Asymmetric Catalysis

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Silver-Catalyzed Allenylation and Enantioselective Propargylation Reactions of Ketones**

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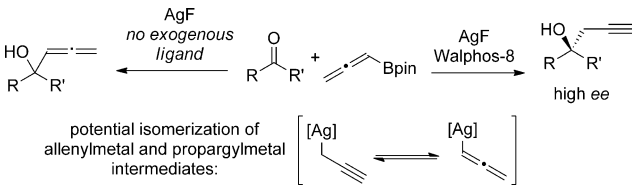
Homopropargylic alcohols have garnered significant interest as useful building blocks for complex molecule synthesis.[1] This structural motif is frequently formed through the addition of propargylic nucleophiles to the corresponding aldehyde or ketone.[2,3] Early advances focused on the development of stoichiometric addition reactions of chiral allenylboron reagents to aldehydes. In the early 1990s, the first catalytic asymmetric methods to form chiral secondary alcohols were reported, spurring renewed interest in the field.[2] Additions to aldehydes have been extensively studied and new asymmetric catalysts have recently been identified for enantioselective propargylation reactions of ketones, which employ propargyl- or allenylboron reagents or propargyl bromide as starting materials, to form the corresponding tertiary alcohols.[4,5] Several of these catalyst systems provide high enantioselectivity in additions to methyl ketones. Enantioselective propargylation reactions of prochiral diaryl ketones have not been reported, however.[6] Herein, we report silver-catalyzed allenylation and propargylation reactions on a wide range of ketones (Scheme 1). Allenylation predominates in the absence of exogenous ligands, whereas enantioselective propargylation takes place in the presence of a chiral phosphine ligand. To the best of our knowledge, this is the first report of catalytic enantioselective propargylation reactions of prochiral benzophenones.

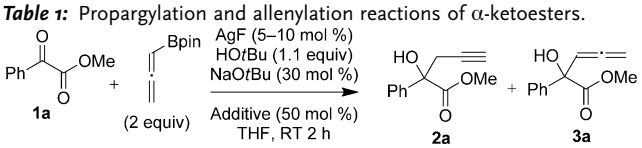


Scheme 1. Silver-catalyzed allenylation and enantioselective propargylation reactions of ketones.

In previous work, our group has investigated the metal-catalyzed reactions of allenylboronic acid pinacol ester with a series of electrophiles, using both palladium and silver catalysts.[7] We found that silver complexes ligated by phosphine ligands catalyze the enantioselective propargylation reaction of imines to provide enantioenriched homopropargyl amines.[8,9] We hypothesized that a silver catalyst could also facilitate the enantioselective propargylation reactions of ketones.[10,11]

We sought to identify suitable silver catalysts for allenylation and propargylation reactions of ketones with control of chemo- and enantioselectivity. As the formation of either allenyl or propargylic products could stem from isomerization of allenyl and propargylmetal intermediates (Scheme 1),[12] we hypothesized that controlling the relative reactivity of these intermediates would be essential in achieving highly selective reactions. We first examined reactions of α-ketoesters using silver catalysts in the absence of exogenous ligands. In contrast to our studies with imines, where Walphos-1 (see Table 2 for structure) was required, we determined that silver fluoride alone provided good yield and chemoselectivity, giving allenyl alcohol as the major product (Table 1, entries 1 and 2).[8] To our surprise, upon addition of a halide, the selectivity of the reaction switched to favor propargylation as the major pathway (entries 3–6).[13] Therefore, under optimized conditions, either allene **3a** (entry 2) or alkyne **2a** (entry 6) can be accessed as the major product using the same starting materials, depending upon the presence or absence of nBu$_4$NI. The ability to form either product supports a mech-

Table 1: Propargylation and allenylation reactions of α-ketoesters.



Entry	Base	Additive	Yield [%][a]	Ratio (**2a**/**3a**)[b]
1[c]	KO*t*Bu	–	61	1:11
2[c]	**NaO*t*Bu**	–	**75**	**1:5.8**
3	NaO*t*Bu	LiCl	65	1.8:1
4[c]	NaO*t*Bu	nBu$_4$Cl	78	8.8:1
5	NaO*t*Bu	nBu$_4$Br	79	6.2:1
6	**NaO*t*Bu**	**nBu$_4$I**	**77**	**14.4:1**

[a] Determined by ^{1}H NMR spectroscopy using PhSiMe$_3$ or 1,4-dimethoxybenzene as an internal standard. [b] Ratio determined by ^{1}H NMR spectroscopic analysis of the purified mixture of **2** and **3** after silica gel column chromatography. [c] 18 h reaction time.

