ChemPubSoc Europe

DOI: 10.1002/cctc.201300655

Catalytic Asymmetric Arylation of Enals to Enantioenriched Linear Trisubstituted Allylic Secondary Alcohols by using Aryl Lithiums Generated In Situ from Aryl Bromides

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Catalytic asymmetric addition of nucleophiles to enals is a straightforward method towards enantioenriched allylic alcohols, which are important for the synthesis of natural and pharmaceutically active compounds. Reactive aryl lithiums, produced in situ from readily available and inexpensive aryl bromides and butyl lithium, were used to enantioselectively arylate a number of α-substituted cinnamaldehydes in the presence of tetramethylethylenediamine (TMEDA), $AlCl_3$, and $Ti(OiPr)_4$. This enabled enantioenriched linear trisubstituted allylic secondary alcohols in the catalysis of (*S*)-H_8-BINOL-$(TiOiPr)_2$ complex. TMEDA coordinated the lithium salt generated in situ during transmetallation and effectively inhibited the unwanted background reaction catalyzed by the Lewis acidic lithium salt.

Linear allylic secondary alcohols are key structural motifs in a considerable number of natural products and pharmaceutically active compounds[1] and an important class of versatile building blocks for a wide range of organic transformations.[2] Dynamic kinetic resolutions[3] and catalytic asymmetric allylic substitutions[4] are the most general among the numerous disclosed methods towards enantioenriched allylic alcohols to date.[5] The acyclic α-substituted terminal diaryl allylic secondary alcohols, one class of trisubstituted allylic alcohols, are rarely disclosed regarding their asymmetric synthesis although a number of allylic secondary alcohols have been prepared through a variety of methods.[6] The catalytic asymmetric 1,2-addition of organometallics to enals is a straightforward approach through carbon–carbon bond formation from readily available and inexpensive starting materials and, therefore, of considerable importance.[7] There are only one or two examples of these alcohols scattered in several reports on the catalytic asymmetric arylation of aldehydes.[8] The most reported methods in this topic mainly employ alkylzinc reagents and diphenylzinc to react with enals.[9] Aryl lithiums can be readily and conveniently prepared in situ from the corresponding aryl bromides and *n*BuLi and are used widely in organic and pharmaceutical syntheses. To the best of our knowledge, there has been no related report on the catalytic asymmetric arylation of the α-substituted cinnamaldehydes to prepare linear trisubstituted allylic terminal diaryl secondary alcohols by using aryl lithiums as reactive nucleophiles. In this Communication, we employed aryl lithiums generated in situ from aryl bromides as reactive starting nucleophiles, with $AlCl_3$ and tetramethylethylenediamine (TMEDA) as appropriate additives, and (*S*)-H_8-BINOL as the ideal chiral ligand to realize the catalytic highly enantioselective arylation of α-substituted cinnamaldehydes. The chiral linear trisubstituted allylic diaryl secondary alcohols were achieved in up to 94% enantioselectivity and up to 99% yield.

We have used 2,2′-oxybis(*N*,*N*-dimethylethanamine) (BDMAEE) and $AlCl_3$ to modify the reactivity of aryl Grignard reagents and realize the highly enantioselective arylation of aldehydes.[8c] By using the combination of the additives, the background racemic reaction catalyzed by the intermediate Lewis acid magnesium salt was inhibited and removal of the intermediate salts from the reaction mixture was not required, avoiding tedious and laborious work. Aryl lithiums are more reactive than aryl Grignard reagents. We tried the previous strategy with $AlCl_3$ and some coordinative additive to perform the catalytic asymmetric arylation of cinnamaldehydes with aryl lithiums as the starting nucleophiles. TMEDA is much cheaper and more readily available than BDMAEE.[10] Therefore, we first chose TMEDA and $AlCl_3$ as the reactive modifying additives to investigate the enantioselectivity of the reaction (Table 1). Phenyllithium was prepared in situ from PhBr and *n*BuLi according to the conventional procedure at −78 °C. The chiral catalyst (*S*)-H_8-BINOL-$Ti(OiPr)_2$ complex was produced in situ from (*S*)-H_8-BINOL and equimolar $Ti(OiPr)_4$ in THF at room temperature. The reaction temperature was then optimized (Table 1, entries 1–3). The results indicated that 40 °C was optimum as

