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New Access to Trisubstituted 3-Pyrrolines under Phosphine Catalysis

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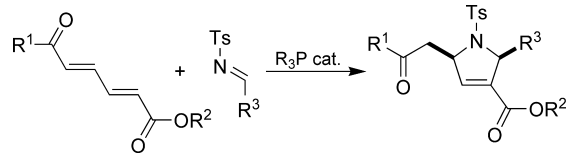
ABSTRACT



Conjugated dienes, properly activated by electron-withdrawing groups on both ends, are shown to be suitable substrates for phosphine-promoted organocatalytic processes. Their reactions with imines, under phosphine catalysis, afford a new and efficient synthetic approach to functionalized 3-pyrrolines.

Nucleophilic phosphines are known to be useful mild catalysts for the conversion of imines into nitrogen heterocycles via [3 + 2][1] and [4 + 2][2] cyclization reactions, in which either electron-poor allenes or alkynes behave as the three- or four-carbon synthons.[3] The synthetic potential of these reactions has been largely demonstrated by the preparation of biologically relevant natural products[4] as well as by using them to access a range of pyrrolidines and piperidines for pharmaceutical applications.[5] In this context, with the aim of extending the scope of phosphine organocatalysis, we disclose here a new approach to 2,3,5-trisubstituted 3-pyrrolines, based on the use of conjugated dienes as the three carbon units in annulation reactions on activated imines. This new method complements the previous ones, as far as it allows access to a different range of 3-pyrrolines from easily available new substrates.

Our strategy of using conjugated dienes as starting materials has been developed, based on the well-known activation of bis(enones) by phosphorus nucleophiles leading to the so-called intramolecular Rauhut−Currier reactions,[6]

(1) (a) Xu, Z.; Lu, X. *Tetrahedron Lett.* **1997**, *38*, 3461–3464. (b) Xu, Z.; Lu, X. *J. Org. Chem.* **1998**, *63*, 5031–5041. (c) Xu, Z.; Lu, X. *Tetrahedron Lett.* **1999**, *40*, 549–552. (d) Zhao, G.-L.; Shi, M. *J. Org. Chem.* **2005**, *70*, 9975–9984. (e) Zhu, X.-F.; Henry, C. E.; Kwon, O. *Tetrahedron* **2005**, *61*, 6276–6282. (f) Tang, X.; Zhang, B.; He, Z.; Gao, R.; He, Z. *Adv. Synth. Catal.* **2007**, *349*, 2007–2017. (g) Meng, L.-G.; Cai, P.; Guo, Q.; Xue, S. *J. Org. Chem.* **2008**, *73*, 8491–8496. (h) Zhang, B.; He, Z.; Xu, S.; Wu, G.; He, Z. *Tetrahedron* **2008**, *64*, 9471–9479. (i) Jean, L.; Marinetti, A. *Tetrahedron Lett.* **2006**, *47*, 2141–2145. (j) Fleury-Brégeot, N.; Jean, L.; Retailleau, P.; Marinetti, A. *Tetrahedron* **2007**, *63*, 11920–11927. (k) Scherer, A.; Gladysz, J. A. *Tetrahedron Lett.* **2006**, *47*, 6335–6337. (l) Fang, Y.-Q.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 5660–5661. (m) Pinto, N.; Fleury-Brégeot, N.; Marinetti, A. *Eur. J. Org. Chem.* **2009**, 146–151.

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(3) Nitrogen heterocycles are also available by combining imines with enones, acrolein, or allylic carbonates, under phosphine catalysis: (a) Shi, M.; Xu, Y.-M. *Eur. J. Org. Chem.* **2002**, 696–701. (b) Meng, X.; Huang, Y.; Chen, R. *Chem. Eur. J.* **2008**, *14*, 6852–6856. (c) Ma, G.-N.; Wang, F.-J.; Gao, J.; Shi, M. *Chem. Commun.* **2008**, 4998–5000. (d) Zheng, S.; Lu, X. *Org. Lett.* **2008**, *10*, 4481–4484.

