ORGANIC LETTERS

2012
Vol. 14, No. 13
3324–3327

Ligand-Controlled Iron-Catalyzed Coupling of α-Substituted β-Ketoesters with Phenols

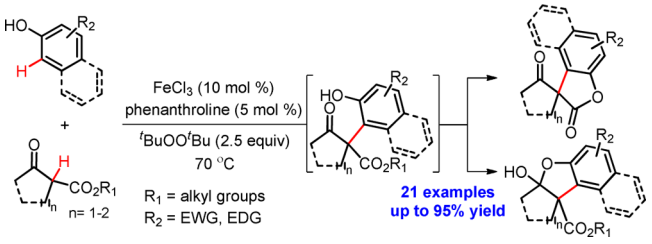
Regev Parnes, Umesh A. Kshirsagar, Aviya Werbeloff, Clil Regev, and Doron Pappo*

Department of Chemistry, Ben-Gurion University of the Negev, Beer-Sheva 84105, Israel

pappod@bgu.ac.il

Received May 10, 2012

ABSTRACT



A chemo-, regio-, and stereoselective $FeCl_3$/1,10-phenanthroline-catalyzed cross dehydrogenative coupling (CDC) reaction between phenols and α-substituted β-ketoesters was developed. The reaction creates a new quaternary carbon center within a polycyclic hemiacetal or polycyclic spirolactone architecture. The applicability of the new method to the synthesis of natural products was demonstrated by a possible biomimetic synthesis of the lachnanthospirone core.

The cross-coupling between 1,3-dicarbonyl compounds and phenols or masked phenols is an important transformation, because it provides an easy entry to multifunctional synthetic intermediates applicable in the synthesis of complex phenol based materials. The most useful technology to achieve α-arylation of 1,3-dicarbonyls in general,[1] and of cyclic-β-ketoesters[2] in particular, is based on transition-metal-catalyzed (mainly Pd and Cu) cross-coupling between aryl halides and stable enolates. Lead(IV),[3] bismuth(V),[3] iodine(III),[4] and Mn(III)[2,5] have also been found to be effective reagents, with the former two being applied by Yang and Baran in their syntheses of maoecrystal V.[3] Other methods, based on aryne coupling[6] and aromatic substitution reactions,[7] have also been developed.

The cross dehydrogenative coupling (CDC) reactions have recently become powerful tools for C−C bond formation.[8] These reactions are usually catalyzed by simple copper or iron ions in the presence of an organic peroxide, mainly *t*BuOOH. The reactions are based on the mechanistic premise that a cation radical intermediate, generated selectively from the oxidation of a weak C−H bond, reacts with a π-electron-rich nucleophilic coupling partner. Chao-Jun Li[9] and others have applied the CDC reaction for the coupling of a variety of C−H groups, ranging from two sp^3 carbons,[10] an sp^2 and an sp^3 carbon,[11] two sp^2 carbons,[12] or an sp^3 and an sp carbon.[13] Zhiping Li, for example, prepared polysubstituted benzofurans

