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Chiral allene-containing phosphines in asymmetric catalysis

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Abstract

Traditionally, ligands used in asymmetric catalysis have contained either stereogenic atoms or hindered single bonds (atropisomerism), or both. Here we demonstrate that allenes, chiral 1,2-dienes, appended with basic functionality can serve as ligands for transition metals. We describe an allene-containing bisphosphine that, when coordinated to Rh(I), promotes the asymmetric addition of aryl boronic acids to α-keto esters with high enantioselectivity. Solution and solid-state structural analysis reveals that one olefin of the allene can coordinate to transition metals generating bi- and tri-dentate ligands.

Stereochemistry is often critical to the function of small molecules. Their activity depends on their three-dimensional shape–a direct consequence of stereochemistry. Indeed, it is instructive that nearly all natural products and most new drugs are chiral[1] and there is increasing pressure to manufacture chiral pharmaceuticals in optically active form.[2] Accordingly, synthetic chemists seek to prepare these substances as single enantiomers to understand and exploit their structure and function. Among common approaches to control absolute stereochemistry, asymmetric catalysis offers significant advantages. These methods have been the subject of academic inquiry and industrial implementation.[3] In particular, the last several decades have witnessed continued introduction and development of chiral ligands for transition metals.[4] Future developments in asymmetric catalysis will likewise depend on the discovery of novel ligand scaffolds.

Most existing ligands for asymmetric catalysis are characterized by either of two types of chirality: some species owe their chirality to stereogenic atoms, usually tetrahedral carbon or phosphorus. Chiraphos (**1**, Fig 1) is a representative example. Many others are chiral by virtue of hindered rotation around a carbon-carbon single bond, exemplified by BINAP (**2**). Some of the most successful catalysts, such as the phosphoramidite **3**, combine the elements of both central and axial chirality.[5] Planar chirality (e.g. **4**[6]) and spiro-type axial chirality (e.g. **5**)[7] have been exploited in asymmetric catalysis, although less frequently.

Allenes can be chiral, but have never been incorporated into ligands involved in asymmetric catalysis. Soai's group demonstrated that optically active disubstituted allenes could induce asymmetry in the addition of diisopropyl zinc to pyrimidine carboxaldehyde.[8] This unique system combines a strong non-linear effect and auto-catalysis, and so neither the nature nor the extent of asymmetric induction by the allene is clear.[9] In pioneering work, Krause and

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Supporting Information Available: Experimental details, characterization data, and crystal structure files.

coworkers reported allene-containing ligands for silver, but catalysis, asymmetric or otherwise, was not reported.[10] Our own efforts in this area led to the invention of bisphosphine oxide **6**, which promotes the addition of $SiCl_4$ to *meso*-epoxides with high enantioselectivity.[11] We report here a new class of phosphine-containing allenes that serve as ligands for transition metals and enable asymmetric catalysis with rhodium. Furthermore, we describe crystallographic studies of the first optically active transition metal-allene complexes.

Allenes can be formed in the presence of, and are thus stable to, many main group[12] and transition metals.[13] Nonetheless, allenes are known to react with both electrophiles and nucleophiles, and they are prone to racemization by transition metals.[14] For these reasons, we designed a synthesis of allene-containing phosphines (AllenePhos ligands) that offered flexibility in terms of the substituents on the allene and the identity of the phosphine (Scheme 1). For example, sulfoxide **7** was prepared as a single diastereomer by means of an acetylide addition to the corresponding ketone according to a protocol we recently disclosed.[15] Subsequent acylation and propargylic substitution with a dialkyl cuprate provided the allene **9**. Lithiation of both the sulfoxide and aryl bromide moieties followed by trapping with a chlorodiarylphosphine yielded the bisphosphine **10**. Recrystallization from hexanes provided AllenePhos **10** in optically pure form.

