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An Expedient Phosphine-Catalyzed [4 + 2] Annulation: Synthesis of Highly Functionalized Tetrahydropyridines

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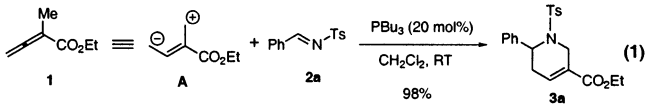
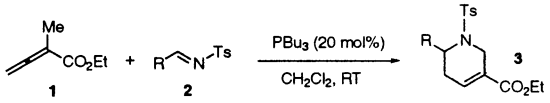
Functionalized tetrahydropyridines and piperidines are common substructures found in biologically active natural products and synthetic pharmaceuticals.[1] One of the most versatile methods to prepare six-membered heterocycles is the [4 + 2] cycloaddition reaction. Among the [4 + 2] cycloadditions, examples of 1,4-dipolar cycloadditions providing six-membered heterocycles are scarce.[2] For the most part, this is due to the fact that Diels−Alder reactions rather than 1,4-dipolar cycloadditions have provided the means to construct heterocyclic six-membered rings.[3] The reactivity and regioselectivity of Diels−Alder reactions, however, are predetermined by the molecular orbital coefficients of dienes and dienophiles and limit the scope of accessible heterocycles. For example, while Diels−Alder reaction of 2-methylene-but-3-enoates[4] with imines could potentially provide tetrahydropyridine derivatives, this diene only dimerizes in the presence of *N*-tosylbenzaldimine.[5] As part of a program focused on the development of organic phosphine-catalyzed annulation reactions[6] to form heterocycles, and inspired by recent accounts of phosphine-catalyzed reactions of 2,3-butadienoates or 2-butynoates, we herein report the discovery of a 2-methylene-but-3-enoate synthon and its phosphine-catalyzed [4 + 2] annulation with aldimines to provide highly substituted tetrahydropyridine derivatives.

The formation of pyrroline derivatives upon mixing imines with 2,3-butadienoates in the presence of a phosphine catalyst is triggered by α-addition of the zwitterionic intermediate to the imine.[7] We envisioned that substitution of the hydrogen at the 2-position of 2,3-butadienoates with a methyl group might block the α-attack of the zwitterionic intermediate and lead to an unprecedented reaction mode initiated by γ-addition of the zwitterionic intermediate to imines (see discussion on mechanism below). To our delight, mixing 2-methyl-2,3-butadienoate **1** with *N*-tosylbenzaldimine in the presence of a catalytic amount of PBu_3 resulted in the formation of tetrahydropyridine **3a** (eq 1). In the present reaction, ethyl 2-methyl-2,3-butadienoate acts as a 1,4-dipole synthon **A**.



Using conditions optimized for the formation of **3a**, we prepared various tetrahydropyridine derivatives (Table 1). Several characteristics of this annulation reaction are noteworthy. Tetrahydropyridines (Table 1, **3a**−**3k**) were obtained in over 90% yield when **1** was allowed to react with various aryl *N*-tosylimines[8] **2** in the presence of 20 mol % PBu_3, with the exception of an aryl group bearing a nitro-substituent (Table 1, **3l**). Interestingly, salicyl and 2-pyrrolyl *N*-tosylmines provided none of the desired product (Table 1, **3m** and **3o**) while their *O*-TBS and *N*-Boc protected counterparts underwent the annulation uneventfully (Table 1, **3n** and **3p**). The presence of acidic protons is believed to be detrimental to the reaction. For alkyl and vinyl *N*-tosylimines, none or trace amounts of cycloadducts were isolated. Only *N*-tosylpivalaldimine afforded the desired product (Table 1, **3r**) in 86% yield in the presence of Na_2CO_3.