(4) Tran, Y. S.; Kwon, O. *Org. Lett.* **2005**, *7*, 4289–4291.

(5) (a) Wager, T. T.; Welch, W. M.; O'Neill, B. T. WO 2004/110996, Pfizer Products Inc., U.S., 2004. (b) Segelstein, B. E.; Wager, T. T.; Welch, W. M. *Pfizer Prod. Inc. US Patent Appl. 2005/272800,* 2005. (c) Castellano, S.; Fiji, H. D. G.; Kinderman, S. S.; Watanabe, M.; de Leon, P.; Tamanoi, F.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 5843–5845. (d) Watanabe, M.; Fiji, H. D. G.; Guo, L.; Chan, L.; Kinderman, S. S.; Slamon, D. J.; Kwon, O.; Tamanoi, F. *J. Biol. Chem.* **2008**, *283*, 9571–9579.

(6) (a) Rauhut, M.; Currier, H. U.S. Patent American Cyanamide Co., 3074999: 1963. (b) Wang, L.-C.; Luis, A. L.; Agapiou, K.; Jang, H.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 2402–2403. (c) Frank, S. A.; Mergott, D. J.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 2404–2405. (d) Brown, P. M.; Käppel, N.; Murphy, P. J. *Tetrahedron Lett.* **2002**, *43*, 8707–8710. (e) Aroyan, C. E.; Dermenci, A.; Miller, S. J. *Tetrahedron* **2009**, *65*, 4069–4084.

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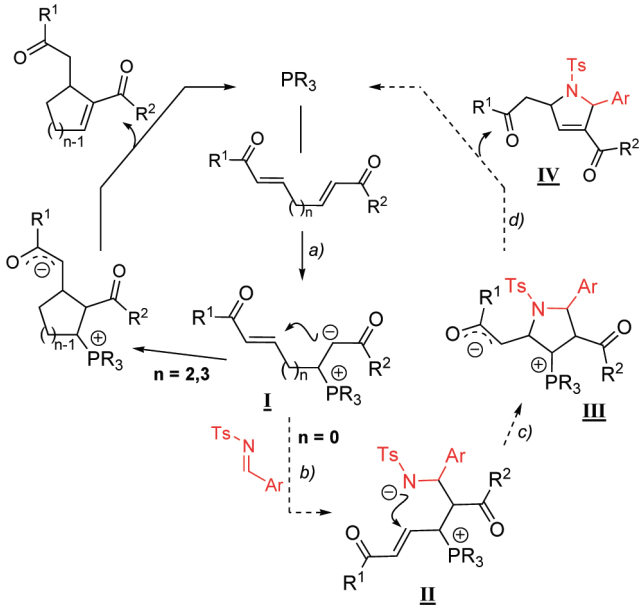
when the enone functions are tethered by either two or three atoms chains. The postulated mechanism of these reactions is depicted in Scheme 1 (left). We reasoned that if the two

Scheme 1. Intramolecular Rauhut−Currier Reaction (Left) and the Suggested Variant Involving Trapping of **I** by Imines (Right)

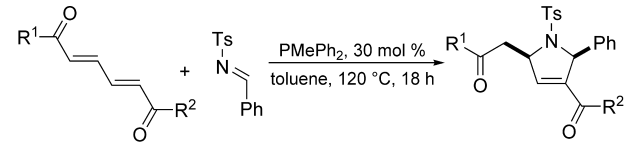


electron-poor olefinic functions of the substrates were directly connected, as in conjugated dienes ($n = 0$ in Scheme 1), the Rauhut−Currier type reactions would be disfavored due to the short distance between the carbanionic center of **I** and the potential olefinic acceptor. In this case, it should be possible to trap the zwitterionic intermediate **I** with electrophilic substrates, such as activated imines (step *b* in Scheme 1, right). This would create a three atom spacer between the negatively charged atom (the nitrogen center in **II**) and the enone function, thus enabling an intramolecular nucleophilic addition to take place (step *c*), following a classical Rauhut−Currier type process. Pyrrolines **IV** are expected to be quickly accessed in this way, from a reaction sequence which formally combines intramolecular Rauhut−Currier and aza-Morita−Baylis−Hillman[7] type reactions.