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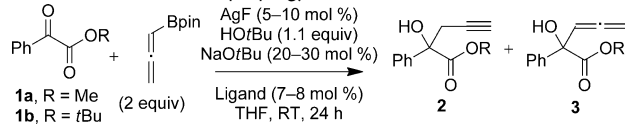
anism that includes the opportunity for isomerization of allenyl– and propargyl–metal intermediates.

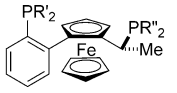
We hypothesized that the halide additives promoting the propargylation reaction act as ligands for the silver catalyst.[14] Therefore, replacing the halide with a chiral ligand, such as a phosphine, could result in the formation of enantioenriched products. Based on the knowledge gained from our identification of enantioselective catalysts for propargylation reactions of imines, we examined a series of bidentate phosphine ligands.[8] As expected, propargylation was favored in the presence of phosphine ligands (Table 2). This is consistent

Table 2: Enantioselective propargylation reactions of α-ketoesters.



Entry	Ligand	R	Yield [%][a]	Ratio (**2**/**3**)[b]	*ee* [%] **2**[c]
1	Walphos-1	Me	87	3.3:1	45
2	Walphos-2	Me	58	6.5:1	15
3	Walphos-8	Me	79	4:1	72
4[d]	Walphos-8	Me	74	13:1	63
5	Walphos-8	*t*Bu	95	3.2:1	79
6[e]	Walphos-8	*t*Bu	88	3.0:1	86
7[e,f]	**Walphos-8**	***t*Bu**	**67**	**2.5:1**	**91**

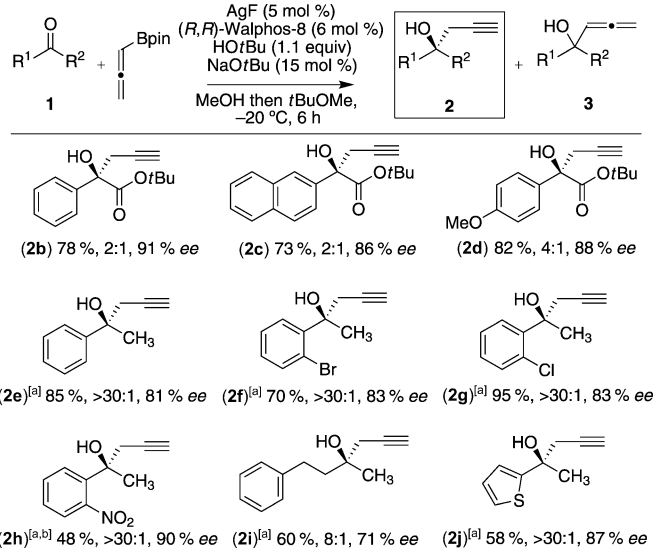
[a] Yield determined after isolation of **2** and **3** by flash column chromatography. [b] Ratio determined by ^{1}H NMR spectroscopic analysis of the purified mixture of **2** and **3** after silica gel column chromatography. [c] Enantioselectivity determined by analysis of purified reaction mixture by SFC analysis on a chiral stationary phase. [d] nBu$_4$NI (50 mol%) added (we acknowledge Charlotte A. Osborne for this data). [e] Reaction performed at −20°C. [f] Reaction performed in *tert*-butyl methyl ether as solvent.



Walphos-1: R' = Ph; R"= 3,5-(CF$_3$)-C$_6$H$_3$
Walphos-2: R'= Ph; R"= Ph
Walphos-8: R' = Cy; R"= 3,5-(CF$_3$)-C$_6$H$_3$

with our findings for imines, the Walphos ligand scaffold provided the highest levels of enantioselectivity.[15] Whereas Walphos-1 gave an initial promising result of 45% *ee*, Walphos-8, which combines a more electron-rich phosphine with the electron-poor phosphine found in Walphos-1, provided higher enantioselectivities (entries 3–6). Increasing the steric bulk of the ester and cooling the reaction to −20°C further improved the *ee* to 86% (entry 6). Examining alternative solvents gave an additional increase in enantioselectivity to afford the tertiary homopropargylic alcohol in 91% *ee* (entry 7).

