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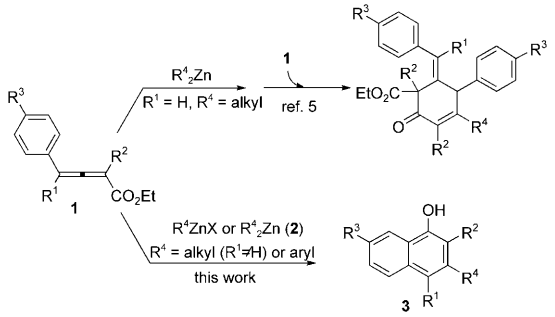
Studies on the Tandem Reaction of 4-Aryl-2,3-allenoates with Organozinc Reagents: A Facile Route to Polysubstituted Naphthols

Guobi Chai, Zhan Lu, Chunling Fu, and Shengming Ma*[a]

Substituted naphthalenes and their derivatives are important classes of organic compounds[1] with wide applications in academic laboratory and industry.[2] They are also basic skeletons of many biologically active natural products and pharmaceuticals, such as nanaomycin A, a member of the family of pyranonaphthoquinone antibiotics, and rifampicin, used as an antibacterial and antiviral agent.[3] Thus, the development of efficient and general methods for the synthesis of this class of compounds has received much attention.[4] However, the synthesis of these compounds with different substituents at specific locations starting from easily available materials are far from being well-established. In this communication, we wish to report an unexpected tandem reaction of 4-aryl-2,3-allenoates with organozinc reagents affording polysubstituted naphthols, which have been demonstrated to be percursors for the efficient synthesis of naphthalenes with location-defined substituents from organozinc reagents and 4-aryl-2,3-allenoates (Scheme 1).

Rencently, we reported a domino intermolecular double Michael addition/cyclization of 4-aryl-2,3-allenoates with dialkyl zinc to afford 5-benzylidenecyclohex-2-enones with high regio- and stereoselectivities (Scheme 1).[5] The reactivity of the intermediate involved towards the second molecule of 2,3-allenoate is very high: we tried to add many electrophiles or Michael acceptors to trap this intermediate, but all failed. However, when we studied the reaction of ethyl 2-methyl-4-phenyl-2,3-butadienoate with diphenyl zinc in toluene, the corresponding 5-benzylidenecyclohex-2-enone obtained in our previous work was not formed! Instead, a new product was isolated unexpectedly. It was confirmed to have a naphthol skeleton[6] through careful NMR spectroscopy, MS, and X-ray diffraction analysis (Figure 1).[7] However,



Scheme 1. Non-catalyzed conjugate addition and cyclization of 2,3-allenoates with organozinc reagents.

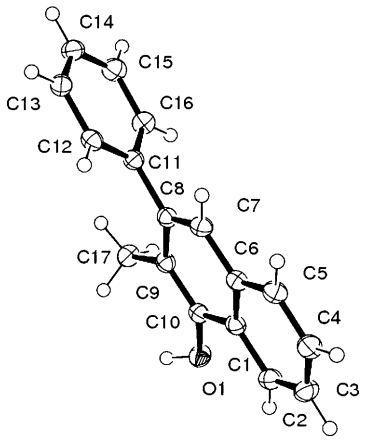


Figure 1. ORTEP representation of **3aa**.

the yield was still quite low (entry 1, Table 1). To improve the yield of new transformation, we studied the effect of the amount of diphenyl zinc, solvent, and temperature on the reaction of **1a** with Ph_2Zn (**2a**) and the results are summarized in Table 1. The yield of **3aa** decreased when smaller amounts of diphenyl zinc was used (entries 1–3, Table 1). Other solvents such as Et_2O, THF, *n*-hexane, benzene, DMSO, and 1,4-dioxane failed to give better results (en-

[a] G. Chai, Dr. Z. Lu, Prof. Dr. C. Fu, Prof. Dr. S. Ma
Laboratory of Molecular Recognition and Synthesis
Department of Chemistry, Zhejiang University
Hangzhou 310027, Zhejiang (P.R. China)
Fax: (+86) 21-6260-9305
E-mail: masm@mail.sioc.ac.cn

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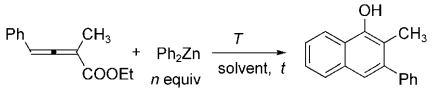
Table 1. Effect of the amount of diphenyl zinc, solvent, and temperature on tandem reaction of 2,3-allenoate **1a** with diphenyl zinc (**2a**).