The synthesis of several related ligands was attempted, but not all attempts were successful. For example, the use of electron-withdrawing groups on the phosphine proved critical for the stability of the resulting ligand. Trapping with chlorodiphenyl phosphine was successful, but bisphosphine **11a** immediately oxidized to the bisphosphine oxide **11b** upon exposure to air. This sensitivity is surprising given that triphenyl phosphine is quite stable to ambient oxygen, and steric hindrance tends to impede oxidation.[16] Likewise, diphenylallene **12** was inaccessible because the trapping with chlorodiarylphosphines failed. Products were isolated that had the desired molecular weight, but were too polar. A clue to the structure of this product was provided by the attempted synthesis of **13** and **14**. In these cases, the phosphines were obtained, but displayed no optical activity. We hypothesized that reversible cyclization to zwitterion **19** allowed rotation around the C-C single bond and consequent racemization.[17] Thus, in the case of phenyl-substituted bisphosphine **12**, the zwitterion appears more stable than the allene, and was likely what we isolated instead of the desired ligand.

We reasoned that the stereochemical integrity of **10** arose from the steric environment around the allene. This congestion may prevent addition to the allene and may prevent rotation of the resultant zwitterion (i.e. **19**) even if addition occurs. Accordingly, we prepared optically active monophosphines **15** and **16** possessing bulky *tert*-butyl and *ortho*-substituted phenyl rings on one side of the allene. Additionally, we synthesized the diastereomeric sulfoxides **17** and the unfunctionalized allene **18**.[18]

We were interested in the coordination properties of the Al-lenePhos class of ligands. Thus, bisphosphine **10** and $Rh(CH_2{=}CH_2)_2(acac)$ (acac = acetylacetonato) were combined in CH_2Cl_2; single crystals of Rh(**10**)(acac) were deposited upon slow evaporation of a pentane solution. X-ray analysis revealed that **10** acts as a tridentate ligand (Fig 2) with both phosphorus atoms and the less hindered olefin coordinating to a Rh(I) center. The acac ligand completes a very distorted trigonal bipyramidal coordination sphere (P-Rh-P angle = 147°). In effect, the allene ligand adopts a helical conformation, wrapped around the Rh center. Coordination to the olefin bends the allene substantially (C-C-C angle = 148°), but the π-systems of the allene remain nearly orthogonal. The solid-state structure appears to be maintained in solution since ^{31}P NMR revealed a $^2J_{P\text{-}P}$ coupling (442 Hz) consistent with *trans*-chelation to Rh.[19] Likewise, the complex formed from AllenePhos **10** and

$[Rh(CH_2=CH_2)Cl]_2$, the optimal Rh source for the asymmetric addition,[20] displayed nearly identical ^{31}P chemical shifts and P-P and P-Rh couplings.[18]

AllenePhos ligands form stable complexes with several other transition metals. For example, monophosphine **14** coordinated with a 1:1 stoichiometry with both Ag(I) and Pt(II). Interestingly, Ag(TFA)(**14**) features little interaction between the silver ion and the allene, and the allene remains nearly linear (C-C-C angle = 179°; Fig 3a). In contrast to silver, $PtCl_2$ forms a square planar complex through interaction with both the phosphorus and allene functionalities (Fig 3b). Consequently, the allene shows substantial bending, with a C-C-C bond angle of 152°. The allene is coordinated approximately perpendicular to the coordination plane of Pt. Finally, $PtCl_2$ was found to react with bisphosphine **10** via the elimination of HCl and the formation of a C-Pt covalent bond (Fig 3c). Allenes have been observed in the coordination sphere of transition metals in a variety of contexts. Complexes of Au[21], Os[22], Mn[23], W[24], and Co[25] are known that involve direct binding of an allene to a transition metal. Furthermore, allene-containing phosphines have been characterized as ligands for Fe[26] and Os.[27] However, this study is the first to demonstrate that optically active allenes can coordinate to transition metals and maintain their stereochemical integrity. These observations suggested they might represent effective ligands for asymmetric catalysis.

