DOI: 10.1002/adsc.201300503

Copper-Catalyzed Synthesis of α-Naphthols from Enol Esters

Niranjan Panda,[a,*] Raghavender Mothkuri,[a] Arpan Pal,[a] and Alok R. Paital[b]

[a] Department of Chemistry, National Institute of Technology, Rourkela – 769008, Odisha, India
Fax: (+91)-661-246-2651; phone: (+91)-661-246-2653; e-mail: npanda@nitrkl.ac.in
[b] Salt and Marine Division, CMCRI, Bhavnagar, Gujuarat – 364021, India

Received: June 8, 2013; Revised: August 5, 2013; Published online: October 9, 2013

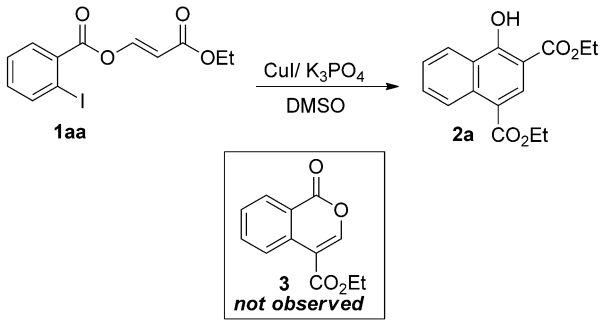
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201300503.

Abstract: An unprecedented synthesis of α-naphthol derivatives from the reactions of two molecular equivalents of enol esters in the presence of a copper catalyst is described. This protocol is mild and tolerates various functional groups.

Keywords: copper catalysts; enol esters; ethyl propiolate; *ortho*-halobenzoic acids; α-naphthols

Naphthalene derivatives are found abundantly in various natural and synthetic products with important biological properties such as antimalarial, anti-HIV and anticancer activities.[1] They also exhibit applications in agrochemical and dye preparations.[2] Apart from this, naphthols, the most important naphthalene derivatives, serve as versatile chiral ligands in synthetic organic chemistry.[3] The profound usage of naphthalene derivatives stimulates the development of new and complementary methods for their synthesis. Stepwise electrophilic aromatic substitution to a naphthalene ring is recognized as a conventional method to access polysubstituted naphthalenes by functionalization of aromatic C–H bonds to C–C and C–-N/O bonds. Complex reaction conditions and frequent formation of regioisomeric mixtures are the inevitable drawbacks associated with the above process.[4] Thus, a number of eminent methods including the Diels–Alder reaction, Hauser phthalide annulations, rearrangement of cyclopropanes or cyclobutanes, and acid-catalyzed cyclization reactions have been developed.[5] Numerous transition metal catalysts encompassing Cr, Mn, Pd, Rh, and Cu were also successfully employed for the construction of naphthalene rings from their monocyclic precursors owing to their advantages over the regioselectivity problem.[5] In contrast, the regioselective synthesis of naphthols with predetermined substituents is less well endowed with literature precedents. Very recently, Wang and coworkers developed an efficient method to achieve naphthols from the intramolecular formal diazo carbon insertion of tosyl hydrazones to keto C–C bonds.[6] Besides, Wirth,[7] Jiang[8] and Yoan[9] independently made significant advances for the synthesis of α-naphthol derivatives from the intramolecular cyclization of their monocyclic β-keto ester precursors. As part of our continued interest on transition metal-catalyzed C–C and C–N bond forming processes,[10] we here disclose a *de novo* copper-catalyzed protocol involving two molecular equivalents of enol esters to produce substituted α-naphthols under mild reaction conditions.

Our work initiated with a serendipitous discovery: on treatment of (*E*)-2-(ethoxycarbonyl)vinyl 2-iodobenzoate (**1aa**) in the presence of a copper salt and base, an intramolecular cyclization to isocoumarin derivative **3** did not occur, rather a new product with a molecular weight of 288 (as shown by the ESI-MS) was produced predominantly (Scheme 1). The product was purified and an attempt was made to characterize it by NMR spectroscopy. The NMR data shows a phenolic proton giving a singlet at 12.52 ppm, which gradually disappears on treatment with D_2O by deuterium exchange. The appearance of distinguishing signals for ethyl groups indicates the presence of two ethyl ester substituents in the new product. In consideration of the ^1H and ^{13}C NMR spectra, we anticipated the structure to be that of diethyl 4-hydroxynaphthalene-



Scheme 1. Cu-catalyzed reaction enol esters to afford α-naphthols.