To test the feasibility of the catalytic manifold above, we examined the reactions between *N*-tosylbenzaldimine **3a** and both symmetrical and unsymmetrical dienic substrates, i.e., the diester **1a**,[8] the diketone **1b**,[9] and the enone-ester **2a**[10] in the presence of $MePPh_2$ as the Lewis base catalyst (Scheme 2).

Dimethyl *trans*−*trans* muconate **1a** failed to react with the imine, while the anticipated cyclization products **4b** and **5a** were obtained from 1,4-dibenzoyl-1,3-butadiene **1b** and the 6-oxo-6-phenylhexadienoic acid methyl ester **2a**, respec-

Scheme 2. Attempted Reactions of Conjugated Dienes with Imines in the Presence of $PMePh_2$



1a, $R^1 = R^2 = OMe$
1b, $R^1 = R^2 = Ph$
2a, $R^1 = Ph$ $R^2 = OMe$

3a

$R^1 = R^2 = OMe$, *no reaction*
4b, $R^1 = R^2 = Ph$, 55% yield[a]
5a, $R^1 = Ph$, $R^2 = OMe$, 65% yield[b]

[a] *Syn:anti* ratio = 90:10. [b] *Syn:anti* ratio = 85:15.[11]

tively. Pyrrolines **4b** and **5a** were produced as mixtures of two isomers in about 9:1 ratios, tentatively assigned as the 2,5-*syn* and *anti* diastereomers. The *syn* isomer is the major product.[11] When starting from the unsymmetric substrate **2a**, the cyclization might occur, in principle, on each one of the electron-poor C−C double bonds. The reaction proceeded, actually, with high regioselectivity, leading to pyrroline **5a**.

The inertness of the diester toward the above cyclization reactions is in line with the known reluctance of bisenoates to undergo intramolecular Rauhut−Currier type cyclizations.[6b−d] The behavior of the mixed enone-enoate substrate **2a** is however rather surprising. Indeed, the isolated product **5a** results from the initial addition of the phosphorus nucleophile to the enoate double bond ($R^2 = OMe$, step *a* in Scheme 1), while the enone function serves as the Michael acceptor in the subsequent ring-closing step *c*. This contrasts with literature data showing that intramolecular Rauhut−Currier reactions on enone-enoates take place with the opposite regiochemistry: enones being the more electrophilic of the two Michael acceptors of the bifunctional substrates, they preferentially undergo the initial addition of the phosphorus nucleophile.[6b−d,12] The observed, unusual cyclization manifold leading to **5a** might be determined by either electronic effects and orbitals distribution on the diene or the relative reaction rates of the two possible phosphine−diene adducts with the imine in step *b*.

It must be pointed out here that cyclizations in Scheme 1 seem to be uniquely susceptible to phosphine catalysis since they did not proceed in the presence of nitrogen Lewis bases such as DABCO, DMAP, or Et_3N.

After optimization of the reaction conditions,[13] the method appeared to be applicable to a wide range of substrates and notably to dienic enone-esters with various R^1 substituents. The 6-oxo-dienoates **2b**−**2o** were conveniently accessed as *E*/*Z* mixtures from the commercially available (*E*)-4-oxobut-2-enoic acid ethyl ester, via Wittig-type reactions (Scheme 3).