For our initial studies we focused on the addition of aryl boronic acids to α-ketoesters (Table 1).[28] This transformation provides synthetically valuable tertiary alcohols in a direct and atom economical way using air-stable nucleophilic reagents. Furthermore, the generation of quaternary stereocenters remains an ongoing challenge in organic synthesis.[29] Previous work from the Zhou group revealed encouraging asymmetric induction using a phosphite ligand.[30] Thus, we examined the addition of methoxy-phenyl boronic acid (**21a**) to benzyl ester **20a** in the presence of various allene-containing ligands. Bisphosphine **10** gave the most promising reactivity and stereoselectivity. We evaluated several Rh:ligand ratios and observed no effect of excess ligand (Entry 1 vs. 2) and a small decrease in selectivity and reaction rate in the presence of excess Rh (Entry 1 vs. 3). Taken together, these data suggest that a 1:1 Rh:bisphosphine ratio is optimal, although precise control of this ratio is not necessary. The monophosphines **15** and **16** proved much less selective. Interestingly, ligand **15**, in which the phosphine is distal to the *tert*-butyl group, generated a more active catalyst than **16**, in which the phosphine is proximal to the *tert*-butyl group (entries 4 vs. 5). Likewise, the diastereomeric sulfoxides both promoted the addition, but with little asymmetry (entries 6–7).[34] Finally, unfunctionalized allene **18** did not form an active complex with Rh, (entry 8). Additional optimization demonstrated that cyclohexyl esters performed better than either smaller (entry 1 vs. 9) or larger (entry 9 vs. 11) groups, allowing the isolation of the tertiary alcohol in nearly quantitative yield and >90% ee. Lower reaction temperatures provided a slight increase in ee but lengthened the reaction time.

Several α-ketoesters were subjected to the optimized reaction conditions in the presence of AllenePhos **10** (Table 2). In general, the additions are faster and more enantioselective with electron deficient α-ketoesters. For example, a cyano-substituted ketone reacted completely with **21a** within 6 h (91% ee, entry 10) while a methyl-substituted ketone required 48 h and reacted less selectively (84% ee, entry 17). The opposite trend is observed with the aryl boronic acid component: electron rich arylboronic acids react more quickly than electron deficient ones (table 2, entry 1 vs. 2; 21 vs. 22), although the enantioselectivities are similar. An electron rich α-ketoester and an electron deficient arylboronic acid react inefficiently, even at elevated temperature (entry 20). However, the same product can be accessed by reversing the components and using an electron-rich boronic acid and electron-deficient α-ketoester (entry 21). While meta- and para- substitution on the α-ketoester are tolerated under the standard conditions, ortho substitution necessitated elevated temperatures to obtain

high yields. Fortunately, high enantioselectivity was observed even at 40 °C. (Table 2, entry 25). The reaction was similar on a small scale and on a multi-millimole scale (Table 2, entry 1). Hindered arylboronic acids do not perform well in the reaction.

Vinylboronic acids can also participate in the addition (Table 2, entries 27–34). High reactivity and moderate enantioselectivity were observed with a *trans*-disubstituted vinylboronic acid (entry 27). Lower temperature provided slight increases in optical purity. The more hindered α-substituted vinyl boronic acid gave good ee with electron deficient α-ketoesters (entries 31, 32), but lower ee with more electron rich α-ketoesters (entries 33, 34).

Several conclusions can be drawn from these studies. First, substantial steric bulk around the allene appears necessary to ensure chemical and stereochemical integrity. Even though transition metals can racemize allenes[14], bisphosphine **10** retains optical activity in the presence of Rh(I), Ag(I) and even cationic Au(I). Thus it appears that significant opportunities for catalysis exist.

Second, all of the solid-state structures we have obtained contain a π-stacking interaction between two aryl rings on opposite termini of the allene. This interaction does not require CF_3 groups because we previously observed it in the crystal structure of **6**, which lacks CF_3 groups.[11] We speculate that this characteristic may provide rigidity around the large coordination sphere and may be beneficial to asymmetric induction.