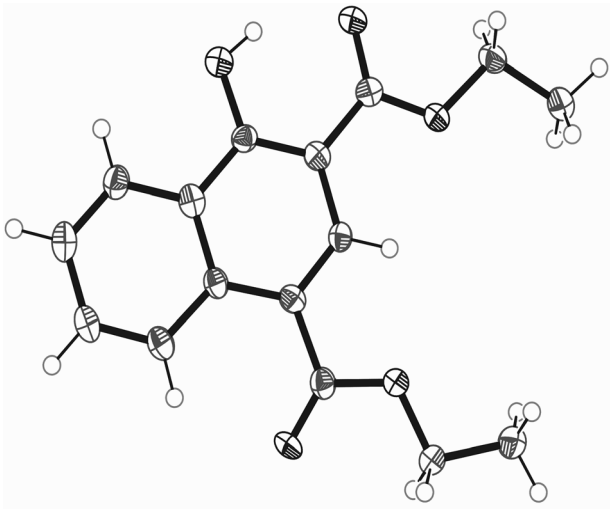


Figure 1. ORTEP drawing of **2a**.[12]

1,3-dicarboxylate (**2a**). The exact structure of **2a** was further confirmed from X-ray crystallography (Figure 1).[11] This result is completely unprecedented, although encouraging. Thus, efforts have been made to study the feasibility of this novel coupling reaction to access multisubstituted α-naphthols.

To test the feasibility of the process, a number of enol esters (**1**) were prepared by the reaction of alkyl propiolates with *ortho*-halobenzoic acids following the similar procedure reported earlier[13] (see the Supporting Information for details). Recently, a vast number of reports invoked the potential of copper catalysts in cross-coupling reactions.[14] Thus, having in hand a pool of enol esters, the cyclization reaction was attempted in the presence of copper catalysts. The results are summarized in Table 1.

It was observed that, among the tested solvents, the reaction only proceeds in the presence of DMSO and DMF, whereas no naphthol **2a** was isolated in other solvents such as $ClCH_2CH_2Cl$, THF, methanol, 1,4-dioxane and toluene (entries 14–18). The reactivities of different copper catalysts and bases were also investigated. It was observed that CuI (10 mol%) served as the best catalyst to provide **2a** in optimum yield (82%).[15] A decrease in CuI concentration from 10 mol% to 5 mol% afforded the naphthol in poor yield (62%), whereas an increase in catalyst concentration to 20 mol% did not produce better results (75%). Among the tested bases (Cs_2CO_3, K_2CO_3, KOAc, *t*-BuOK and K_3PO_4), K_3PO_4 provided **2a** in the highest yield in DMSO at 50 °C. The concentration of base is also revealed to be important. Two equivalents of base were needed to produce the naphthol in a maximum yield. Lowering the temperature from 50 °C to room temperature or increasing the temperature to 90 °C afforded **2a** with nearly the same yield within 24 h and 2 h, respectively.[16] Importantly, this reaction protocol required neither an anhydrous atmosphere nor extra pure solvent to produce multisubstituted naphthols **2a** in good yield.

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

Entry	Catalyst	Base	Solvent	Yield [%] of **2a**
1	CuI	Cs_2CO_3	DMSO	62
2	CuI	K_2CO_3	DMSO	0
3	CuI	KOAc	DMSO	0
4	CuI	*t*-BuOK	DMSO	48
5	CuI	K_3PO_4	DMSO	82
6	–	K_3PO_4	DMSO	0
7	CuI	–	DMSO	n. r.
8	CuBr	K_3PO_4	DMSO	33
9	$Cu(OAc)_2$	K_3PO_4	DMSO	58
10	$Cu(OTf)_2$	K_3PO_4	DMSO	0
11	CuCl	K_3PO_4	DMSO	43
12	CuO	K_3PO_4	DMSO	0
13	CuI	K_3PO_4	DMF	62
14	CuI	K_3PO_4	THF	0
15	CuI	K_3PO_4	1,4-dioxane	0
16	CuI	K_3PO_4	toluene	n.r.
17	CuI	K_3PO_4	$ClCH_2CH_2Cl$	n.r.
18	CuI	K_3PO_4	methanol	0

[a] *Reaction conditions:* **1aa** (100 mg, 0.29 mmol), catalyst (10 mol%), base (2 equiv.), of solvent (3 mL), 50 °C for 5 h; n.r. represents no reaction.