(1) Johansson, C. C. C.; Colacot, T. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 676.
(2) Bhat, V.; Mackay, J. A.; Rawal, V. H. *Org. Lett.* **2011**, *13*, 3214.
(3) (a) Gong, J.; Lin, G.; Sun, W.; Li, C.-C.; Yang, Z. *J. Am. Chem. Soc.* **2010**, *132*, 16745. (b) Krawczuk, P. J.; Schone, N.; Baran, P. S. *Org. Lett.* **2009**, *11*, 4774.
(4) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299.
(5) Citterio, A.; Fancelli, D.; Finzi, C.; Pesce, L.; Santi, R. *J. Org. Chem.* **1989**, *54*, 2713.
(6) Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 5340.
(7) (a) Sastry Mudiganti, N. V.; Claessens, S.; De Kimpe, N. *Tetrahedron* **2009**, *65*, 1716. (b) Kobbelgaard, S.; Bella, M.; Jorgensen, K. A. *J. Org. Chem.* **2006**, *71*, 4980. (c) Sarhan, A. A.; Bolm, C. *Chem. Soc. Rev.* **2009**, *38*, 2730. (d) Aleman, J.; Richter, B.; Joergensoen, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 5515.
(8) (a) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (b) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780.
(9) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335.
(10) (a) Zhang, Y.; Li, C.-J. *Angew. Chem., Int. Ed.* **2006**, *45*, 1949. (b) Li, Z.; Bohle, D. S.; Li, C.-J. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 8928. (c) Zhao, L.; Li, C.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 7075. (d) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 3672. (e) Liu, W.; Liu, J.; Ogawa, D.; Nishihara, Y.; Guo, X.; Li, Z. *Org. Lett.* **2011**, *13*, 6272. (f) Li, Z.; Yu, R.; Li, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7497.
(11) (a) Zhang, Y.; Li, C.-J. *Eur. J. Org. Chem.* **2007**, 4654. (b) Li, Y.-Z.; Li, B.-J.; Lu, X.-Y.; Lin, S.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3817. (c) Song, C.-X.; Cai, G.-X.; Farrell, T. R.; Jiang, Z.-P.; Li, H.; Gan, L.-B.; Shi, Z.-J. *Chem. Commun.* **2009**, 6002. (d) Guo, X.; Pan, S.; Liu, J.; Li, Z. *J. Org. Chem.* **2009**, *74*, 8848. (e) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 6968. (f) Guo, X.; Li, W.; Li, Z. *Eur. J. Org. Chem.* **2010**, *2010*, 5787.
(12) (a) Egami, H.; Katsuki, T. *J. Am. Chem. Soc.* **2009**, *131*, 6082. (b) Egami, H.; Matsumoto, K.; Oguma, T.; Kunisu, T.; Katsuki, T. *J. Am. Chem. Soc.* **2010**, *132*, 13633. (c) Liu, W.; Li, Y.; Liu, K.; Li, Z. *J. Am. Chem. Soc.* **2011**, *133*, 10756.

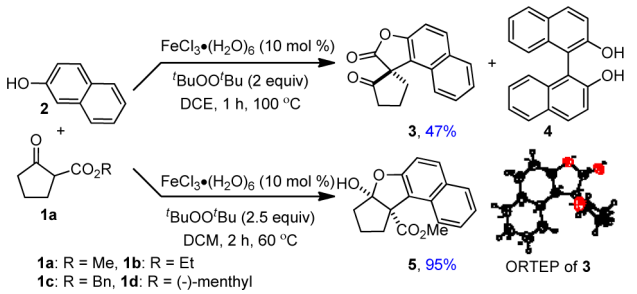
10.1021/ol301297k
Published on Web 06/13/2012

by reacting ethyl 3-oxo-3-arylpropanoates with phenols in the presence of $FeCl_3•(H_2O)_6$ (10 mol %) and di-*tert*-butylperoxide (DTBP).[14] The proposed mechanism involved coordination of both the β-ketoester and the phenol to iron, followed by an intermolecular electron transfer step and annulation.[15] The introduction of ligands into iron-based CDC reactions has previously met with only partial success,[16] in contrast to the considerable progress in copper-based CDC transformations,[17] which enabled the development of asymmetric versions of these reactions.[18]

Here we report a new, synthetically useful technology, based on iron(III), for the direct coupling of simple phenols with either cyclic β-ketoesters or α-substituted β-ketoesters. The reaction, which involves oxidative coupling and annulation steps, does not require any preadjustment of the coupling partners and creates a new quaternary carbon center within a polycyclic hemiacetal or polycyclic spirolactone architecture. Moreover, the addition of 1,10-phenanthroline or 2,2′-bipyridine significantly affects the reactivity and selectivity in this transformation, by favorably promoting the cross-coupling path over other side reactions, such as naphthol dimerization or Friedel−Crafts alkylation. In addition, we demonstrate here the synthetic utility of the methodology, as well as its biogenesis relevance, by presenting a single-step synthesis of the central core of lachnanthospirone.