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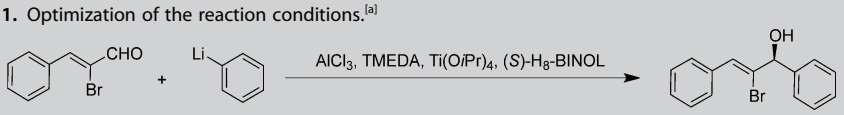
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cctc.201300655.

Table 1. Optimization of the reaction conditions.[a]



Entry	PhLi[b] [mmol]	$AlCl_3$ [mmol]	Additive[c] [mmol]	$Ti(OiPr)_4$ [mmol]	(S)-H_8-BINOL [mmol%]	T [°C]	Solvent	Conv. [%][d]	ee [%][e]
1	2.0	0.5	TMEDA 1.5	0.525	10	0	THF/hexane	56	77
2	2.0	0.5	TMEDA 1.5	0.525	10	20	THF/hexane	81	92
3	**2.0**	**0.5**	**TMEDA 1.5**	**0.525**	**10**	**40**	**THF/hexane**	**99**	**92**
4	2.0	0.5	BDMAEE 1.5	0.525	10	40	THF/hexane	99	85
5	2.0	0.5	TEEDA 1.5	0.525	10	40	THF/hexane	99	85
6	2.0	0.5	PMDETA 1.5	0.525	10	40	THF/hexane	99	89
7[f]	2.0	0.5	TMEDA 1.5	0.525	10	40	THF/hexane	99	86
8[g]	2.0	0.5	TMEDA 1.5	0.525	10	40	THF/hexane	99	82
9	1.5	0.5	TMEDA 1.5	0.525	10	40	THF/hexane	60	78
10	2.5	0.5	TMEDA 1.5	0.525	10	40	THF/hexane	99	92
11[h]	2.0	0.5	TMEDA 1.5	0.525	10	40	THF/hexane	99	88
12	2.0	0.5	TMEDA 1.5	0.525	10	40	THF	99	91
13	2.0	0.5	TMEDA 1.5	0.525	10	40	Et_2O	99	76
14	2.0	0.5	TMEDA 1.5	0.525	10	40	CH_2Cl_2	99	59
15	2.0	0.5	TMEDA 1.5	0.525	10	40	toluene	99	75
16	2.0	0.5	TMEDA 1.5	0.525	10	40	MeCN	99	87
17	2.0	0.5	TMEDA 1.0	0.525	10	40	THF/hexane	99	90
18	2.0	0.5	TMEDA 1.25	0.525	10	40	THF/hexane	99	91
19	2.0	0.5	TMEDA 1.75	0.525	10	40	THF/hexane	99	90
20	2.0	0.5	TMEDA 1.5	0.375	10	40	THF/hexane	99	89
21	2.0	0.5	TMEDA 1.5	0.625	10	40	THF/hexane	99	91
22	2.0	0.5	TMEDA 1.5	0.525	5	40	THF/hexane	99	58
23	2.0	0.5	TMEDA 1.5	0.525	15	40	THF/hexane	99	92
24	1.5	0.375	TMEDA 1.125	0.4	10	40	THF/hexane	99	90
25	2.5	0.625	TMEDA 1.875	0.65	10	40	THF/hexane	99	91