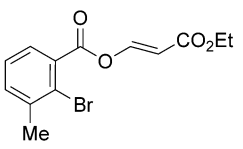
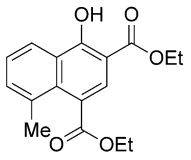
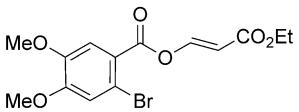
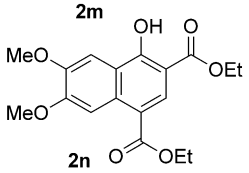
Having the optimum reaction conditions (10 mol% CuI, 2 equiv. of K_3PO_4, DMSO), the scope of the copper-catalyzed transformation of enol esters to α-naphthols was investigated (Table 2).[15] When the (*E*)-2-(ethoxycarbonyl)vinyl 2-bromobenzoate (**1ba**) was treated under similar reaction conditions, no trace of product was identified (from TLC) even on prolonged heating at 50 °C. However, on raising the reaction temperature to 90 °C, **1ba** gave the target naphthol (**2a**) over a period of 12 h, albeit in lower yield (44%). Similarly, as expected, the less reactive (*E*)-2-(ethoxycarbonyl)vinyl 2-chlorobenzoate (**1ca**) requires an even higher temperature (i.e., 150 °C) to give **2a** in 30% yield over a period of 24 h. To our delight, reactions of other enol esters having variable chain lengths as well as substituents on the aromatic ring produced the substituted α-naphthols in moderate to good yield (55–82%).[17]

To gain an insight into the copper-catalyzed cyclization of enol esters several controlled experiments, as presented in Scheme 2, were performed to elucidate the mechanism. Initially, the involvement of a [2+2+2]cycloaddition of benzyne with the generated enol (Scheme 2a) derived from the hydrolysis step was considered. However, a trapping experiment with furan was unsuccessful, implying that benzyne is not involved as an intermediate for this reaction. Furthermore, no radical intermediate was trapped by the radical scavenger TEMPO (2,2,6,6-tetramethylpiperidin-

Table 2. Cu-catalyzed synthesis of α-naphthols.[a]

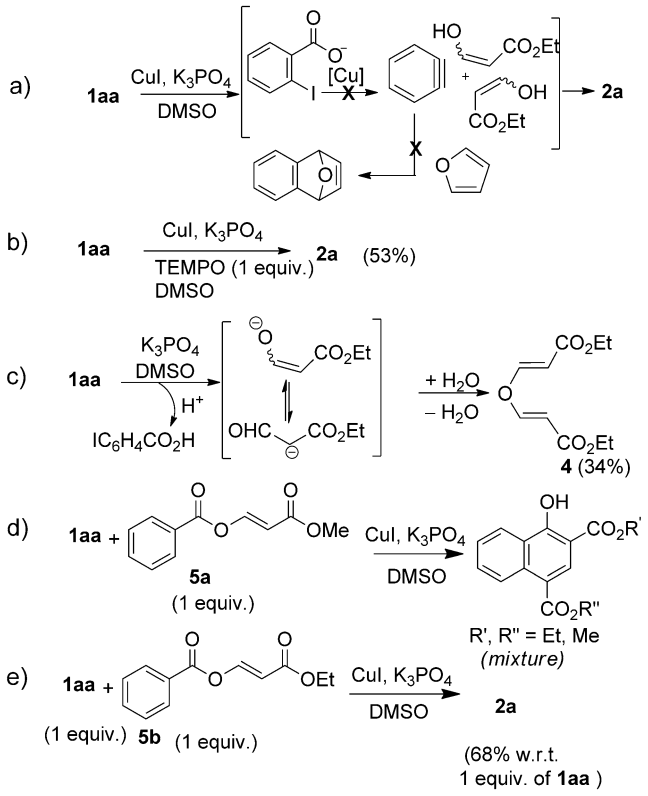
Entry	1	2	Time	Yield [%][a]
1	X = I, **1aa**	**2a**	5 h	82
2[b]	X = Br, **1ba**	**2a**	12 h	44
3[c]	X = Cl, **1ca**	**2a**	24 h	30
4	n = 2; **1ab**	**2b**	5 h	78
5	n = 3; 1**ac**	**2c**	5 h	72
6	n = 4; 1**ad**	**2d**	5 h	75
7	n = 5; 1**ae**	**2e**	5 h	73
8	n = 7; 1**af**	**2f**	5 h	74
9[d]	**1ag**	**2g**	24 h	77
10	**1ah**	**2h**	5 h	84
11[d]	**1ai**	**2i**	24 h	67
12[d]	**1aj**	**2j**	24 h	55
13	**1ak**	**2k**	5 h	68
14[b]	**1bb**	**2l**	12 h	77

