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Copper-catalyzed coupling of 2-vinyl benzaldehydes with 3-alkenyl 2-bromocarbonyls for the rapid construction of 3,4-cyclopenta-1-tetralones

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ABSTRACT

A straightforward, efficient, and highly diastereoselective method for the synthesis of 3,4-cyclopenta-1-tetralones has been realized via the copper-catalyzed coupling of 2-vinyl benzaldehydes with 3-alkenyl 2-bromocarbonyls. Subsequent reduction with L-selectride leads to the formation of benzannulated tricyclic alcohols, possessing four continuous stereogenic centers, in high yields with excellent diastereoselectivity.

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Among the family of tetralones, 3,4-cyclopenta-1-tetralones are common structural motifs found in a number of bioactive molecules, including the hemigeran-type natural products (Scheme 1).[1] Consequently, synthetic chemists have devoted great efforts to the exploration of efficient and practical methods for their construction.[2] However, most of the precedented methods require the utilization of multi-step process. As such, forming benzannulated tricyclic ketones in a single reaction is particularly attractive, but it has met very limited success. A well-designed one-pot procedure for building these skeletons, featuring the CO-trapping strategy under the thermolysis of alkoxyamines, has been developed by Ryu, Studer, and co-workers (Scheme 1a).[3] Despite the advance, the realization of straightforward, mild, and diastereoselective method for the construction of cyclopentane-fused 1-tetralones remains to be underdeveloped.

On the other hand, the radical reactions have emerged as effective protocols for the direct synthesis of ketones from aldehydes.[4,5] Among these, the version featuring the use of aldehydes as acceptors for the addition of carbon radicals has not been achieved till our recent report,[6] in which a wide range of cyclohexenone-fused polycyclic compounds were successfully assembled via a Cu-catalyzed cascade annulation of enynals with alkenyl or alkynyl α-bromocarbonyls (Scheme 1b). As part of our[7a] ongoing program geared toward the Cu-catalyzed atom-transfer radical addition (ATRA),[7,8] we describe here a copper-catalyzed coupling of 2-vinyl benzaldehydes with 3-alkenyl 2-bromocarbonyls, allowing a rapid access to benzannulated tricyclic ketones, with three contiguous stereogenic centers, in good to excellent yields under very mild reaction conditions (Scheme 1c). Indeed, three new C–C bonds and two new carbocycles can be constructed simultaneously via this reaction. It represents a novel, direct, and highly diastereoselective method for the synthesis of 3,4-cyclopenta-1-tetralones.

To check the feasibility, 2-vinyl benzaldehyde **1a** was treated with 1.2 equiv of diethyl 2-bromo-2-cinnamylmalonate **2a**, 20 mol % of CuBr, 40 mol % of PMDETA (pentamethyldiethylenetriamine, **L1**), and 1.2 equiv of K_2CO_3 in DMSO at room temperature (25 °C) for 12 h. As a result, 2-phenyl-3,4-cyclopenta-1-tetralone **3aa** was obtained in 53% yield as a single diastereoisomer (Table 1, entry 1), whose structure was elucidated by the single-crystal X-ray crystallography.[9] Using 40 mol % of diethylazodicarboxylate (DEAD) as the reducing reagent for in situ generation of the active Cu(I) catalyst from $CuBr_2$, **3aa** was obtained in 79% yield (entry 2). Other copper reagents such as $Cu(OTf)_2$, $Cu(OAc)_2$, and $Cu(acac)_2$ resulted in inferior results (entries 3–5). Replacing PMDETA with other ligands had no beneficial effect on this reaction (entries 6–9). Among the solvents we examined, DMSO proved to be the most suitable reaction medium (entries 12–14). As such, the optimized reaction conditions consisted of 20 mol % of $CuBr_2$, 40 mol % of DEAD, 40 mol % of PMDETA, 1.2 equiv of K_2CO_3, and DMSO at room temperature for 12 h.[10]

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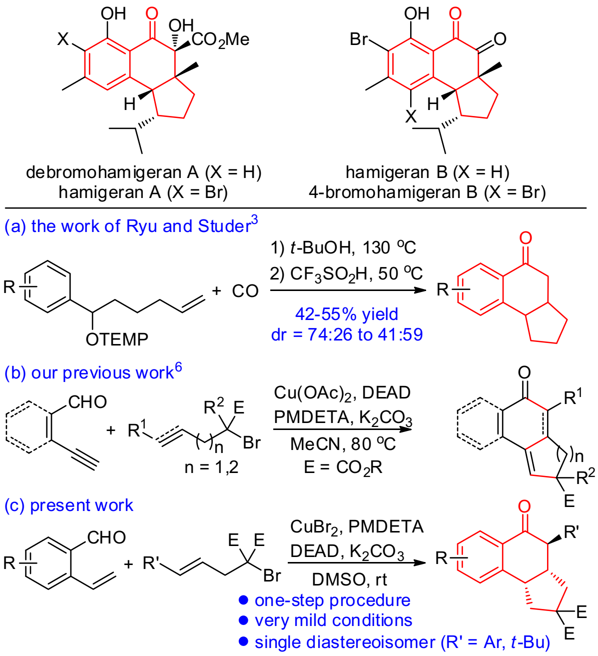
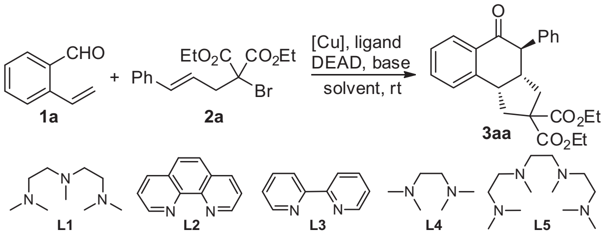


Scheme 1. Summary of this work.