Their reactions with *N*-tosylbenzaldimine have been performed with either PBu_3 or $PMePh_2$, at 50 and 120 °C, respectively. Neither PPh_3 nor PCy_3 were efficient catalysts for

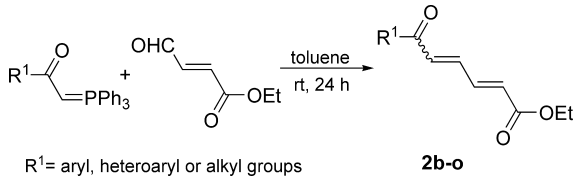
(7) (a) Perlmutter, P.; Teo, C. C. *Tetrahedron Lett.* **1984**, *25*, 5951–5952. (b) Shi, Y.-L.; Shi, M. *Eur. J. Org. Chem.* **2007**, 2905–2916. (c) Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 4614–4628.

(8) Boisvert, L.; Beaumier, F.; Spino, C. *Org. Lett.* **2007**, *9*, 5361–5363.

(9) Perlmutter, H. D.; Trattner, R. B. *J. Org. Chem.* **1978**, *43*, 2056–2057.

(10) Allen, J. V.; Bergeron, S.; Griffiths, M. J.; Mukherjee, S.; Roberts, S. M.; Williamson, N. M.; Wu, L. E. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3171–3179.

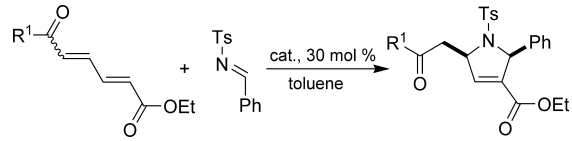
Scheme 3. Synthesis of the 6-Oxo-dienoates **2b−o**



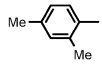
R[1]= aryl, heteroaryl or alkyl groups **2b-o**

these cyclizations. Depending on the substrate, yields and diastereomeric ratios may vary slightly, as a function of the phosphorus catalyst and the reaction temperature. For each substrate, the optimized conditions and results are reported in Table 1.

Table 1. Synthesis of Pyrrolines **5b−o** from Various 6-Oxodienoates[a]



2b-o **3a** **5b-o**

	substrate R[1]		product	cat.	yield (%)	dr[d]
1	C_6H_5	**2b**	**5b**	$PMePh_2$[b]	64	90:10
2	*p*-ClC_6H_4	**2c**	**5c**	$PMePh_2$[b]	76	85:15
3	*p*-BrC_6H_4	**2d**	**5d**	$PMePh_2$[b]	65	85:15
4	*p*-FC_6H_4	**2e**	**5e**	$PMePh_2$[b]	66	80:20
5	*p*-NCC_6H_4	**2f**	**5f**	PBu_3[c]	39	90:10
6	*p*-$NO_2C_6H_4$	**2g**	**5g**	PBu_3[c]	52	90:10
7	*p*-MeC_6H_4	**2h**	**5h**	PBu_3[c]	50	90:10
8	*p*-$MeOC_6H_4$	**2i**	**5i**	PBu_3[c]	45	90:10
9		**2j**	**5j**	$PMePh_2$[b]	73	90:10
10		**2k**	**5k**	PBu_3[c]	34	90:10
11		**2l**	**5l**	PBu_3[c]	32	90:10
12	*t*-Bu	**2m**	**5m**	$PMePh_2$[b]	92	>99:1
13		**2n**	**5n**	$PMePh_2$[b]	70	>99:1
14	$C_{14}H_{29}$	**2o**	**5o**	$PMePh_2$[b]	22	90:10

[a] Reactions performed at a 0.3 mmol scale, with a 1:1 diene:imine ratio, under Ar in toluene (1 mL) for 18 h. [b] Reaction temperature: 120 °C. [c] Reaction temperature: 50 °C. [d] In the crude reaction mixture.

As shown in Table 1, these reactions delivered the expected pyrrolines in moderate to good yields, starting from aryl ketones with both electron-donating and -withdrawing substituents (entries 1−9), as well as from naphthyl (entry 10) and thienyl ketones (entry 11). Alkyl ketones may also be suitable substrates, and especially high yields were obtained from dienone **2m** which displays a *t*-Bu substituted carbonyl function (entry 12). Decreasing yields are given by dienones with secondary and primary alkyl groups (entries 13 and 14).