Table 2. (Continued)

Entry	1	2	Time	Yield [%][a]
15[b]	 **1bc**	 **2m**	12 h	73
16[b]	 **1bd**	 **2n**	12 h	70

[a] *Reaction conditions:* enol ester **1** (100 mg), CuI (10 mol%), K_3PO_4 (2 equiv.) in 3 mL of DMSO, 50 °C.
[b] Reaction was carried out at 90 °C.
[c] Reaction was carried out at 150 °C.
[d] Reaction was carried out at room temperature.
[e] Reaction was carried out at room temperature and resulted in the incomplete conversion of enol ester **1aj**.

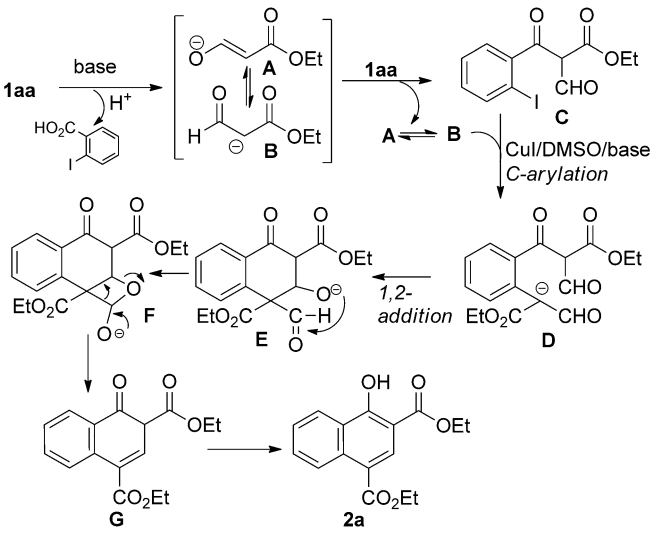
1-yl oxyl), which ruled out the possibility of a radical pathway to achieve **2a** (Scheme 2b). Next, when **1aa** was treated under the optimum reaction conditions in the absence of CuI, ether[18] **4** (34%) as well as benzoic acid (from the acidification of the corresponding aqueous extract) were produced (Scheme 2c). This suggests that the first step of the reaction may be the hydrolysis step. Indeed, the presence of two ester groups in the naphthol product **2a**, indicates the involvement of two equivalents of enol esters (e.g., **1aa**) to produce one equivalent of **2a**. Notably, when an equimolar mixture of different enol esters (**1aa** and **5a**) was treated under the optimum reaction conditions, an inseparable mixture of naphthols (from NMR spectra) was obtained (Scheme 2d). Moreover, the similar experimentation in the presence of 1 equiv. of **5b**, resulted in **2a** in higher yield (68% with regard to 1 equiv. of **1aa**); which further proves the involvement of enolate (e.g., **A** or **B**) intermediate in the tandem annulation process. Based on the above observations, thus, a plausible pathway for the regioselective synthesis of α-naphthol (**2a**) is outlined in Scheme 3. Initially, enol ester **1aa** undergoes hydrolysis to enolate **A**, which on tautomerization leads to the intermediate **B**.



Scheme 2. Control experiments for insights into the mechanism.

Presumably, the intermediate **B**, thus formed reacts with another molecule of **1aa** to produce **C**. In the presence of CuI and base in DMSO, intermolecular *C*-arylation[19] may take place to produce **D**. Next, the annulated intermediate **E** forms through the intramolecular 1,2-addition reaction of **D**. Subsequently, **E** undergoes rearrangement, followed by aromatization (**E**→**F**→**G**→**2a**) to afford the desired product **2a**.

In conclusion, a novel method for the synthesis of polysubstituted α-naphthols from simple monocyclic enol esters has been demonstrated. The reaction con-



Scheme 3. Plausible mechanism.

ditions are mild and do not require any anhydrous medium or expensive catalytic protocol to access such products in good yield. Further investigations to expand the application of this protocol to the synthesis of novel heterocyclic derivatives with detailed mechanistic studies are currently underway in our laboratory.