We began our study by coupling methyl 2-oxocyclopentanecarboxylate (**1a**, 1 mmol) with 2-naphthol (**2**, 3 mmol) under conditions similar to those previously reported [$FeCl_3•(H_2O)_6$ (10 mol %), DTBP (2 mmol), DCE (0.5 M), 100 °C,[19] 1 h; Scheme 1].[14] Under these conditions, lactone **3** was isolated in 47% yield, accompanied by large quantities of BINOL (**4**), resulting from the oxidative homocoupling reaction of two naphthols. An optimization study (see Table S1 in the Supporting Information) was conducted, in which several of the reaction parameters, such as the metal source and loading, the effect of solvent, solvent concentration, and temperature on the reaction were examined. Based on these studies, a new set of conditions was adopted: β-ketoester **1a** (1 mmol), naphthol **2** (1.5 mmol), $FeCl_3•(H_2O)_6$ (10 mol %), and DTBP (2.5 mmol) were reacted in dichloromethane (0.5 M) at 60 °C for 2 h. Surprisingly, under these conditions, the annulation step adopted an alternative path, affording polycylic hemiacetal **5** in 95% isolated yield. It was found that while the initial oxidative coupling step proceeds smoothly at 60 °C, the subsequent trans-esterification step leading to spirolactone **3** is not favored at temperatures below 80 °C, the point at which the formation of the hemiacetal is preferred. In addition, it was observed that, under these mild conditions, the competitive dimerization side reaction leading to **4** is minimized, and therefore, only a small excess (1.2 equiv instead of 3 equiv) of naphthol is required for full conversion of the β-ketoester.

Scheme 1. Cross-Coupling between Methyl 2-Oxocyclopentanecarboxylate (**1a**) and 2-Naphthol



Next, we examined the reaction between ethyl cyclohexanone-2-carboxylate (**6**) and naphthol **2**. Under the developed conditions, lower reactivity was observed, and the hemiacetal coupling product **7** was isolated in a disappointing yield (35%, Table 1, entry 1). We assumed that the observed difference in reactivity when switching from the five- to the six-membered ring β-ketoester could be a result of different binding affinities to the metal center. Therefore, a search for a suitable ligand that would influence the binding properties of the substrates was undertaken (Table 1). The addition of 2-cyanopyridine (10 mol %), *N*,*N*-dimethylglycine hydrochloride (10 mol %), TMHD (2,2,6,6-tetramethyl-3,5-heptanedione; 10 mol %), ethylene glycol (20 mol %), L-proline (5 mol %), or pyridine (10 mol %) to the reaction mixture either hindered the reaction or had no effect at all (entries 2−7), and BINOL formation dominated. To our delight, however, when 2,2′-bipyridine (**L1**, 5 mol %) or 1,10-phenanthroline (**L2**, 5 mol %) was introduced, a significant amplification in the formation of hemiacetal **7** was observed, and the compound was obtained in 71% and 69% HPLC yields, respectively (entries 8 and 9). Subsequently, it was found that a second addition of naphthol (0.5 equiv) after 1 h was needed to obtain full consumption of **6**; under these conditions, hemiacetal **7** was isolated in 93% yield. Solvent-free conditions were also examined (entry 11), and under these conditions product **7** was isolated in 77% yield. However, these conditions were found to be less effective for other coupling partners.[20]

To study the ligand effect in the oxidative coupling reaction between β-ketoester **6** with **2**, a set of comparative experiments was carried out. In these reactions, equal amounts of β-ketoester **6** (1.5 equiv) and 2-naphthol **2**

(13) (a) Volla, C. M. R.; Vogel, P. *Org. Lett.* **2009**, *11*, 1701. (b) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 11810. (c) Jiang, H.-F.; Li, J.-H.; Chen, Z.-W. *Tetrahedron* **2010**, *66*, 9721.

(14) Guo, X.; Yu, R.; Li, H.; Li, Z. *J. Am. Chem. Soc.* **2009**, *131*, 17387.

(15) (a) Barton, D. H. R.; Deflorin, A. M.; Edwards, O. E. *J. Chem. Soc.* **1956**, 530. (b) DeMartino, M. P.; Chen, K.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 11546.

(16) (a) Ohta, M.; Quick, M. P.; Yamaguchi, J.; Wunsch, B.; Itami, K. *Chem.—Asian J.* **2009**, *4*, 1416. (b) Yang, L.; Qin, L. H.; Bligh, S. W.; Bashall, A.; Zhang, C. F.; Zhang, M.; Wang, Z. T.; Xu, L. S. *Bioorg. Med. Chem.* **2006**, *14*, 3496.

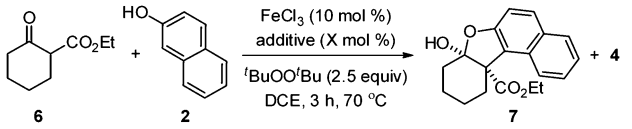
(17) Bi, H.-P.; Zhao, L.; Liang, Y.-M.; Li, C.-J. *Angew. Chem., Int. Ed.* **2009**, *48*, 792.