1a 2a 3aa

	n	Solvent	*T* [°C]	*t* [h]	Yield[a] of **3aa** [%]
1	3	toluene	RT	16	35
2	2	toluene	RT	17	18
3	1	toluene	RT	17	12
4	3	Et_2O	RT	19	0
5	3	THF	RT	19	0
6	3	*n*-hexane	RT	19	17
7	3	benzene	RT	19	34
8	3	DMSO	RT	19	0
9	3	1,4-dioxane	RT	19	0
10	3	toluene	70	1	50
11	3	xylenes	140	0.5	65

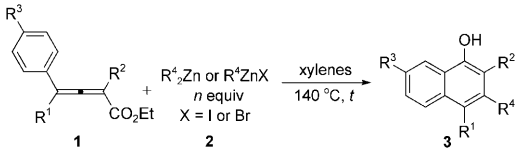
[a] Determined by NMR spectroscopy using dibromomethane as internal standard.

tries 4–9, Table 1). Fortunately, we found that the product **3aa** was formed in 50% yield in toluene at 70°C (compare entry 1 with entry 10, Table 1). Finally, we were able to improve the yield of **3aa** to 65% by conducting the corresponding reaction in xylenes with diphenyl zinc at 140°C (entry 11, Table 1, defined as Method A).

The scope of the organozinc reagents and allenoates is summarized in Table 2. Different 4,4-disubstituted, 2,4-disubstituted allenoates, and fully substituted allenoates could react with Ph_2Zn affording corresponding polysubstituted naphthols in 56–91% yields under Method A (entries 1–5, Table 2). As only limited numbers of diaryl zinc reagents were commercially available and organozinc reagents of the type RZnX are easily available[8] with good thermal stability, and tolerate functional groups even at elevated temperature,[9] we prepared solutions of this type of organozinc reagent in xylenes by adding RZnX in the original solvent to anhydrous xylenes and then distilling off the original solvent with a low boiling point, such as THF, *n*-hexane, or *n*-heptane, in xylenes at 140°C for 0.5 h for further use (Method B).[10] These solutions of substituted aryl and heteroaryl zinc reagents in xylenes, that is, *p*-BrC_6H_4ZnI (**2b**) and 2-thienyl zinc bromide (**2c**), could react with 2,3-allenoates to afford the corresponding naphthols **3ab**–**3bc** in 69–89% yields (entries 6–10, Table 2). It is worth noting that the chlorine atom on the aryl ring of the substrate **1d** did not affect the yield, affording the corresponding naphthol **3db** in 70% yield, allowing further elaboration (entry 8, Table 2). Furthermore, the reactions of fully substituted allenoates **1b** and **1c** with dialkyl zinc reagents under these new conditions could also afford the corresponding naphthols **3bd**–**3be** in high yields (entries 11–13, Table 2). However, when *p*-FC_6H_4ZnBr (**2f**) was used, naphthol **3bf** was only afforded in 40% yield and 40% of the starting material **1b** was recovered under Method B (entry 14, Table 2). To solve this problem, a solution of **2f** in mesitylene was prepared as above and the reaction was run at 160°C (defined as Method C) to get a complete conversion, affording naphthol **3bf** in 70% yield (entry 15, Table 2). It should be noted that compared with 2,4-disubstituted allenoates **1a** and **1d**, fully substituted allenoates **1b**, **1c**, **1e**, and **1f** often afforded much better results.

