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$CuBr_2$-catalyzed enantioselective routes to highly functionalized and naturally occurring allenes†

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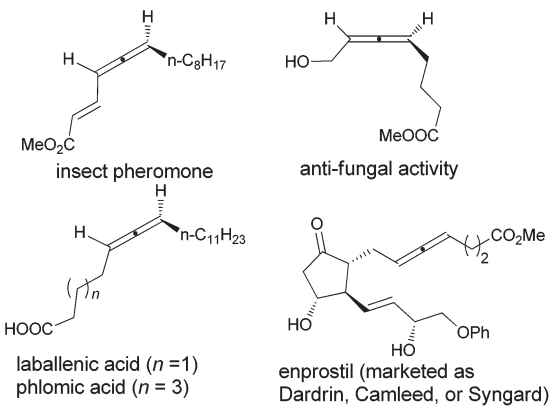
Here we show the $CuBr_2$-catalyzed approach for highly enantioselective synthesis (90–98% ee) of allenes bearing a very broad array of unmasked synthetically attractive functionalities from aldehydes and terminal alkynyl bearing reactive functionalities with the absolute configuration controlled by applying readily available (*R*)- or (*S*)-α,α-diphenylprolinol. Following this protocol, the highly enantioselective synthesis of some naturally occurring allenes loaded with reactive functionalities becomes simple: a terminal alkyne plus an aldehyde. In comparison, they were reported to be synthesized either from similar level generic chemicals with much more steps or in lower ees.

Allenes are unique unsaturated hydrocarbons in comparison with alkenes and alkynes due to the 1,2-diene-based axial chirality, which are found in over 150 biologically active natural compounds and marketed drugs (Scheme 1).[1–4] The reported synthetic routes to these compounds are either with long steps or low ees.[1,5]

Known preparations from not-easily-available optically active propargylic derivatives and organometallic reagents, in which low efficiency of chirality transfer was often observed, led to simple non-functionalized chiral allenes with limited synthetic potentials (Fig. S1†).[6] For the enantioselective synthesis of allenyl amides or malonates, the only reports are the Pd-catalyzed enantioselective reaction of racemic non-readily available 2,3-allenyl derivatives or 1,3-alkadien-3-yl bromides with moderate ees. If targeting >90% ee, one has to start with very bulky nucleophiles and substituents on the starting materials (Scheme 2, for details, see Fig. S2†).[5a,7] Recently, we have developed a non-catalytic ZnX_2-mediated[8,9] (in some cases together with CuBr)[9e] allenylation reaction of terminal alkynes or propargylic ethers with aldehydes and α,α-diphenylprolinol providing entries to chiral allenes in practical ee.



Scheme 1 Some typical naturally occurring optically active 1,3-disubstituted allenes and drugs with hydroxyl, carboxylic acid, and ester.

However, when terminal alkynyl amides or malonate were used under these reported reaction parameters, the results are rather poor (Scheme 2). Here we show that our newly developed $CuBr_2$-catalyzed enantioselective allenylation of terminal alkynols[10] may be applied to the highly efficient synthesis of some highly functionalized allenes and natural allenes.

The $CuBr_2$-catalyzed protocol enables a one-pot synthesis from terminal propargyl amides **1a–1b** to afford 2,3-allenyl tosylamine (R_a)-**4aa** (entry 1, Table 1) or benzamide (R_a)-**4bb** (entry 2, Table 1) with fairly high ees. Even the easily removable Boc group may be applied (entries 3–6, Table 1), which is vital for the introduction of other functionality to the nitrogen atom.[7a–c] Of course, such synthetically attractive chiral 2,3-allenyl tosylamine could also be prepared from propargyl alcohol, however, 5 steps are required.[9c]

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†Electronic supplementary information (ESI) available: Experimental section, characterization of all compounds, and copies of ^1H and ^{13}C NMR spectra of all the compounds prepared. See DOI: 10.1039/c5qo00084j