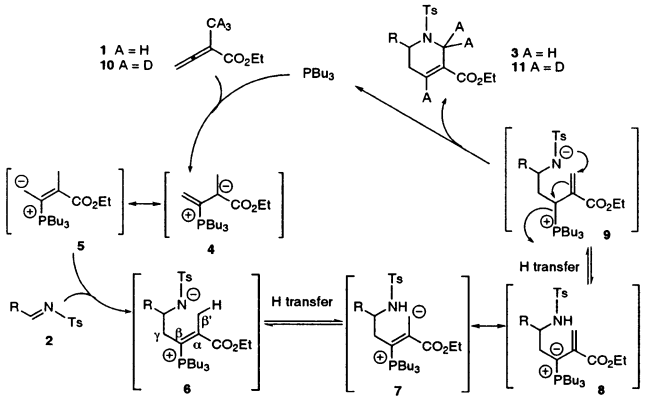
Table 1. Synthesis of Tetrahydropyridines **3** from Ethyl 2-Methyl-2,3-butadienoate and *N*-Tosylaldimines[a]



entry	R	product	yield (%)[b]
1	Ph (**2a**)	**3a**[c]	98
2	4-OMeC$_6$H$_4$ (**2b**)	**3b**	99
3	4-MeC$_6$H$_4$ (**2c**)	**3c**	95
4	3-ClC$_6$H$_4$ (**2d**)	**3d**	96
5	2-ClC$_6$H$_4$ (**2e**)	**3e**	93
6	4-FC$_6$H$_4$ (**2f**)	**3f**	95
7	4-CNC$_6$H$_4$ (**2g**)	**3g**	98
8	2-CF$_3$C$_6$H$_4$ (**2h**)	**3h**	98
9	1-naphthyl (**2i**)	**3i**	96
10	2-furyl (**2j**)	**3j**	97
11	4-pyridyl (**2k**)	**3k**	92[d]
12	4-NO$_2$C$_6$H$_4$ (**2l**)	**3l**	86
13	2-OHC$_6$H$_4$ (**2m**)	**3m**	0
14	2-OTBSC$_6$H$_4$ (**2n**)	**3n**	93
15	2-pyrrolyl (**2o**)	**3o**	0
16	*N*-Boc-2-pyrroyl (**2p**)	**3p**	99
17	*trans*-styrenyl (**2q**)	**3q**	trace[e]
18	*t*-butyl (**2r**)	**3r**	86[f]
19	*n*-propyl (**2s**)	**3s**	0[g]

[a] See Supporting Information for a detailed experimental procedure. [b] Isolated yields. [c] The structure was confirmed by X-ray crystallographic analysis. [d] 30 mol % PBu_3 was used. [e] The product was inseparable from the starting imine. [f] 3 equiv of Na_2CO_3 was added. [g] The imine was decomposed to aldehyde and *p*-toulenesulfonamide.

Scheme 1. Mechanistic Rationale for the Formation of **3**



The mechanism of this unprecedented cyclization reaction has not been unequivocally established, but one reasonable possibility is outlined in Scheme 1. Tri-*n*-butylphosphine acts as a nucleophilic trigger and forms intermediate **4**, which exists as a resonance-stabilized zwitterionic intermediate **4** ↔ **5**. Allylic carbanion **5** adds

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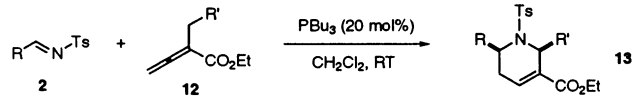
Table 2. Synthesis of Tetrahydropyridines **13** from Ethyl 2-Benzyl-2,3-butadienoates and *N*-Tosylaldimines[a]