This transformation is rationalized as follows: the conjugate addition of organozinc reagent with the electron-deficient C=C bond in 2,3-allenoate[5,11] affords intermediate **A**. Subsequent 6π electrocyclization involving the aryl group[12] followed by the elimination of EtOH would afford inter-

Table 2. Tandem reaction of 2,3-allenoates **1** with orangozinc reagents **2** affording diversified polysubstituted α-naphthols.[a]

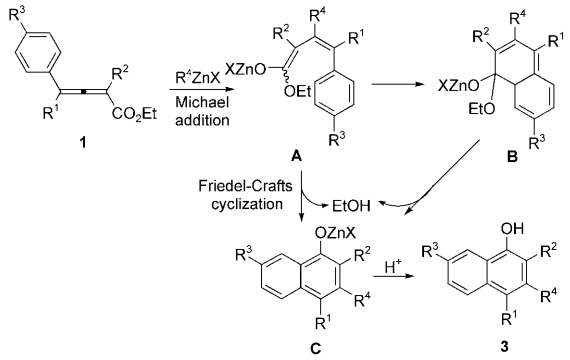


1 2 3

	1 $R^1/R^2/R^3$	R^4	*n*/X/*t* [h]	Method[a]	Isolated yield of **3** [%]
1	H/Me/H (**1a**)	Ph (**2a**)	3/–[b]/0.5	A	56 (**3aa**)
2	Ph/Me/H (**1b**)	Ph (**2a**)	3/–[b]/1	A	90 (**3ba**)
3	Ph/*n*-Pr/H (**1c**)	Ph (**2a**)	3/–[b]/1	A	91 (**3ca**)
4	Ph/H/H (**1e**)	Ph (**2a**)	3/–[b]/0.25	A	81 (**3ea**)
5	Ph/Ph/H (**1f**)[c]	Ph (**2a**)	3/–[b]/1	A	86 (**3fa**)
6	H/Me/H (**1a**)	*p*-BrC_6H_4 (**2b**)	6/I/0.5	B	82 (**3ab**)
7	Ph/Me/H (**1b**)	*p*-BrC_6H_4 (**2b**)	6/I/6.5	B	88 (**3bb**)
8	H/Me/Cl (**1d**)	*p*-BrC_6H_4 (**2b**)	6/I/1.5	B	70 (**3db**)
9	H/Me/H (**1a**)	2-Thienyl (**2c**)	6/Br/1	B	69 (**3ac**)
10	Ph/Me/H (**1b**)	2-Thienyl (**2c**)	6/Br/8	B	89 (**3bc**)
11	Ph/Me/H (**1b**)	Et (**2d**)	3/–[b]/2	B	93 (**3bd**)
12	Ph/*n*-Pr/H (**1c**)	Et (**2d**)	3/–[b]/1	B	92 (**3cd**)
13	Ph/Me/H (**1b**)	*n*Bu (**2e**)	6/–[b]/10.5	B	68 (**3be**)
14	Ph/Me/H (**1b**)	*p*-FC_6H_4 (**2f**)	6/Br/12	B	40[d] (**3bf**)
15	Ph/Me/H (**1b**)	*p*-FC_6H_4 (**2f**)	6/Br/10.5	C	70 (**3bf**)

