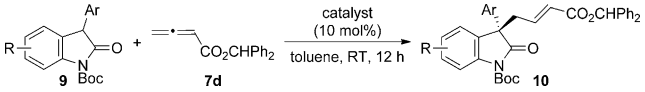
Table 2: Substrate scope for the asymmetric γ-addition of 3-alkyl-substituted oxindoles to allenoate **7b**.[a]



Entry	R^1	R^2	8	Yield[b] [%]	*ee*[c] [%]
1	H	nC_5H_{11}	**8a**	95	94
2	H	Me	**8b**	96	88
3	H	Et	**8c**	96	92
4	H	*n*Pr	**8d**	95	89
5	H	*i*Pr	**8e**	98	94
6	H	nC_4H_9	**8f**	95	93
7	H	nC_6H_{13}	**8g**	98	90
8	H	$CH(CH_2)_4$	**8h**	92	90
9	H	$CH(CH_2)_5$	**8i**	97	93
10	H	$CH(CH_2)_6$	**8j**	91	92
11	5-MeO	Me	**8k**	98	89
12	5-Br	*i*Pr	**8l**	98	85
13	H	CH_2Ph	**8m**	97	81

[a] Reactions were performed with **6** (0.10 mmol), **7b** (0.15 mmol), and **2a** (0.01 mmol) in toluene (1.0 mL) at room temperature for 15 h. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase.

Table 3: Asymmetric γ-addition of 3-aryl-substituted oxindoles **9** to allenoate **7d**.[a]

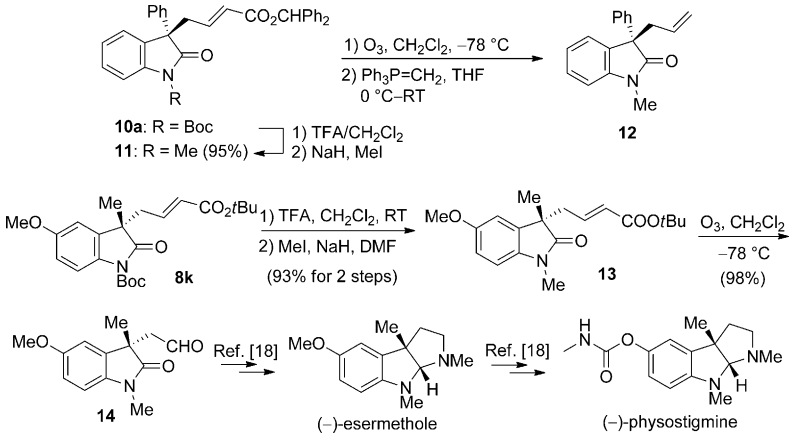


Entry	Ar	R	Cat.	10	Yield[b] [%]	*ee*[c] [%]
1	C_6H_5	H	**4a**	**10a**	89	80
2	C_6H_5	H	**4b**	**10a**	87	66
3	C_6H_5	H	**5a**	**10a**	94	83
4	C_6H_5	H	**5b**	**10a**	90	89
5	C_6H_5	H	**5c**	**10a**	89	88
6	C_6H_5	H	**5d**	**10a**	95	91
7	3-Me-C_6H_4	H	**5d**	**10b**	94	86
8	4-Me-C_6H_4	H	**5d**	**10c**	96	90
9	4-*t*Bu-C_6H_4	H	**5d**	**10d**	93	88
10	4-Ph-C_6H_4	H	**5d**	**10e**	91	90
11	4-MeO-C_6H_4	H	**5d**	**10f**	92	90
12	4-F-C_6H_4	H	**5d**	**10g**	96	88
13	4-Cl-C_6H_4	H	**5d**	**10h**	86	89
14	3,5-Me-C_6H_3	H	**5d**	**10i**	96	90
15	C_6H_5	5-MeO	**5d**	**10j**	95	92
16	C_6H_5	5-Me	**5d**	**10k**	96	90
17	C_6H_5	5-F	**5d**	**10l**	90	86
18	C_6H_5	5,7-Me	**5d**	**10m**	94	82

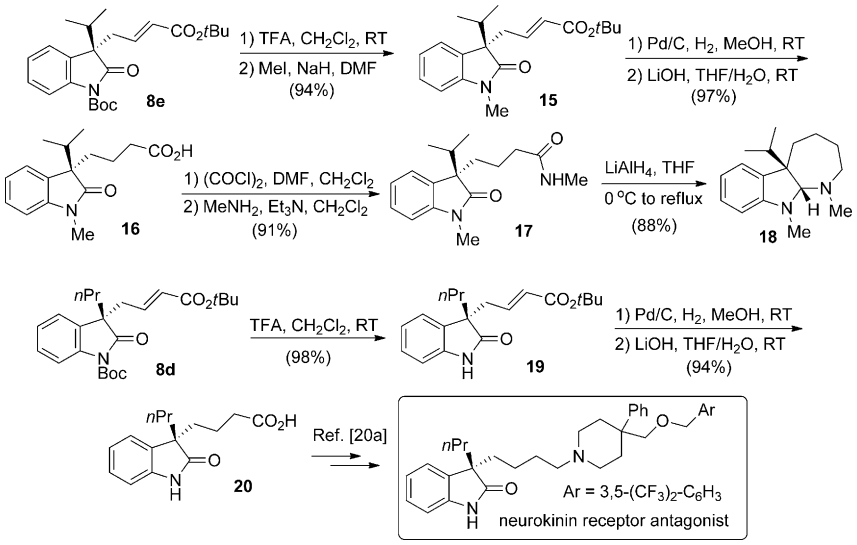
[a] Reactions were performed with **9** (0.1 mmol), **7d** (0.12 mmol), and the catalyst (0.01 mmol) in toluene (1.0 mL) at room temperature for 12 h. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase.