After a brief reaction optimization to increase the yield, a selection of pyruvates was examined (Scheme 2). Overall, α-ketoesters afford the tertiary alcohols in high yield, with good enantioselectivity for the propargylic products (**2b**–**2d**). These substrates provided modest selectivity of propargyl over allenyl products, ranging from 2:1 to 4:1. We next examined reactions of simple ketones and found that acetophenone derivatives furnished homopropargyl tertiary alcohols with good enantioselectivities,[17] high selectivity for propargylation over allenylation (>30:1), and good yield



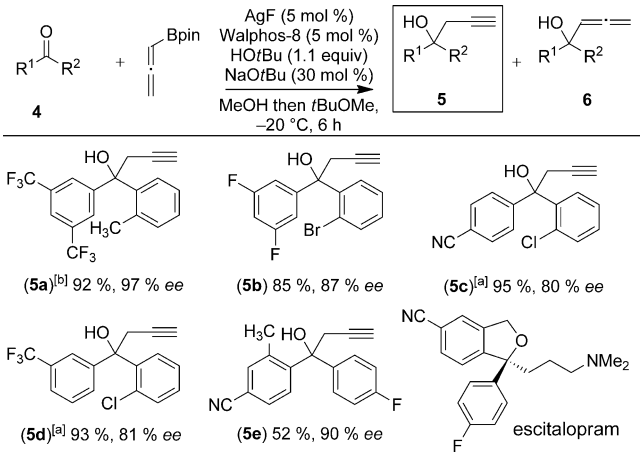
Scheme 2. Ketoester and ketone scope. [a] Reaction run with AgF (10 mol%), Walphos-8 (11 mol%), and NaO*t*Bu (30 mol%). [b] Product **2h** was isolated as an inseparable mixture with **1h**; see the Supporting Information for details. Pin = pinacolyl.

(**2e**–**2h**). A heterocyclic ketone and an aliphatic ketone also performed well under the reaction conditions (**2i** and **2j**). In all reactions with ketones, no aldol-type products are observed.[18] After consumption of the allenylboronic acid pinacol ester, only ketone and desired product remain in the reaction mixture.

Asymmetric addition to ketones typically requires a large steric difference between the two carbon fragments in order to differentiate the *re* and *si* faces. We were intrigued by the challenge presented by prochiral diaryl ketones, as few methods for the asymmetric addition to this class of ketones exist.[19–21] In 2006, the Leighton group reported the highly enantioselective allylation of prochiral 2′-hydroxyphenylketones, where the phenol directing group accelerates reaction rates and differentiates the arenes.[6] To the best of our knowledge, however, enantioselective propargylation of prochiral benzophenones has not been demonstrated. The ability of the silver catalyst to distinguish between two aromatic rings would lead to enantioenriched diaryl carbinols, which are present in a variety of drugs[22] and medicinal agents.[23]

We were pleasantly surprised to find that *ortho*-substituted benzophenones provide the desired products in high enantioselectivity (Scheme 3).[24] Various substituents are tolerated in the *ortho*-position, including methyl groups (**5a** and **5e**) and halogens (**5b**, **5c**, and **5d**). Substrate **5e** is structurally similar to escitalopram, currently used clinically for treatment of major depressive and generalized anxiety disorders.[21,25]

In summary, we have developed silver-catalyzed addition reactions of allenylboronic acid pinacol esters to ketones, to provide tertiary alcohols. The reaction conditions can be easily modified to selectively promote either allenylation or propargylation reactions. Asymmetric synthesis of homopropargylic tertiary alcohols using a chiral silver complex has been achieved. Diverse substrates, including *ortho*-substi-



Scheme 3. Asymmetric propargylation reactions of benzophenones. The **5**/**6** ratio in all reactions is >30:1, as determined by ^{1}H NMR spectroscopic analysis of the purified mixture of **5** and **6** after silica gel column chromatography. [a] Reaction run in THF solvent. [b] Enantiomers of **5a** were not separable by supercritical fluid chromatography (SFC) on a chiral stationary phase; *ee* was determined after Sonagashira coupling; see the Supporting Information for details.

tuted prochiral benzophenones, undergo smooth reaction to provide optically enriched diaryl alcohols in good yields and high enantioselectivities. Experiments designed to elucidate the mechanism of this reaction are underway.

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