In most of the isolated products the *syn:anti* ratio is higher than 9:1, and it increases to >99:1 for pyrroline **5g** as well as for the alkyl-substituted ketones of entries 12 and 13. The *syn:anti* ratios of **5** are irrespective of the *E*/*Z* isomer ratios of the starting dienes.

The *syn* stereochemistry has been assigned to the major isomers of **5**, based on X-ray diffraction studies on a representative compound, **5g** (entry 6). Crystals of **5g** have been obtained from a dichloromethane solution by slow addition of pentane. The ORTEP drawing is shown in Figure 1.[14]

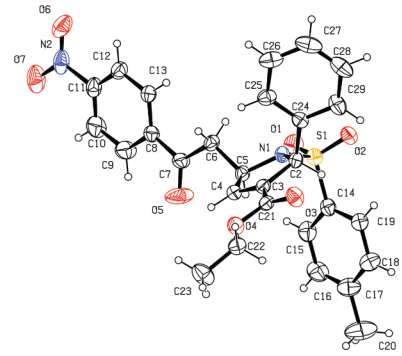


Figure 1. ORTEP view of pyrroline **5g** showing the relative *syn* arrangement of the ring substituents. Displacement ellipsoids are at the 30% level.

Finally, to further establish the scope of this new cyclization reaction, a variety of *N*-Ts imines have been prepared and reacted then with the 6-oxo-hexadienoates **2b** (R^1 = Ph) and **2m** (R^1 = *t*-Bu). Representative results are given in Table 2, showing that the reaction may tolerate electron-rich and electron-poor aryl substituents on the imine carbon.

Most notably, not only aryl-substituted but also a representative alkyl-substituted imine **3h** could be reacted with dienoates **2b**,**m** to afford the corresponding 2-alkyl-substituted pyrrolines **6h** and **7h** in good yields.

As a general trend, the *t*-Bu substituted 6-oxo-dienoate **2m** (entries 8−13) gives very clean reactions, almost total diastereoselectivity and higher yields than the benzoyl-substituted diene **2b** (entries 1−7).

(11) The molecular structure and the syn stereochemistry of the major product have been established by X-ray diffraction studies (see Figure 1). The minor isomer has not been unambiguously characterized; nevertheless, selected NMR signals have been assigned by COSY experiments. Assignments support the 3-pyrroline structure. For compound **5a′** (minor product), NMR data are the following: δ 3.32 (dd, $^2J_{HH}$ = 18.3 Hz, $^3J_{HH}$ = 9.3 Hz, 1H, CH_2CO), 4.54 (dd, $^2J_{HH}$ = 18.3 Hz, $^3J_{HH}$ = 3.9 Hz, 1H, CH_2CO), 5.39 (m, 1H, $^3J_{HH}$ = 9.3 Hz, $^4J_{HH}$ = 5.7 Hz, $^3J_{HH}$ = 3.9 Hz, $^3J_{HH}$ = 1.8 Hz, $NCHCH_2$), 5.85 (dd, $^4J_{HH}$ = 5.7 Hz, $^4J_{HH}$ = 1.5 Hz, 1H, CHPh) ppm. The corresponding NMR data for the major product **5a** are the following: δ 3.36 (dd, $^2J_{HH}$ = 17.7 Hz, $^3J_{HH}$ = 10.6 Hz, 1H, CH_2CO), 4.04 (dd, $^2J_{HH}$ = 17.7 Hz, $^3J_{HH}$ = 3.8 Hz, 1H, CH_2CO), 5.10 (ddt, $^3J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 3.8 Hz, $^3J_{HH}$ = $^4J_{HH}$ = 1.9 Hz, 1H, $NCHCH_2$), 5.58 (t, $^4J_{HH}$ = 1.9 Hz, 1H, CHPh) ppm.