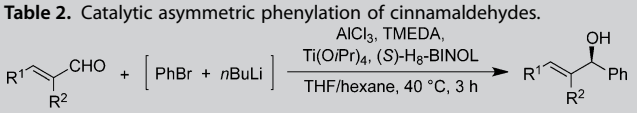
[a] 0.25 mmol aldehyde was used. [b] PhLi was prepared in situ from PhBr/*n*BuLi = 1.0:1.2 at −78 °C. [c] Coordinative additive: TEEDA = tetraethylethylenediamine, PMDETA = pentamethyldiethylenetriamine. [d] Determined by using HPLC with diphenyl as inner standard. [e] Determined by using chiral HPLC. [f] PhLi was prepared in situ from PhBr/*n*BuLi = 1.0:1.0 at −78 °C. [g] PhLi was prepared in situ from PhBr/*n*BuLi = 1.0:1.4 at −78 °C. [h] (*S*)-BINOL was used instead of (*S*)-H_8-BINOL.

the highest conversion and enantioselectivity was reached within 3 h at this temperature (entry 3). The other three coordinative additives were then screened to select the most suitable one to improve the enantioselectivity (entries 4–6); the results clearly showed that TMEDA was optimal (entry 3). The other three additives are all more expensive than TMEDA, making this protocol cost-effective. PhLi was generated in situ from PhBr and *n*BuLi; the ratio of PhBr to *n*BuLi could impact on the enantioselectivity. The investigation showed that ratios of PhBr/*n*BuLi higher or lower than 1.0:1.2 decreased the enantioselectivity (entries 3, 7, and 8). The lower ratio of PhLi/$AlCl_3$ = 3:1 resulted in lower conversion and enantioselectivity (entry 3 vs. 9). A higher ratio of PhLi/$AlCl_3$ = 5:1 did not contribute to higher conversion or *ee* (entry 3 vs. 10). Therefore the ratio 4:1 of LiPh/$AlCl_3$ was optimum (entry 3) in terms of conversion and *ee*. In comparison with (*S*)-H_8-BINOL, (*S*)-BINOL introduced reduced enantioselectivity (entry 11). The solvent had a great effect on the enantioselectivity. A series of solvents were investigated with respect to *ee* (entries 3, 12–16). The use of mixed solvent THF/hexane resulted in a slightly higher *ee* than THF; both of these achieved higher enantioselectivity than the other four solvents. Hence, THF/hexane was the ideal solvent. Considering TMEDA loading (entries 3 and 17–19), 1.5 mmol TMEDA resulted in the highest enantioselectivity. A lesser amount of $Ti(OiPr)_4$ gave lower *ee* (entries 3 vs. 20) but loadings higher than 0.525 mmol did not enhance the enantioselectivity further (entries 3 vs. 21). This showed 0.525 mmol $Ti(OiPr)_4$ to be the ideal amount (entry 3). The same was investigated for the chiral ligand loading (entries 3 and 22–23); only a decreased loading of (*S*)-H_8-BINOL introduced a big drop in *ee*. These experimental results finely determined the optimal loadings of the three additives TMEDA, $AlCl_3$, and $Ti(OiPr)_4$ (of 0.525 mmol $Ti(OiPr)_4$, 0.025 mmol $Ti(OiPr)_4$ could, in theory, have been consumed by 0.025 mmol (*S*)-H_8-BINOL to generate the 0.025 mmol chiral catalyst (*S*)-H_8-BINOL-$Ti(OiPr)_2$ complex in situ). The ratio of the additives to PhLi greatly influenced the enantioselectivity and their loadings were adjusted accordingly as the effect of PhLi loading on *ee* was investigated (entries 3 and 24–25). Loadings of PhLi higher or lower than 2.0 mmol led to decreased enantioselectivity. Therefore, the reaction conditions described in entry 3 were optimal.

Herein, TMEDA took the same role as BDMAEE did in our previous work with Grignard reagents in the catalytic asymmetric arylation of aldehydes.[8c] It coordinated the in situ produced Lewis acid lithium salt in the transmetalation process of ArBr and *n*BuLi to ArLi, which, in combination with $AlCl_3$, proffered Ar_3Al. The coordination strongly suppressed the racemic background reaction promoted by the lithium salt. Therefore, the transformation proceeded predominantly in an asymmetric catalytic manner.