Experimental Section

Typical Procedure for the Synthesis of 2a

A mixture of enol ester **1aa** (100 mg, 0.29 mol), CuI (3 mg, 10 mol%), K_3PO_4 (122 mg, 0.58 mmol) in 3 mL of DMSO was stirred at 50 °C. The progress of the reaction was monitored by TLC. After 5 h the reaction mixture was quenched with 1 N HCl solution and then extracted with ethyl acetate. The solvent was removed under reduced pressure and the crude reaction mixture was purified by column chromatography to yield diethyl 4-hydroxynaphthalene-1,3-dicarboxylate (**2a**) as a white crystalline solid; yield: 82%.

Acknowledgements

*This work was financially supported in part by DST, New Delhi (No. SR-S1/OC-60/2011), and BRNS (No. 2012/37C/3/BRNS), DAE, Government of India. DST, New Delhi (No. SR/FST/CS1-018/2010) is also acknowledged for providing the MS facility at NIT Rourkela. ARP (solved the crystal structure of **2a**) is thankful to the analytical division of CMCRI for HR-MS data.*

References

[1] a) R. H. Thomson, *Naturally Occuring Quinones IV. Recent Advances*, 4th edn., Chapman & Hall: London, **1997**; b) G. Bringmann, G. Günther, M. Ochse, O. Schupp, S. Tasler, in: *Progress in the Chemistry of Organic Natural Products*, (Eds.: W. Herz, H. Falk, G. W. Kirby, R. E. Moore, C. Tamm), Springer, New York, **2001**, Vol. 82, p 1; c) R. S. Ward, *Nat. Prod. Rep.* **1995**, *12*, 183–205; d) A. Y. Shena, M. H. Hwanga, S. Roffler, C. F. Chenc, *Arch. Pharm. (Weinheim)* **1995**, *328*, 197–201; e) R. Burtner, J. M. Brown, *J. Am. Chem. Soc.* **1951**, *73*, 897–900; f) T. Kometani, Y. Takeuchi, E. Yoshii, *J. Org. Chem.* **1983**, *48*, 2630–2632; g) K. L. Rinehart Jr, *Acc. Chem. Res.* **1972**, *5*, 57–64; h) *Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry*, 11th edn., (Eds.: J. M. Beale Jr, J. H. Block), Lippincott Williams & Wilkins, Philadelphia, **2004**, pp 255–257; i) M. Brasholz, S. Sörgel, C. Azap, H.-U. Reißig, *Eur. J. Org. Chem.* **2007**, 3801–3814.

[2] a) R. T. Mason, M. Talukder, C. R. Kates, in: *Kirk-Othmer Encyclopedia of Chemical Technology*, (Ed.: R. E. Kirk), Wiley, New York, 4th edn., **1995**, vol. 16, pp 963–1017; b) P. E. Georghiou, Z. Li, M. Ashram, S. Chowdhury, S. Mizyed, A. H. Tran, H. Al-Saraierh, D. O. Miller, *Synlett* **2005**, 879–891; c) M. Medarde, A. B. S. Maya, C. Pérez-Melero, *J. Enzyme Inhib. Med. Chem.* **2004**, *19*, 521–540.

[3] a) G. Bringmann, R. Walter, R. Weirich, *Angew. Chem.* **1990**, *102*, 1006–1019; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 977–991; b) R. Noyori, T. Ohkuma, *Angew. Chem.* **2001**, *113*, 40–75; *Angew. Chem. Int. Ed.* **2001**, *40*, 40–73; c) R. Noyori, M. Yamakawa, S. Hashiguchi, *J. Org. Chem.* **2001**, *66*, 7931–7944; d) H. Kumobayashi, T. Miura, N. Sayo, T. Saito, X. Zhang, *Synlett* **2001**, 1055–1064; e) G. Bringmann, A. J. P. Mortimer, P. A. Keller, M. J. Gresser, J. Garner, M. Breuning, *Angew. Chem.* **2005**, *117*, 5518–5563; *Angew. Chem. Int. Ed.* **2005**, *44*, 5384–5427; f) M. C. Kozlowski, B. J. Morgan, E. C. Linton, *Chem. Soc. Rev.* **2009**, *38*, 3193; g) J. D. Hoefelmeyer, M. Schulte, M. Tschinkl, F. P. Gabbaï, *Coordination Chem. Rev.* **2002**, *235*, 93–103; h) M. D. Watson, A. Fechtenkötter, K. Müllen, *Chem. Rev.* **2001**, *101*, 1267–1300; i) M. Shibasaki, S. Matsunaga, *BINOL* in: *Privileged Chiral Ligands and Catalysts*, (Eds.: Q.-L. Zhou), Wiley, New York, **2011**, pp 295–332.