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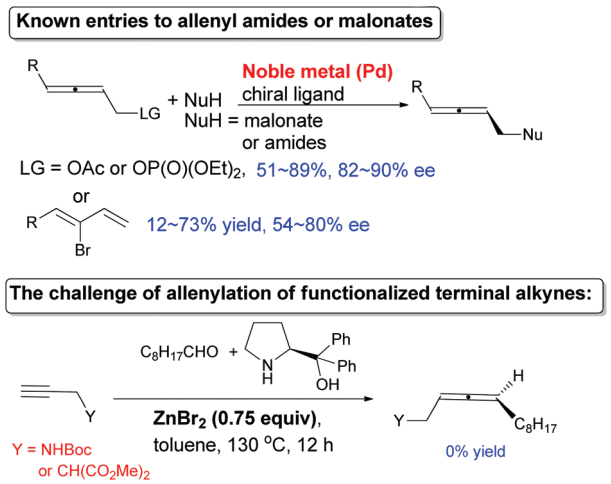
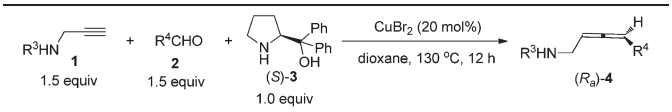


Scheme 2 Known approaches to functionalized allenes.

Table 1 The reaction of terminal propargyl amides with different aldehydes and prolinol (*S*)-3[a]

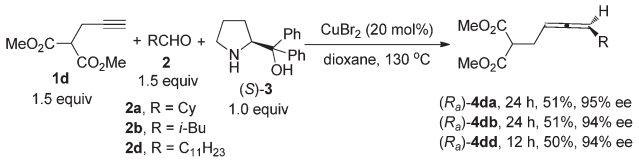


Entry	R^3	R^4	(R_a)-4 Isolated yield (%)	ee (%)
1	Ts (**1a**)	Cy (**2a**)	59 ((R_a)-**4aa**)	98
2	Bz (**1b**)	*i*-Bu (**2b**)	59 ((R_a)-**4bb**)	93
3	Boc (**1c**)	n-C_8H_{17} (**2c**)	78 ((R_a)-**4cc**)	97
4[b]	Boc (**1c**)	n-C_8H_{17} (**2c**)	54 ((R_a)-**4cc**)	98
5	Boc (**1c**)	n-$C_{11}H_{23}$ (**2d**)	74 ((R_a)-**4cd**)	96
6	Boc (**1c**)	Et_2CH (**2e**)	67 ((R_a)-**4ce**)	96
7[b,c]	Boc (**1c**)	*p*-BrC_6H_4 (**2f**)	60 ((R_a)-**4cf**)	98

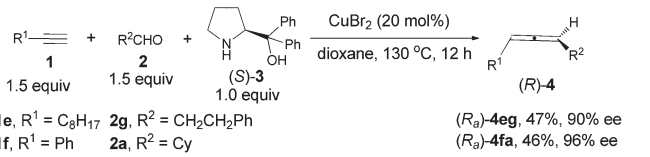
[a] The reaction was carried out using **1** (1.5 mmol), **2** (1.5 mmol), (*S*)-**3** (1.0 mmol), and $CuBr_2$ (20 mol%) in dioxane at 130 °C for 12 h unless otherwise noted. [b] The reaction was conducted at 70 °C for 24 h. [c] 40 mol% of $CuBr_2$ was used.

Highly optically active (2,3-butadienyl)malonates (R_a)-**4da**–(R_a)-**4dd**, which were previously prepared through 5 steps from propargyl alcohol, may also be prepared directly from dimethyl (2-propargyl)malonate **1d** with one active proton remaining, which is surprising since only the terminal alkynic proton is exclusively reacted (Scheme 3).[9c] This also leaves opportunity for further introduction of functional groups *via* alkylation and synthesis of γ-allenoic acid esters due to the useful reactivity of the malonate unit.[5a,7g–i]

It may also be extended to simple terminal alkynes with aldehydes (Scheme 4), which has to be mediated with 50 mol% of $ZnBr_2$ and 10–20 mol% of CuBr.[9e]

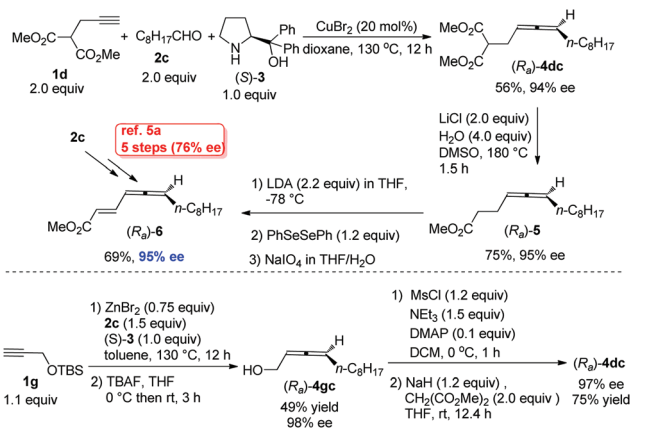


Scheme 3 Reaction of terminal alkyne with the malonate unit.