Applying the optimized reaction conditions, we started to observe the scope of trisubstituted allylic secondary alcohols that could be accessed with this protocol. The catalytic asymmetric phenylation of a variety of α-substituted cinnamaldehydes was first investigated and the results included in Table 2. The α-substituted group was vital to high enantioselectivity (entries 1–6). If the α-substituted group R^2 was H, Et, or *n*Pr, the enantioselectivity was lower than 85%. If the α-substituted group was methyl or bromine, the enantioselectivity was higher than 90%. For the phenylation of α-methyl cinnamaldehydes, mostly high enantioselectivity was achieved (entries 4, 7–13), and the highest *ee* was up to 94% (entry 7). If the terminal R^1 group was heteroarylic, the enantioselectivity was only

Table 2. Catalytic asymmetric phenylation of cinnamaldehydes.

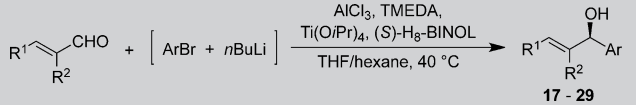


1 - 16

Entry	R^1	R^2	Yield [%][a]	*ee* [%][b]
1	C_6H_5	H	91	84
2	C_6H_5	Me	95	90
3	C_6H_5	Br	96	92
4	3-MeO-C_6H_4	Me	87	93
5	3-MeO-C_6H_4	Et	85	82
6	3-MeO-C_6H_4	*n*Pr	87	82
7	2-MeO-C_6H_4	Me	85	94
8	2-Me-C_6H_4	Me	88	93
9	3-Me-C_6H_4	Me	89	90
10	2-Cl-C_6H_4	Me	81	89
11	3-Cl-C_6H_4	Me	95	91
12	1-naphthyl	Me	91	91
13	2-naphthyl	Me	90	92
14	2-thienyl	Me	84	63
15	2-furanyl	Me	88	62
16	cyclohexyl	Me	63	90

[a] Isolated yield. [b] Determined by using chiral HPLC; the absolute configuration was determined by comparison of the optical rotation direction of the allylic alcohol with the reported datum.[8c]

Table 3. The catalytic asymmetric arylation of enals.



17 - 29

Entry	R^1	R^2	Ar	Yield [%][a]	*ee* [%][b]
1	3-MeO-C_6H_4	Me	4-Me-C_6H_4	99	89
2	2-naphthyl	Me	4-Me-C_6H_4	99	88
3	3-Me-C_6H_4	Me	4-Me-C_6H_4	72	90
4	3-MeO-C_6H_4	Me	4-Cl-C_6H_4	88	90
5	C_6H_5	Br	4-Cl-C_6H_4	91	82
6	3-MeO-C_6H_4	Me	4-MeO-C_6H_4	99	88
7	2-naphthyl	Me	4-MeO-C_6H_4	91	88
8	C_6H_5	Br	4-MeO-C_6H_4	97	80
9	3-MeO-C_6H_4	Me	3-MeO-C_6H_4	83	84
10	3-MeO-C_6H_4	Me	2-naphthyl	97	86
11	2-naphthyl	Me	2-naphthyl	82	86
12	3-MeO-C_6H_4	Me	2-thienyl	83	80
13	2-naphthyl	Me	2-thienyl	62	83

[a] Isolated yield. [b] Determined by using chiral HPLC; the absolute configuration was determined by comparison of the optical rotation direction of the allylic alcohol with the reported datum.[8c]

moderate (entries 14–15). If the R^1 group was cyclohexyl, a high enantioselectivity was obtained (entry 16).