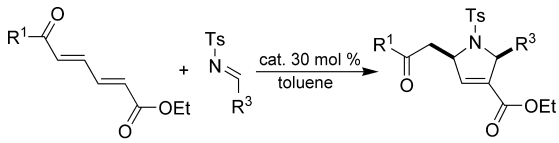
(12) Brown, P. M.; Käppel, N.; Murphy, P. J.; Coles, S. J.; Hursthouse, M. B. *Tetrahedron* **2007**, *63*, 1100–1106.

(13) For full details on solvents and catalyst screenings, see Supporting Information.

(14) Crystallographic data for this compound have been deposited at the CCDC, Cambridge, UK, with the deposit number 741184.

(15) Guan, X.-Y.; Shi, M. *J. Org. Chem.* **2009**, *74*, 1977–1981.

Table 2. Variations of the Imine Partners[a]



2b, R^1 = Ph
2m, R^1 = *t*-Bu

3b-h

6b-h, R^1 = Ph
7b-h, R^1 = *t*-Bu

	diene	imine R^3		prod.	cat.	yield (%)	dr
1	**2b**	*p*-ClC_6H_4	**3b**	**6b**	$PMePh_2$[b]	64	85:15
2	**2b**	*p*-$NO_2C_6H_4$	**3c**	**6c**	PMe_2Ph[c]	38	90:10
3	**2b**	*p*-$CF_3C_6H_4$	**3d**	**6d**	PBu_3[c]	42	90:10
4	**2b**	*p*-$MeOC_6H_4$	**3e**	**6e**	PMe_2Ph[c]	24	85:15
5	**2b**	1-naphthyl	**3f**	**6f**	PBu_3[c]	46	>95:5
6	**2b**	2-thienyl	**3g**	**6g**	$PMePh_2$[b]	67	85:15
7	**2b**	*i*-Pr	**3h**	**6h**	PBu_3[c]	68	>99:1
8	**2m**	*p*-ClC_6H_4	**3b**	**7b**	$PMePh_2$[b]	71	>99:1
9	**2m**	*p*-$CF_3C_6H_4$	**3d**	**7d**	$PMePh_2$[b]	85	>99:1
10	**2m**	*p*-$MeOC_6H_4$	**3e**	**7e**	$PMePh_2$[b]	71	>95:5
11	**2m**	1-naphthyl	**3f**	**7f**	$PMePh_2$[b]	88	>95:5
12	**2m**	2-thienyl	**3g**	**7g**	$PMePh_2$[b]	70	>99:1
13	**2m**	*i*-Pr	**3h**	**7h**	$PMePh_2$[b]	69	>99:1

[a] Reactions performed at a 0.3 mmol scale, with a 1:1 diene:imine ratio, under Ar in toluene (1 mL) for 18 h. [b] Reaction temperature: 120 °C. [c] Reaction temperature: 50 °C.

The above results show that, compared to other phosphine-based organocatalytic methods, the use of the conjugated dienes **2** as substrates gives access to a new range of 2,3,5-trisubstituted 3-pyrrolines. The known approaches, which make use of 3-substituted allenoates or butynoates,[1c−f,h,5c,15] alkynyl ketones,[1g] enones[3a] or allylic compounds,[3d] and aryl imines as reactants, have been applied so far to the synthesis of 2-aryl-substituted pyrrolines, with either simple alkyls (Me, Et, Pr, *n*-Bu, *t*-Bu, *n*-Pent, *n*-Hex, *c*-$C_5H_9CH_2$) or aryl groups in the 5 position. As shown in Tables 1 and 2 above, the new method opens the way to both 2-alkyl- and 2-aryl-substituted pyrrolines with carbonylmethyl functions on the C-5 carbon.

In conclusion, we have developed a simple, general, and practical method for the synthesis of new 2,3,5-trisubstituted 3-pyrrolines from easily available dienic derivatives, under phosphine catalysis. Future studies will focus on the development of related organocatalytic transformations of dienic substrates, as well as on synthetic applications of the functionalized pyrroline scaffolds above.

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Supporting Information Available: General experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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