(18) (a) Li, Z.; Li, C.-J. *Org. Lett.* **2004**, *6*, 4997. (b) Li, Z.; MacLeod, P. D.; Li, C.-J. *Tetrahedron: Asymmetry* **2006**, *17*, 590. (c) Guo, C.; Song, J.; Luo, S. W.; Gong, L. Z. *Angew. Chem., Int. Ed.* **2010**, *49*, 5558. (d) Zhang, J.; Tiwari, B.; Xing, C.; Chen, X.; Chi, Y. R. *Angew. Chem., Int. Ed.* **2012**, *51*, 3649.

(19) Oil bath temperature.

(20) For example see Table S1, entry 18 in the Supporting Information.

Table 1. Effect of Additives in the Coupling of Ethyl 2-Oxocyclohexanecarboxylate (**6**) with 2-Naphthol (**2**)[a]



entry	additive (X mol %)	yield (%)[b]
1	none	[39], 35
2	2-cyanopyridine (10)	[35]
3	*N*,*N*-dimethylglycine HCl (10)	[27]
4	TMHD (10)	[33]
5	ethylene glycol (20)	[42]
6	L-proline (5)	[25]
7	pyridine (10)	[2][c]
8	2,2′-bipyridine (**L1**, 5)	[71]
9	1,10-phenanthroline (**L2**, 5)	[69], 93[d]
10	1,10-phenanthroline (**L2**, 5)	[53][e]
11	none (solvent-free)	77[f]

[a] Reaction conditions: **6** (1 mmol), **2** (1.7 mmol), $FeCl_3$ (10 mol %), additive (X mol %), DTBP (2.5 mmol), DCE, 70 °C, 3 h. [b] Isolated yields, HPLC yields are given in square brackets and were determined using mesitylene as the internal standard. [c] BINOL formation dominated. [d] Similar reaction conditions, addition of **2** (0.5 mmol) after 1.5 h. [e] $FeCl_3{\bullet}(H_2O)_6$ (10 mol %) was used. [f] The reaction was carried out under solvent-free conditions: **6** (1 mmol), **2** (1.5 mmol), $FeCl_3$ (10 mol %), DTBP (3 mmol), 70 °C, 8 h.

(1.5 equiv) were coupled with only 1 equiv of DTBP [$FeCl_3$ (10 mol %), DCE, 70 °C] in the presence of various quantities of phenanthroline or bipyridine (0−10 mol %). The reactions were stopped at 1 h, and the yields of both **7** and **4** were determined by HPLC; the results are given in Figure 1. In the absence of phenanthroline, hemiacetal **7** and **4** were formed in 39% and 29% yields, respectively, but when 5 mol % of phenanthroline were added, the reaction proceeded with high chemoselectivity, affording compound **7** in 45% yield with the formation of only 16% of **4** (Figure 1b). Significantly, when the concentration of phenanthroline was increased, the efficiency of the catalyst was reduced, and at 10 mol % of phenanthroline (1:1 iron/**L2** ratio) the reaction was completely shut down, leaving the starting materials unchanged. The role of phenanthroline in this reaction is not yet fully elucidated, but we postulate that the phenanthroline ligand competes with labile naphthyl groups for coordination sites around the iron, leading to the arrangement of a more organized complex. As a result, the number of naphthyl groups attached to the metal is reduced, and the possibility for homodimerization of two naphthols is decreased.

We then examined the scope of the reaction, applying the method to a variety of β-ketoesters and to additional phenol derivatives (Figure 2). Substituted naphthols bearing electron-withdrawing or -donating groups and the sterically hindered 3-bromo-2-naphthol were all coupled successfully with **1a**, affording polycyclic hemiacetals (**8**−**11**) in good to high yields (90%, 70%, 95%, and

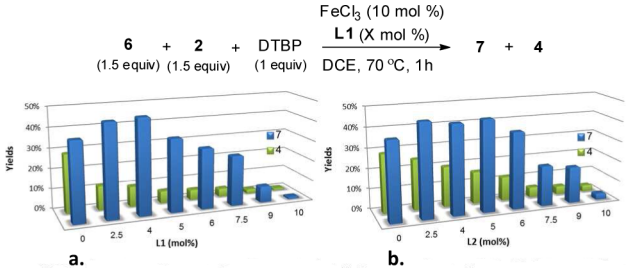


Figure 1. Formation of **7** and **4** as a function of 2,2′-bipyridine (**L1**) or 1,10-phenanthroline (**L2**) concentration.