Next, the catalytic asymmetric arylation of α-substituted cinnamaldehydes to trisubstituted allylic secondary alcohols was investigated and the results summarized in Table 3. For 4-methyl phenyllithium, the three investigated substituted cinnamaldehydes gave similar high enantioselectivity (entries 1–3), with a yield up to 99%, and *ee* values up to 90%. 4-Chlorophenyllithium also gave the same high 90% enantioselectivity to *o*-methyl cinnamaldehyde (entry 4). However, to α-bromocinnamaldehyde, the *ee* dropped to 82% with 4-chlorophenyllithium (entry 5). This similar phenomenon was also found for 4-methoxyphenyllithium (entry 8). For 2-naphthyllithium, two cinnamaldehydes afforded identical enantioselectivities (entries 10–11). If the heterocycle aryl lithium was used, the enantioselectivity decreased slightly (entries 12–13).

In summary, we have demonstrated the catalytic enantioselective arylation of α-substituted cinnamaldehydes towards enantioenriched linear trisubstituted terminal diaryl allylic secondary alcohols by using the in situ generated aryl lithiums as starting nucleophiles. The high enantioselectivity was realized by using the combinative additives of $AlCl_3$, TMEDA, and $Ti(OiPr)_4$. The use of inexpensive aryl bromides and TMEDA, and (*S*)-H_8-BINOL, a readily available chiral ligand, made this a cost-effective protocol for the preparation of enantioenriched trisubstituted allylic alcohols.

Experimental Section

Catalytic asymmetric arylation of α-substituted cinnamaldehydes: General procedure: An 10 mL Ar-purged round-bottom flask charged with PhBr (2.0 mmol, 0.21 mL) and 2.0 mL dry THF was cooled to −78 °C for 10 min, to which 1.33 mL *n*BuLi (2.4 mmol, 1.8 mmol mL^{-1} in hexane) was added dropwise. After stirring for 1 h at −78 °C, the flask was warmed to 0 °C and a solution of $AlCl_3$ (67 mg, 0.5 mmol) in 1.0 mL dry THF was introduced. The reaction temperature was allowed to warm to RT and the stirring lasted for 12 h, then TMEDA (223.5 μL, 1.5 mmol) was added. A pre-prepared mixture of (*S*)-H_8-BINOL (7.4 mg, 0.025 mmol) and $Ti(OiPr)_4$ (155.4 μL, 0.525 mmol) in 1.0 mL dry THF was added dropwise after 30 min. The reaction was stirred for another 30 min before α-bromide cinnamaldehyde (52.8 mg, 0.25 mmol) was introduced at RT. The reaction mixture was warmed to 40 °C and stirred to completion, as confirmed by TLC analysis. The flask was cooled to 0 °C and 1.0 mL ice-water was introduced to quench the reaction, then 5.0 mL aqueous 5% HCl was added. The mixture was extracted with ethyl acetate (3×10 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, condensed to dryness in vacuo, and purified with preparative column chromatography (petroleum ether/ethyl acetate = 8:1) to afford the allylic alcohol **3** as a light yellow oil in 91% yield (69.1 mg) and 92% *ee*, as determined by using HPLC (Chiracel OD-H, hexane/*i*PrOH = 90:10, flow rate = 1.0 mL min^{-1}, λ = 269.6 nm; t_{major} = 12.8 min, t_{minor} = 13.8 min). $[\alpha]_D^{25} = +19$ (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66–7.61 (m, 2H), 7.49–7.22 (m, 9H), 5.46 (s, 1H), 2.62 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.4, 134.9, 131.7, 129.1, 128.7, 128.5, 128.3, 126.7, 79.1 ppm;.

Acknowledgements

We are grateful for the financial support from the National Natural Science Foundation of China (No. 21072087) and the Program for Changjiang Scholars and Innovative Research Team in University (IRT1137).

Keywords: allylation · asymmetric synthesis · enantioselectivity · lithium · amines

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Received: August 6, 2013
Published online on October 18, 2013