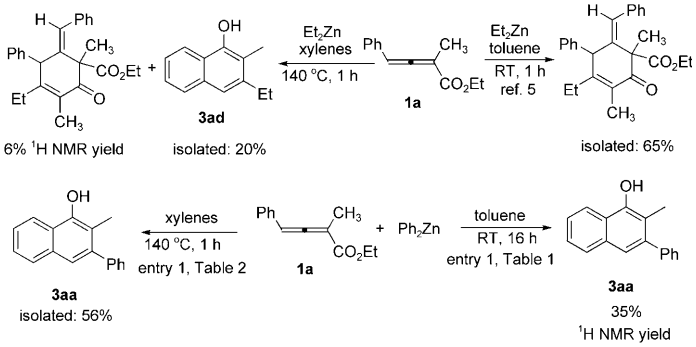
[a] Method A: A solution of **1** (0.2 mmol) in anhydrous xylenes (2 mL) was quickly added dropwise to a solution of Ph_2Zn in anhydrous xylenes (3 mL) at 140°C; Method B: a solution of R^4ZnX in THF (0.5 M), a solution of Et_2Zn in *n*-hexane (0.88 M), or a solution of nBu_2Zn in *n*-heptane (1 M) was added to anhydrous xylenes (3 mL), followed by heating up to 140°C to distill off the original solvent. Then, a solution of **1** (0.2 mmol) in anhydrous xylenes (2 mL) was quickly added dropwise; Method C: a solution of R^4ZnX in THF (0.5 M) was added to anhydrous mesitylene (3 mL), followed by heating up to 160°C to distill off the original solvent THF. Then, a solution of **1** (0.2 mmol) in anhydrous xylenes (2 mL) was quickly added dropwise. See Supporting Information for details. [b] $R^4{}_2Zn$ was used. [c] Methyl 2,3-allenoate was used instead of ethyl 2,3-allenoate. [d] The starting material **1b** was recovered in 40% yield.

mediate **C**. Of course, intermediate **A** may also undergo intramolecular Friedel–Crafts cyclization[13] to afford zinc naphthoxide **C**. Subsequent hydrolysis of intermediate **C** would provide the naphthol product **3** (Scheme 2).



Scheme 2. Rationale for this transformation.

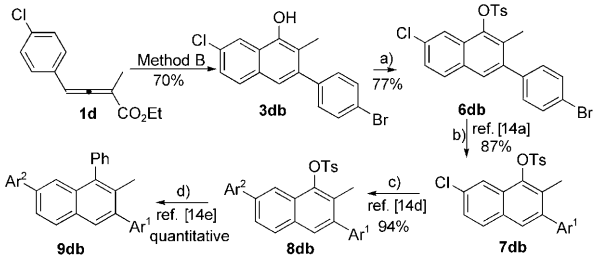
We were quite surprised to note that under Method B, even the reaction of ethyl 2-methyl-4-phenyl-2,3-butadienoate **1a** with diethyl zinc **2d** afforded 3-alkyl-substituted naphthol **3ad** in 20% yield, along with the 5-benzylidenecyclohex-2-enone product, which has been generated exclusively in our previous study,[5] in 6% NMR spectroscopic yield (Scheme 3, top). Furthermore, the reaction of **1a** with



Scheme 3.

diphenyl zinc in toluene at room tempeature[5] also afforded naphthol **3aa** in 35% NMR spectroscopic yield (Scheme 3, bottom). Thus, the chemistry shown here is mostly due to the nature of the zinc reagents and substrates. In addition, the high temperature, which increase the rate of either cyclic Friedel–Crafts reaction[13] or 6π electrocyclization[12] of intermediate **A** with respect to its conjugate addition to the second molecule of allenoate,[5] may also be partially responsible.

The reaction can be easily extended to a scale of 4.0 mmol of the substrates **1d** with 3 equivalents of **2b** affording 3-(*p*-bromophenyl)-7-chloro-2-methyl-1-naphthol (**3db**) in 70% yield (Scheme 4). Under different conditions, **3db** may easily be converted to polysubstituted naphthalene



Scheme 4. Synthetic application of **3db**. a) TsCl (3 equiv), Et_3N (3 equiv), CH_2Cl_2, 0 °C to RT, 24 h; b) *p*-$MeOC_6H_4B(OH)_2$ (2 equiv), $[Pd(PPh_3)_4]$ (5 mol%), K_3PO_4 (2 equiv), toluene, reflux, 3 h; c) *m*-$MeOC_6H_4B(OH)_2$ (1.5 equiv), $Pd(OAc)_2$ (5 mol%), SPhos (10 mol%), K_3PO_4 (2 equiv), toluene, 110 °C, 1.5 h; d) $PhB(OH)_2$ (6 equiv), $Pd(OAc)_2$ (5 mol%), XPhos (12.5 mol%), K_3PO_4 (7.5 equiv), xylenes, reflux, 25 h. Ar^1 = 4-(*p*-methoxyphenyl)phenyl; Ar^2 = *m*-methoxyphenyl.