Third, we observed an interaction between Rh and Pt with the allene itself. In the case of Pt, this interaction is sufficiently activating that, in the presence of a second phosphine, elimination of HCl destroys the allene and forms a C-Pt bond. However, in the case of Rh, the interaction may be important for both catalysis and asymmetric induction. It is noteworthy that in the solid state, coordination only to the less hindered olefin (methyl-substituted) is observed. Furthermore, a comparison between monophosphines **15** and **16** is intriguing. Ligand **15** should allow coordination to the less hindered olefin, and the Rh complex derived from this ligand is very active (Table 1, entry 4). In contrast, ligand **16** contains a more hindered olefin proximal to the phosphine; it is much less active (Table 1 entry 5). Finally, coordination to the allene in bisphosphine **10** may encourage the formation of a trans-chelating complex. Consequently, the Rh center is buried within a deep chiral cavity. Only a limited number of trans-chelating bis-phosphines have been developed for asymmetric catalysis[44] so additional members of this class should be valuable. The utility of these ligands is sure to be expanded by continued developments in ligand design and the exploration of additional chemical reactions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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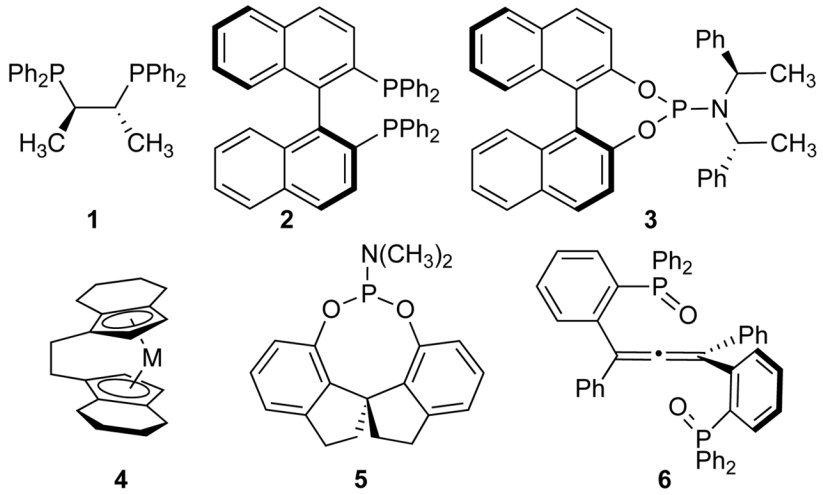


Figure 1.
Central, axial and planar stereochemistry in asymmetric catalysis

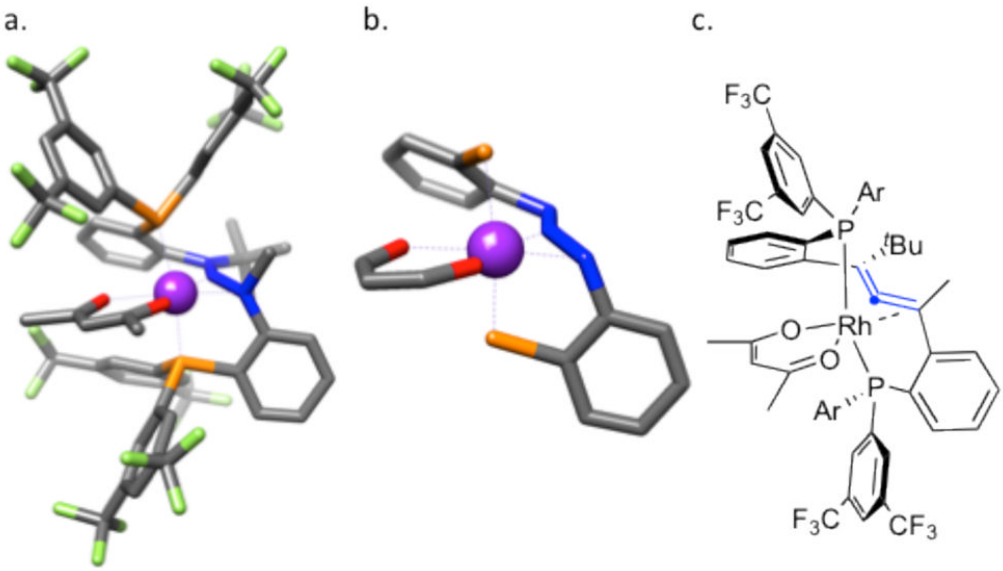


Figure 2.

Structures of Rh(acac)**10**. a. X-ray crystal structure. Two molecules of pentane and disorder in one -CF_3 group have been removed for clarity. b. X-ray crystal structure highlighting key contacts between ligands and Rh. Colors: P: orange; O: red; F: green; Rh: purple; allene highlighted in blue. Images generated with UCSF Chimera. c. Line drawing.