entry	R	R′	product	yield (%)[b]	dr[c]
1	Ph (**2a**)	4-CNC_6H_4 (**12a**)	**13a**	99	98:2
2	Ph (**2a**)	2-FC_6H_4 (**12b**)	**13b**	99	97:3
3	Ph (**2a**)	3-$OMeC_6H_4$ (**12c**)	**13c**	99	98:2
4	Ph (**2a**)	2-MeC_6H_4 (**12d**)	**13d**	82	88:12
5	Ph (**2a**)	Ph (**12e**)	**13e**[d]	99	98:2
6	4-$OMeC_6H_4$ (**2b**)	Ph (**12e**)	**13f**	99	97:3
7	4-$NO_2C_6H_4$ (**2l**)	Ph (**12e**)	**13g**	90	95:5
8	3-ClC_6H_4 (**2d**)	4-CNC_6H_4 (**12a**)	**13h**	99	98:2
9	2-$CF_3C_6H_4$ (**2h**)	4-CNC_6H_4 (**12a**)	**13i**	80	90:10
10	2-ClC_6H_4 (**2e**)	3-$OMeC_6H_4$ (**12c**)	**13j**	96	83:17
11	4-MeC_6H_4 (**2c**)	3-$OMeC_6H_4$ (**12c**)	**13k**	99	98:2

[a] See Supporting Information for a detailed experimental procedure. [b] Isolated yields. [c] Diastereomer ratio determined by ^{1}H NMR (500 MHz). [d] The structure was confirmed by X-ray crystallographic analysis.

to imine **2** to produce intermediate **6**.[9] Two consecutive proton-transfer steps shuffle the proton on the β'-carbon to the β-carbon of intermediate **6**. Thus formed intermediate **9** undergoes 6-*endo* cyclization followed by expulsion of PBu_3 to generate tetrahydropyridine **3**.

The proton-transfer process is believed to be the rate-determining step on the basis of the observation that 2-methyl-d_3-2,3-butadienoate **10** undergoes the annulation reaction with *N*-tosylbenzaldimine (**2a**) much more sluggishly than **1** and provides **11** (R = Ph) only in 31% yield. This observation prompted us to test the reaction of 2-(4-cyanobenzyl)-2,3-butadienoate **12a** with *N*-tosylbenzaldimine (**2a**) (Table 2). Our speculation was that the first proton-transfer process (**6**→**7**) is energetically less favorable than the second one (**8**→**9**) and increased acidity of the proton on the β'-carbon would accelerate the overall reaction. Indeed, **13a** was obtained in 99% yield in 30 min with high diastreoselectivity (dr, 98:2) favoring the formation of 2,6-*cis*-adduct. Syntheses of tetrahydropyridines **13** employing 2-benzyl-2,3-butadienoates[10] **12** are summarized in Table 2.

The [4 + 2] annulation reactions of 2-benzyl-2,3-butadienoates **12** with *N*-tosylbenzaldimine (**2a**) in the presence of PBu_3 incorporated various aryl groups into the 2-position of tetrahydropyridines (Table 2, **13a**−**13e**) in almost quantitative yields with high diastereoselectivities. An exception was noted for ethyl 2-(2-methylbenzyl)-2,3-butadienoate (Table 2, **12d**). Upon investigation of the reactions on further substrate combinations (Table 2, entries 6−11), a clear trend could be discerned, with ortho-substituted aryl groups providing poorer results. Thus, the presence of an ortho-substituent of significant steric bulk (Table 2, entries 4, 9, and 10) on the aryl rings diminishes the reaction yield as well as compromising the reaction diastereoselectivity. On the contrary, the presence of an ortho-fluoro group afforded the desired 2,6-*cis*-tetrahydropyridine **13b** in nearly quantitative yield (99%) with high diastereoselectivity (dr, 97:3). It was again apparent that the reaction yield diminished when a nitro-substituted aryl *N*-tosylimine (**2l**) was employed (Table 2, entry 7).

In conclusion, our effort to expand the scope of phosphine-catalyzed annulations has led us to the discovery of a new class of 1,4-dipole synthons, 2-alkyl-2,3-butadienoates. The importance of this finding was exemplified by their expedient [4 + 2] annulation reaction with *N*-tosylaldimines to form tetrahydropyridine derivatives in excellent yields with complete regioselectivity and high diastereoselectivities. Future effort will focus on expanding the versatility of these new 1,4-dipole synthons as well as on performing the annulation in an enantioselective manner.

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Supporting Information Available: Representative experimental procedures and spectral data for all new compounds (PDF). Crystallographic data for compounds **3a** and **13e** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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