Scheme 4 Synthesis of optically active simple 1,3-disubstituted allenes.

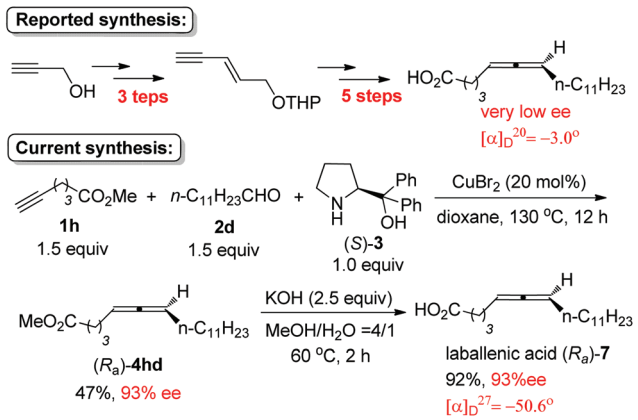
The beauty of functionality tolerance of this methodology has further been extensively demonstrated by the highly efficient enantioselective syntheses of three typical naturally occurring allenes shown in Scheme 1. In the first place, the naturally occurring insect pheromone (R_a)-**6** has been synthesized from octanal in 95% ee as compared to the reported pioneering one with five steps and 76% ee from the same aldehyde *via* a strategy shown in Scheme 5.[5a] As a comparison, we have also synthesized the key intermediate (R_a)-**4dc** from TBS-protected propargyl alcohol **1g** with three more steps including the $ZnBr_2$-mediated construction of the allene unit,[9c] although the ee is slightly higher.



Scheme 5 Syntheses of naturally occurring insect pheromone (R_a)-**6**.

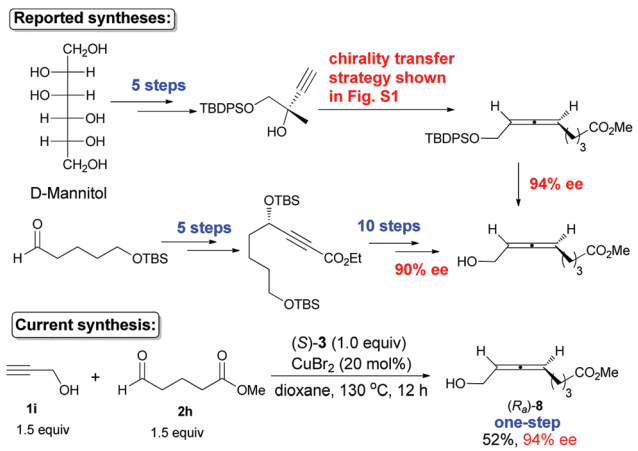
By starting from the readily available methyl 5-hexynoate, laballenic acid (R_a)-**7** could be prepared in just two steps in 93% ee as compared to the enantioselective reduction-based 8-step reported synthesis from propargyl alcohol (Scheme 6).[5b,11]

The naturally occurring 8-hydroxy-5,6-octadienoate (R_a)-**8**, which had been prepared with 94% ee in 7 steps from D-mannitol (based on a chirality transfer strategy)[5c] and 90% ee in 15 steps from 5-TBSO-substituted pentanal (*via* enzymatic resolu-



Scheme 6 Syntheses of naturally occurring laballenic acid (R_a)-**7**.

tion and β-elimination),[5d] was prepared just in one step from propargyl alcohol and 5-methoxycarbonylbutanal in 94% ee, in which both the free hydroxyl group and the ester unit survived smoothly during the transformation without a single protection–deprotection (Scheme 7).



Scheme 7 Concise synthesis of a naturally occurring allene (R_a)-**8**.

In conclusion, the robustness of a $CuBr_2$ catalyst for the highly enantioselective construction of 1,3-disubstituted allenes with a broad spectrum of common and synthetically versatile organic functionalities is noteworthy. Due to the excellent ees, the broad scope, and the synthetic and biological potential of these natural and unnatural chiral allenes, this versatile yet simple solution makes the synthesis of optically active 1,3-disubstituted allenes so simple (just breaking them down to the corresponding aldehydes and terminal alkynes with most of the functionalities unprotected), thus, should greatly stimulate their potential in organic chemistry and related discipline.

Acknowledgements

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