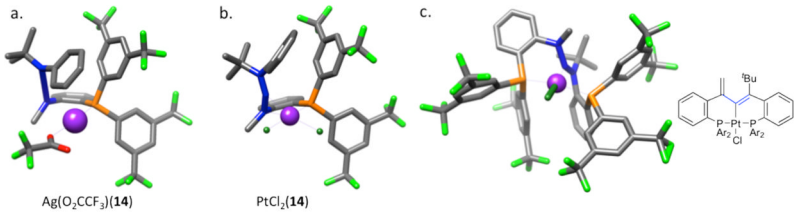
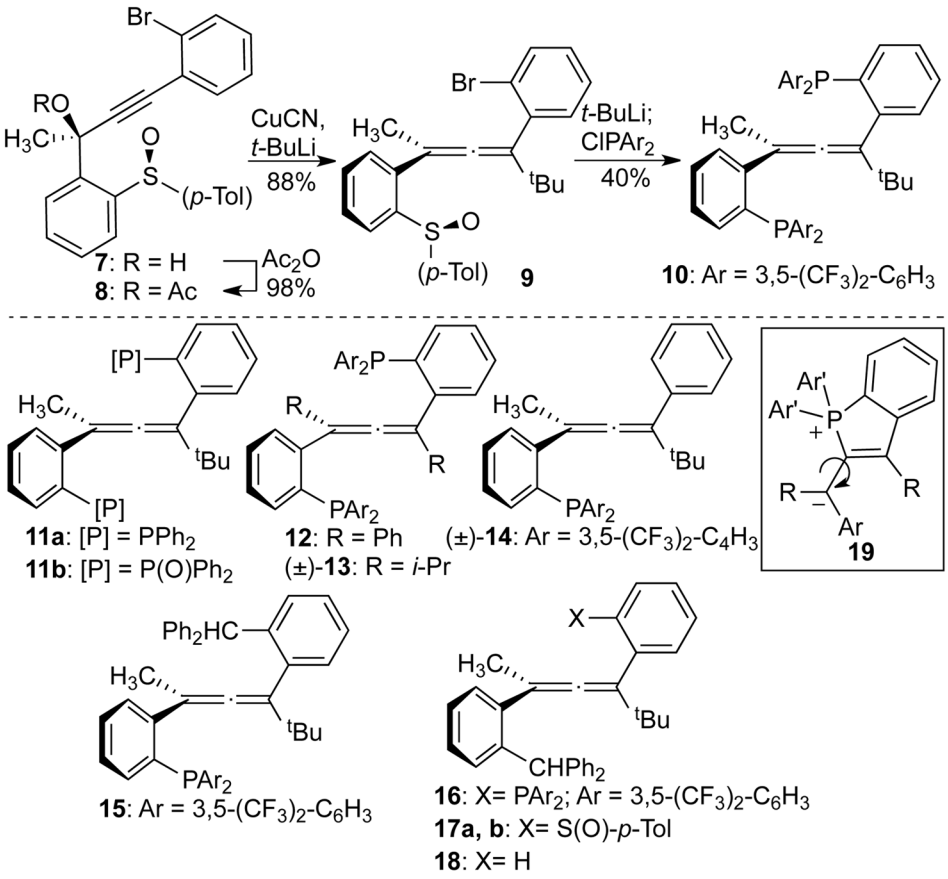


Figure 3.

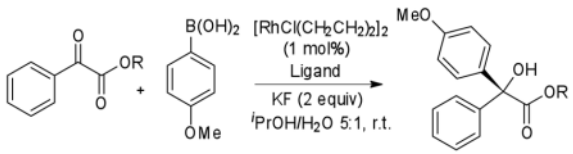
(AllenePhos)M complexes. X-ray structures of complexes formed between AllenePhos ligands and Ag(I) and Pt(II). Colors as in Fig 2. a. Ag-C_{allene} distances: 325 pm and 339 pm. P-Ag-O angle: 164°. C-C-C_{allene} angle: 179°. b. Pt-C_{allene} distances: 221 pm and 209 pm. C-C-C allene angle: 152°. Images generated with UCSF Chimera.



Scheme 1.
Synthesis and structures of allene-containing ligands.