3-{4′-(*p*-methoxyphenyl)phenyl}-7-(*m*-methoxyphenyl)-2-methyl-1-phenylnaphthalene (**9db**) by applying the tosylation and three highly selective sequential Suzuki–Miyaura coupling reactions (Scheme 4), indicating the potential of this methodology.[14]

In summary, we have developed a highly efficient tandem reaction of easily available 4-aryl-2,3-allenoates[15] with organozinc reagents[8] to afford the diversified polysubstituted α-naphthols in moderate to excellent yields. Different substituents may be introduced to different positions of naphthols by just installing these substituents in 2,3-allenoates and organozinc reagents. The product **3db** has been successfully applied to the synthesis of polysubstituted naphthalene **9db** utilizing sequential coupling reactions. This method will be of high interest to synthetic, material, and medicinal chemists. Further studies in this area including the mechanistic study are being conducted in our laboratory.

Experimental Section

A typical procedure for the preparation of 3db: To a dried Schlenk flask equipped with a Teflon-coated magnetic stirring bar were added a solution of 4-bromophenyl zinc iodide (**2b**; 24 mL, 0.5 M in THF, 12 mmol, 3 equiv) and xylenes (30 mL) sequentially with a nitrogen atmosphere at room temperature. The flask was then submerged in an oil bath preheated to 140 °C to distill off THF with a distillation apparatus for 0.5 h with a stream of N_2. A solution of **1d** (0.9485 g, 4.0 mmol) in xylenes (20 mL) was added with a syringe dropwise quickly at 140 °C. After 0.5 h, the reaction was complete as monitored by TLC and quenched subsequently by dropwise addition of saturated aqueous NH_4Cl (5 mL) at 0 °C. After warming up to room temperature and extraction with diethyl ether (3× 60 mL), the organic layer was washed sequentially with diluted HCl (5%, aq.), a saturated aqueous solution of $NaHCO_3$, and brine. After being dried over anhydrous Na_2SO_4, filtration, evaporation, and column chromatography on silica gel (eluent: 30–60 °C petroleum ether/ethyl acetate = 50:1) afforded **3db** (0.9710 g, 70%): Solid; m.p. 157.5–159.0 °C; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.16 (d, J = 1.8 Hz, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.62–7.54 (m, 2H), 7.40 (dd, J_1 = 8.7 Hz, J_2 = 1.8 Hz, 1H), 7.30 (s, 1H), 7.25–7.19 (m, 2H), 5.20 (s, 1H), 2.27 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 148.5, 140.34, 140.28, 131.3, 131.0, 130.6, 129.2, 127.0, 124.1, 121.4, 120.8, 120.6, 115.7, 13.3 ppm; MS (EI): *m/z* (%): 350 (24.95) [M^+($^{81}Br^{37}Cl$)], 348 (100) [M^+($^{79}Br^{37}Cl$ or $^{81}Br^{35}Cl$)], 346 (76.80) [M^+($^{79}Br^{35}Cl$)]; IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3407, 2923, 2852, 1636, 1595, 1570, 1489, 1441, 1418, 1393, 1367, 1298, 1270, 1224, 1203, 1168, 1146, 1112,

1074, 1011 cm^{-1}; HRMS Calcd for $C_{17}H_{12}O^{35}Cl^{79}Br$ [M^+]: 345.9760; found: 345.9761.

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Keywords: allenes · cross-coupling · cyclization · Michael addition · zinc

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