[4] G. Chai, Z. Lu, C. Fu, S. Ma, *Chem. Eur. J.* **2009**, *15*, 11083–11086.

[5] For reviews on naphthalene synthesis: see a) C. B. de Koning, A. L. Rousseau, W. A. L. van Otterlo, *Tetrahedron* **2002**, *59*, 7–36; b) G. Booth, in: *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH, Weinheim, **2005**; c) S. Saito, Y. Yamamoto, *Chem. Rev.* **2000**, *100*, 2901–2916; d) C. K. Bradsher, *Chem. Rev.* **1987**, *87*, 1277–1297; e) N. Asao, *Synlett* **2006**, 1645–1656; f) D. Mal, P. Pahari, *Chem. Rev.* **2007**, *107*, 1892–1918.

[6] Y. Xia, P. Qu, Z. Liu, R. Ge, Q. Xiao, Y. Zhang, J. Wang, *Angew. Chem.* **2013**, *125*, 2603–2606; *Angew. Chem. Int. Ed.* **2013**, *52*, 2543–2546.

[7] A. Shahzad, C. Vivant, T. Wirth, *Org. Lett.* **2010**, *12*, 1364–1367.

[8] H. Xu, S. Li, H. Liu, H. Fu, Y. Jiang, *Chem. Commun.* **2010**, *46*, 7617–7619.

[9] S. W. Yoan, B. S. Kim, A. R. Jagdale, *J. Am. Chem. Soc.* **2012**, *134*, 11308–11311.

[10] a) N. Panda, A. K. Jena, *J. Org. Chem.* **2012**, *77*, 9401–9406; b) N. Panda, R. Mothkuri, *J. Org. Chem.* **2012**, *77*, 9407–9412; c) N. Panda, A. K. Jena, M. Raghavender, *ACS Catal.* **2012**, *2*, 539–543; d) N. Panda, A. K. Jena, S. Mohapatra, *Appl. Catal. A: General* **2012**, *433–434*, 258–264; e) N. Panda, A. K. Jena, S. Mohapatra, *Chem. Lett.* **2011**, *40*, 956; f) N. Panda, A. K. Jena, S. Mohapatra, S. R. Rout, *Tetrahedron Lett.* **2011**, *52*, 1924–1927.
[11] See the Supporting Information for details.
[12] CCDC 936027 (**2a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.
[13] a) K. Zong, S. Shin, D. J. Jeon, J. N. Lee, E. K. Ryu, *J. Heterocycl. Chem.* **2000**, *37*, 75–79; b) N. J. Kerrigan, T. Upadhyay, D. J. Procter, *Tetrahedron Lett.* **2004**, *45*, 9087–9090.
[14] For selected reviews on Cu-catalyzed coupling reactions, see: a) F. Monnier, M. Taillefer, *Angew. Chem.* **2009**, *121*, 7088–7105; *Angew. Chem. Int. Ed.* **2009**, *48*, 6954–6971; b) S. V. Ley, A. W. Thomas, *Angew. Chem.* **2003**, *115*, 5558–5607; *Angew. Chem. Int. Ed.* **2003**, *42*, 5400–5449; c) G. Evano, N. Blanchard, M. Toumi, *Chem. Rev.* **2008**, *108*, 3054–3131; d) I. P. Beletskaya, A. V. Cheprakov, *Coord. Chem. Rev.* **2004**, *248*, 2337–2364; e) C. Fischer, B. Koenig, *Beilstein J. Org. Chem.* **2011**, *7*, 59–74; f) B. C. Ranu, R. Dey, T. Chatterjee, S. Ahammed, *ChemSusChem* **2012**, *5*, 22–44; g) H. Rao, H. Fu, *Synlett* **2011**, 745–769.
[15] Yields were calculated from the reaction of 2 molar equiv. of enol ester to 1 molar equiv. of naphthol.
[16] The reaction results in 75% and 76% yields at room temperature and at 90 °C, respectively.
[17] Structures of naphthols (**2b**–**2n**) were assigned in comparison with the NMR spectra of **2a**.
[18] J. Tae, K.-O. Kim, *Tetrahedron Lett.* **2003**, *44*, 2125–2128.
[19] C. C. Malakar, D. Schmidt, J. Conrad, U. Beifuss, *Org. Lett.* **2011**, *13*, 1972–1975.