Table 1

Enantioselective Rhodium(I)-Catalyzed Addition of Arylboronic Acids to α-Ketoesters: Evaluation of ligands, solvents and esters



20 **21a** **22**

Entry[a]	R	Ligand	Rh:L[b]	Time (h)	Yield (%)[c]	ee (%)[d]
1	Bn (**20a**)	**10**	1:1	12	80	83
2	Bn	**10**	1:2	12	85	82
3	Bn	**10**	2:1	20	83	76
4	Bn	**15**[e]	1:1	1	82	20
5	Bn	**16**	1:1	40	38	26
6	Bn	**17a**	1:1	40	81	15
7	Bn	**17b**	1:1	40	74	13
8	Bn	**18**	1:1	40	1	<5
9	**Cy (20b)**	**10**	**1:1**	**12**	**95**	**91**
10[f]	Cy	**10**	1:1	20	94	92
11	^{i}Pr (**20c**)	**10**	1:1	24	82	86
12	Ad (**20d**)	**10**	1:1	24	49	80

[a] Conditions: 0.06 mmol **20**, 0.12 mmol **21a**, 0.1 M under N_2 atmosphere.

[b] Rh:Ligand ratio.

[c] Isolated yields.

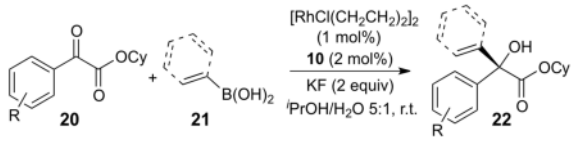
[d] Determined by HPLC.

[e] Ligand **15** approximately 75% ee.

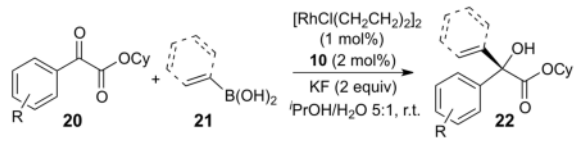
[f] Reaction at 4 °C.

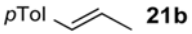
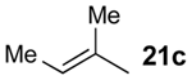
Table 2

Enantioselective Rhodium(I)-Catalyzed Addition of Boronic Acids to α-Ketoesters: Reaction Scope



Entry[a]	R		Time (h)	Yield (%)[b]	ee (%)[c]
1[d]	H	4-MeO-C_6H_4	12	90	91
2	H	4-Ph-C_6H_4	60	88	88
3	H	2-Napht	60	74	87
4	3,5-$(CF_3)_2$-	4-MeO-C_6H_4	6	90	79
5	3,5-$(CF_3)_2$-	Ph	6	89	91
6	3,5-$(CF_3)_2$-	4-Ph-C_6H_4	6	94	89
7	3,5-$(CF_3)_2$-	2-Napht	6	90	90
8	3,5-$(CF_3)_2$-	3-MeO-C_6H_4	6	87	91
9	3,5-$(CF_3)_2$-	4-Cl-C_6H_4	6	80	91
10	4-CN	4-MeO-C_6H_4	6	95	91
11	4-CN	Ph	6	81	95
12	4-CN	4-Ph-C_6H_4	6	88	93
13	4-CN	2-Napht	6	87	92
14	4-CN	3-MeO-C_6H_4	6	93	94
15	4-F	4-Ph-C_6H_4	48	77	92
16	4-F	2-Napht	48	73	83
17	4-Me	4-MeO-C_6H_4	48	81	84
18	4-Me	4-Ph-C_6H_4	72	58	87
19	4-MeO	4-Me_2N-C_6H_4	20	98	83
20[e]	4-MeO	4-Cl-Ph	72	37	80
21	4-Cl	4-MeO-C_6H_4	12	97	90



Entry[a]	R		Time (h)	Yield (%)[b]	ee (%)[c]
22	4-Cl	4-Ph-C_6H_4	24	87	90
23	3-Cl	4-MeO-C_6H_4	16	98	93
24	3-Cl	2-Napht	40	97	86
25[e]	2-Cl	4-MeO-C_6H_4	72	84	92
26	2-CF_3	4-MeO-C_6H_4	72	52	90
27	H	 **21b**	19	87	67
28[f]	H	**21b**	72	75	71
29	4-F	**21b**	24	88	69
30	4-CN	**21b**	2	84	65
31	4-CN	 **21c**	36	75	87
32	4-Cl	**21c**	36	78	85
33	H	**21c**	36	68	76
34	4-Me	**21c**	36	41	48

[a] Conditions: 0.06 mmol **20**, 0.12 mmol **21**, 0.1 M under N_2 atmosphere unless otherwise noted.

[b] Isolated yields.

[c] Determined by HPLC.

[d] 2.6 mmol **20**, 5.2 mmol **21**.

[e] Reaction at 40 °C.

[f] Reaction at −20 °C.

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