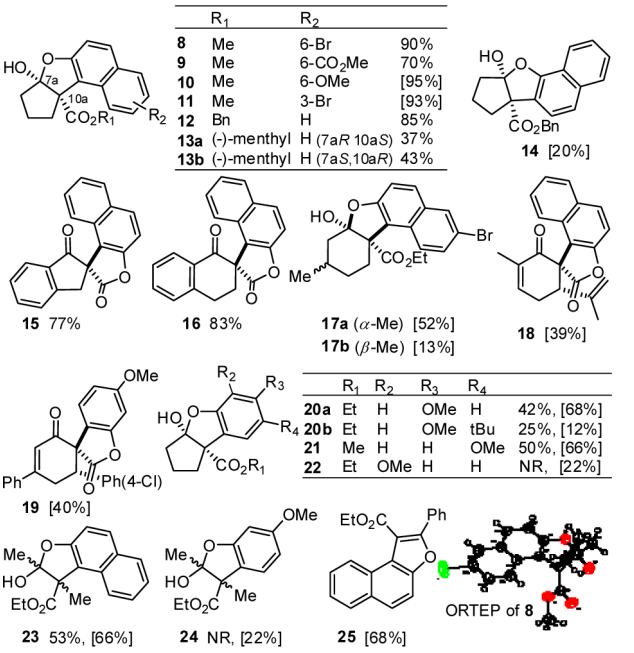


Figure 2. Scope of the coupling of β-ketoesters with phenols. Reaction conditions: β-ketoester (1 equiv), phenol (1.2−1.7 equiv), $FeCl_3$ (10 mol %), DTBP (2.5 equiv), DCE, 70−90 °C, 2−12 h. See Supporting Information for exact conditions. Isolated yield of pure compound is presented. For **10**, **11**, **14**, and **17**−**25**, ligand **L2** (5 mol %) was added to the reaction mixture; yields are given in square brackets. NR = no reaction.

93%, respectively). Other alkyl β-ketoesters were also effective; benzylester **12** was prepared in 85% yield from **1c**, and diastereoisomers **13a** and **13b** were isolated in 37% and 43% yields when (−)-menthyl-chiral auxiliary **1d** was used. 1-Naphthol was found to be unstable under the reaction conditions, and as a result hemiacetal **14** was isolated in only 20% yield. Interestingly, the formation of spirolactone **15** (77% yield) and spirolactone **16** (83% yield) from the indanone and tetralone derivatives may be attributed to the low stability of the corresponding hemiacetals. Moderate stereoselectivity was obtained when cyclohexanone derivatives bearing alkyl substituents were reacted. For example, the reaction between ethyl

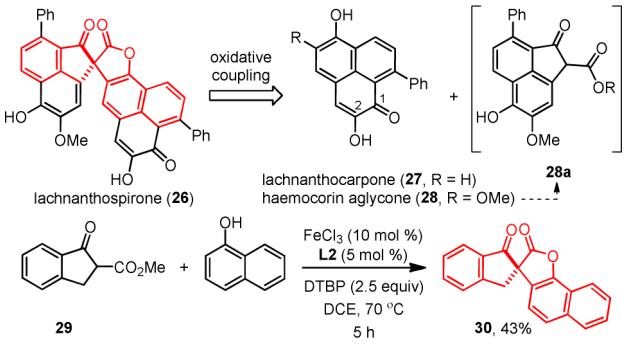
5-methylcyclohexanone-2-carboxylate and 6-bromo-2-naphthol resulted in the formation of diastereomers **17a** and **17b** (52% and 13% yield, respectively, *dr* = 4:1), and spirolactone **18**, prepared from modified carvone and **2**, was obtained as a single stereoisomer in 39% yield (60% yield based on starting material recovery). The fact that the isopropene group was left untouched demonstrates another aspect of the chemoselectivity of this transformation.[15b]