With **2a** as the coupling partner, we then examined the scope and tolerance of this reaction with respect to 2-vinyl benzaldehydes, and the results are summarized in Table 2. Both electron-rich substrates, such as **1b** and **1c**, and electron-deficient substrates like **1i**, were successfully transformed into 2-aryl-3,4-cyclopenta-1-tetralones in satisfactory yields (**3ba**, **3ca**, and **3ia**). The reaction of 4-chloro-2-vinylbenzaldehyde (**1f**) and 5-chloro-2-vinylbenzaldehyde (**1g**) led to the production of **3fa** and **3ga** in 82% and 80% yields, respectively, while that of 2-chloro-6-vinylbenzaldehyde (**1h**) gave **3ha** in a relatively lower yield (65%), indicating that the steric hindrance of the benzene ring of **1** has detrimental effect on this transformation. In addition, the Cu-catalyzed coupling of **1n** with **2a** occurred as well to afford tetracyclic ketone **3na** in good yield. Substrate **1p**, a compound bearing free hydroxy group, was well suited for the cascade annulation reaction (**3pa**). The coupling of **1r** and **1s** proceeded successfully to generate the corresponding products in promising yields (**3ra** and **3sa**), leaving the terminal C–C double and triple bonds untouched under the reaction conditions. The reaction was also applicable to **1t**, a substrate with phthalimidyl group, providing **3ta** in 73% yield. When **1u** was employed as the starting material, **3ua** was obtained in a much less yield. In the case of (*E*)-2-(prop-1-en-1-yl)benzaldehyde (**1v**), the reaction was sluggish, even at an elevated reaction temperature (80 °C) (**3va**), presumably due to increased steric hindrance.

Meanwhile, 3-alkenyl 2-bromocarbonyls **2** were varied. As shown in Table 3, the electronic effect of the aryl ring of **2** has a significant effect on this transformation. Specifically, the reaction between **1a** and **2b** proceeded smoothly to afford **3ab** in 74% yield, while only a trace amount of the desired product was obtained when **2f**, a substrate had CO_2Et group, was employed as the coupling partner (**3af**). The formation of a less nucleophilic radical **III** (see the proposed mechanism) may account for the failure of this reaction. The substitution pattern of the benzene ring of **2** has little influence on this reaction, as demonstrated by the production of **3ac**–**3ae**. Moreover, substitution at the 3-position of **2** with alkyl groups was allowed. For instance, substrate **2j** was amenable to this reaction, delivering 85% yield of **3aj** with a moderate *cis*-diastereoselectivity (*cis*/*trans* = 2:1). The reaction of **2k** occurred efficiently to produce **3ak** in 84% yield, albeit with a dramatically decreased diastereoselectivity. For the sterically demanding substrate **2l**, tricyclic ketone **3al** was isolated as a single diastereoisomer, indicating that the increase of steric hindrance of the R′ group (Scheme 1b) has a positive impact on the

Table 1
Screening of the reaction conditions[a]



Entry	[Cu]	Ligand	Base	Solvent	Yield (%)
1[b]	CuBr	**L1**	K_2CO_3	DMSO	53
2	$CuBr_2$	**L1**	K_2CO_3	DMSO	79
3	$Cu(OTf)_2$	**L1**	K_2CO_3	DMSO	57
4	$Cu(OAc)_2$	**L1**	K_2CO_3	DMSO	24
5	$Cu(acac)_2$	**L1**	K_2CO_3	DMSO	15
6	$CuBr_2$	**L2**	K_2CO_3	DMSO	Trace
7	$CuBr_2$	**L3**	K_2CO_3	DMSO	Trace
8	$CuBr_2$	**L4**	K_2CO_3	DMSO	27
9	$CuBr_2$	**L5**	K_2CO_3	DMSO	65
10	$CuBr_2$	**L1**	Cs_2CO_3	DMSO	55
11	$CuBr_2$	**L1**	DBU	DMSO	17
12	$CuBr_2$	**L1**	K_2CO_3	MeCN	28
13	$CuBr_2$	**L1**	K_2CO_3	THF	Trace
14	$CuBr_2$	**L1**	K_2CO_3	DMF	53

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), [Cu] (20 mol %), ligand (40 mol %), DEAD (40 mol %), base (0.24 mmol), solvent (5 mL), rt, 12 h. Yields of the isolated products are given.

[b] Without the addition of DEAD.

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