challenging as a catalytic system rarely works for both alkyl- and aryl-substituted substrates, but we speculated that we might be able to tackle this task with our highly tunable dipeptide-based catalytic systems. To our delight, γ-addition of 3-phenyloxindole to allenoate **7d** proceeded smoothly in the presence of dipeptide-based phosphines (Table 3).[16] Phosphines that are derived from L-Thr–L-Thr were found to be effective catalysts of this transformation and afforded the desired product in high yields and with excellent enantioselectivity (entries 1–6). When the most suitable catalyst of the series, namely **5d**, was employed, the reaction worked very well for various 3-aryl-substituted oxindoles (entries 7–14) and oxindole cores with different substituents (entries 15–18). The absolute configuration of the γ-addition products was assigned by comparing the optical rotation of derivative **12** (Scheme 3) with a previously reported value.[17]

The products of the γ-addition process possess an all-carbon quaternary stereogenic center at the 3-position with a latent allyl group; these structures are not only interesting from a biological point of view, but also synthetically valuable. Adduct **10a** could be readily converted into 3-allyl-substituted oxindole **12** in high yield through a few simple transformations (Scheme 3). Aside from the metal-mediated allylation processes that were reported by Trost and co-workers[11], this process is the only alternative asymmetric method to access these types of compounds. Moreover, the utility of the oxindole products that were obtained by γ-addition was demonstrated by a formal total synthesis of (−)-esermethole and (−)-physostigmine. Oxindole **8k**, which was obtained by a γ-addition process catalyzed by **2a**, was transformed into the known aldehyde **14** in high yield; this compound can be converted into (−)-esermethole and (−)-physostigmine according to literature precedents.[11c,18] The γ-addition adducts bear a crotonic acid subunit at the quaternary carbon center, which offers great opportunities for further structural elaborations. Compound **8e** was transformed into acid **16** in high yield through a few trivial steps; **16** was further converted into key intermediate **17** (Scheme 4). Treatment of amide **17** with $LiAlH_4$ led to a smooth intramolecular cyclization and furnished **18**, a structural analogue of the core motif of many bioactive natural alkaloids with a seven-membered ring.[19] Furthermore, γ-addition adduct **8d** was transformed into the known acid **20** in high yield,



Scheme 3. Preparation of 3-allyl-substituted oxindoles and formal total synthesis of (−)-esermethole and (−)-physostigmine.



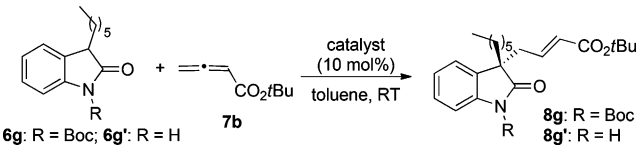
Scheme 4. Synthetic manipulations of γ-addition adducts.

which can be converted into neurokinin receptor antagonists using procedures that are described in the literature.[20a]

The mechanism of the γ-addition described herein was not rigorously studied at this stage, and we believe that the reaction follows the general mechanism that is described in the literature.[8b] When the reaction was performed in the presence of D_2O,[21] deuterium incorporation into the product was observed, which suggests the beneficial role of water in the catalytic cycle; this result is in good agreement with previous mechanistic findings that were reported by Yu and co-workers.[22] In our proposed transition state model, the amide N–H bond forms hydrogen bonds with the oxindole enolate and the carbamate functionality and directs the subsequent attack to the C=C bond. We presumed that both the Brønsted acid moiety of the chiral phosphine and Boc protection of the oxindole nitrogen atom are essential for the observed asymmetric induction. To provide experimental support, we prepared methylated catalyst **2a′** and substrate **6g′** which does not contain a Boc group. The presence of the free NH group in **2a** and the utilization of the *N*-Boc-protected substrate **6g** were crucial for both reactivity and enantioselectivity of the reaction. When methylated **2a′** was used as the catalyst or oxindole **6g′** was employed as the substrate, the reaction proceeded much more slowly, and the enantioselectivities decreased substantially (Table 4).

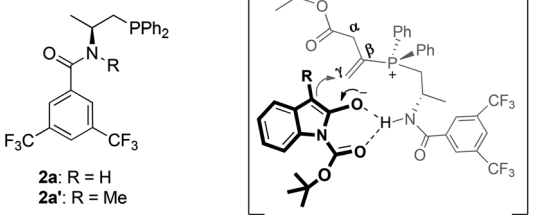
In conclusion, we have developed the first phosphine-catalyzed asymmetric γ-addition reaction that involves 2,3-butadienoates as the reaction partner for the enantioselective allyl-type functionalization of 3-substituted oxindoles. This process enabled the formation of oxindole derivatives with an all-carbon quaternary stereogenic center at the 3-position in high yields and excellent enantioselectivities. Its synthetic utility was amply demonstrated by the formal total synthesis of two natural products and the preparation of molecules and structural motifs of biological significance. We are currently extending the concept described herein to other organic reactions.

Table 4: Asymmetric γ-addition promoted by different phosphines and proposed transition state model.[a]



Entry	6	Catalyst	*t* [h]	8	Yield[b] [%]	*ee*[c] [%]
1	**6g**	**2a**	15	**8g**	98	90
2	**6g**	**2a′**	36	**8g**	77	44
3	**6g′**	**2a**	36	**8g′**	81	53

[a] Reaction conditions: **6** (0.10 mmol), **7b** (0.15 mmol), and catalyst (0.01 mmol) in toluene (1.0 mL). [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase.



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