In general, the coupling of phenols was found to be much more difficult than that of naphthols, and unless activated phenols were used, the yields decreased dramatically.[21] The reaction between ethyl 6-(4-chlorophenyl)-2-oxo-4-phenyl-3-cyclohexene-1-carboxylate and 3-methoxyphenol in the presence of phenanthroline (5 mol %) resulted in the formation of spirolactone **19** in 40% yield. Moreover, when 3-methoxyphenol was reacted with **1b** in the absence of an additive, the desired coupling product **20a** was isolated in only 42% yield, together with a 25% yield of 4-*tert*-butyl substituted hemiacetal **20b**, resulting from a Friedel–Crafts alkylation prior to the coupling step. The addition of phenanthroline (5 mol %) reduced the Lewis acidity of the iron complex, and as a result the Friedel–Crafts reaction became negligible and the desired product **20a** was now isolated in 68% yield. 4-Methoxyphenol is also a suitable coupling partner, affording hemiacetal **21** in 66% yield (50% in the absence of phenanthroline). On the other hand, 2-methoxyphenol failed to react with **1d** in the absence of an additive, and in the presence of phenanthroline (5 mol %) the desired product **22** was obtained in only 22% yield as a 2:1 mixture of hemiacetal and free phenol isomers.

We also examined the reaction of ethyl 2-methylacetoacetate with phenol derivatives. Under our conditions, hemiacetal **23** was isolated in 66% yield. When 3-methoxyphenol was reacted in the absence of additive, the desired hemiacetal could not be detected, and when phenanthroline (5 mol %) was added, the corresponding unstable hemiacetal **24** was isolated in only 22% yield. We have also examined the coupling between ethyl 3-oxo-3-phenylpropanoate and 2-naphthol, a reaction which was reported previously by Li.[14] Under our modified conditions benzofuran **25** was isolated in 68% yield.

The described method can be applied to the synthesis of complex natural products, such as lachnanthospirone **26** (Scheme 2). This dimeric pigment[22] was isolated from the seeds of *Lachnanthes tinctoria* together with lachnanthocarpone (**27**) and hemocorin aglycone (**28**), which possesses the 9-phenylphenalenone ring system. In the paper describing the isolation of **26**, Edwards et al. proposed that an unknown oxidative coupling reaction between **27** and an oxidation product derived from **28** are the precursors of lachnanthospirone.[22] Based on our study, it is now possible to propose a biosynthetic route for the synthesis of **26**. In that case, the coupling partners in the key oxidative coupling step would be phenol **27** and β-ketoester **28a**.[23] To examine the feasibilty of this hypothesis, the reaction between indanone derivative **29** and 1-naphthol was chosen as a model system. Indeed, under our general conditions [$FeCl_3$ (10 mol %), **L2** (5 mol %), DTBP (2.5 equiv), DCE, 70 °C], spirolactone **30**, which contains the centeral polycyclic core of lachnanthospirone, was isolated in 43% yield (not optimized).

Scheme 2. Formation of Lachnanthospirone Polycyclic Central Core



In summary, we have developed a novel CDC method for the coupling of cyclic and acyclic β-ketoesters, based on an inexpensive, nontoxic iron catalyst, which leads to the formation of either polyaromatic spirolactones or polyaromatic hemiacetal architectures. A ligand effect was identified, with 1,10-phenanthroline or 2,2′-bipyridine having a significant influence on the efficiency of the reaction and on the deceleration of side reactions. To demonstrate the wide applicability of this transformation, various β-ketoesters were reacted with different phenol derivatives. The coupling was shown to be chemo-, regio-, and stereoselective and was successfully applied to the synthesis of the lachnanthospirone central core via a possible biomimetic approach. We believe that the powerful synthetic tool afforded by our new method can be applied for the synthesis of many valuable phenolic compounds and is likely to find wide utility in the synthesis of natural products. Efforts to expand the range of substrates, to apply this methodology in target-oriented syntheses, and to further study the role of additives in iron-based CDC reactions are currently underway.

Acknowledgment. We wish to thank Dr. Amira Rudi (BGU) for NMR spectroscopic assistance. This research was supported by the Israel Science Foundation (grant No. 1406/11).

Supporting Information Available. Table 1S, Full experimental procedures, characterization data, NMR spectra, and X-ray crystal data (CIF) for **3**, **8**, **13a**, and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(21) The work that describe the coupling of unactivated phenols with α-substituted-β-ketoesters will be published elsewhere.

(22) Edwards, J. M.; Mangion, M.; Anderson, J. B.; Rapposch, M.; Hite, G. *Tetrahedron Lett.* **1979**, *20*, 4453.

(23) Intermediate **28a** could be obtained from **28** through an oxidative cleavage at C1–C2 follow by Dieckmann condensation.