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N-heterocyclic carbene–palladium catalysts for the bisdiene cyclization-trapping reaction with sulfonamides under thermal and microwave conditions

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Abstract

Simple palladium-N-heterocyclic carbene catalysts readily effect the palladium-catalyzed cyclization-trapping of bisdienes with sulfonamides. The reaction is quite efficient for a variety of sulfonamides and several bisdienes. For example, using 0.1% of the in situ generated or preformed (IMes)Pd(η^3-C_3H_5)Cl complex, the cyclization-trapping of a simple bisdiene with $TsN(H)CH_2Ph$ proceeds in good yield under thermal conditions (74–75%, 75 °C, 9 h). The same reaction run under microwave irradiation proceeds somewhat faster and in even higher yield (86%, 75 °C, 2.5 h).

Keywords: Palladium; Catalysis; N-heterocyclic carbene ligands; Microwave irradiation

1,3-Butadiene undergoes efficient palladium-catalyzed telomerization, that is, linear dimerization with trapping by a variety of pronucleophiles [1]. Many primary and secondary amines are included among the successful trapping reagents employed thus far. The predominant product formed in such reactions is a 1-amino-2,7-octadiene derivative [2]. Generally, more basic amines react better [3], however, a range of non-basic amine derivatives, for example, formamide [4], phthalimides [5] and aryl- or alkylsulfonamides [6], can also serve as nitrogen-centered trapping reagents in the linear dimerization reaction.

We are interested in the intramolecular variant of diene dimerization as a novel means of bisdiene carbocyclization with the incorporation of useful functionalities via the choice of trapping reagent. In the course of our studies, we have reported the successful use of anilines [7], amines [8], and phthalimide [8] as way to introduce nitrogen into the cyclized product. To further explore the scope of the cyclization with respect to the nature of the trapping reagent and, in particular, to expand the variety of N-centered trapping reagents that can be employed in the cyclization-trapping reaction, we carried out a short study on the use of sulfonamides as trapping reagents.

Palladium catalyst systems incorporating phosphorus ligands have traditionally been used for both linear diene dimerization-trapping and our study of the bisdiene cyclization-trapping reactions. As a starting point for the use of sulfonamides, we carried out the reaction of bisdiene **1** with *N*-benzyl (*p*-tolyl)sulfonamide (**2**) using a commonly employed catalyst system, 10% [$Pd(OAc)_2$/2 PPh_3]. The course of the reaction was followed by removing aliquots and analyzing the crude mixture by HPLC (Fig. 1). There is a brief induction period, which is typical for these cyclizations since the presumed catalytically active species is a $L_nPd(0)$ complex formed in situ from the Pd(II) catalyst precursor. After induction, the cyclization proceeds smoothly and rapidly. A mixture of *trans*- and *cis*-products

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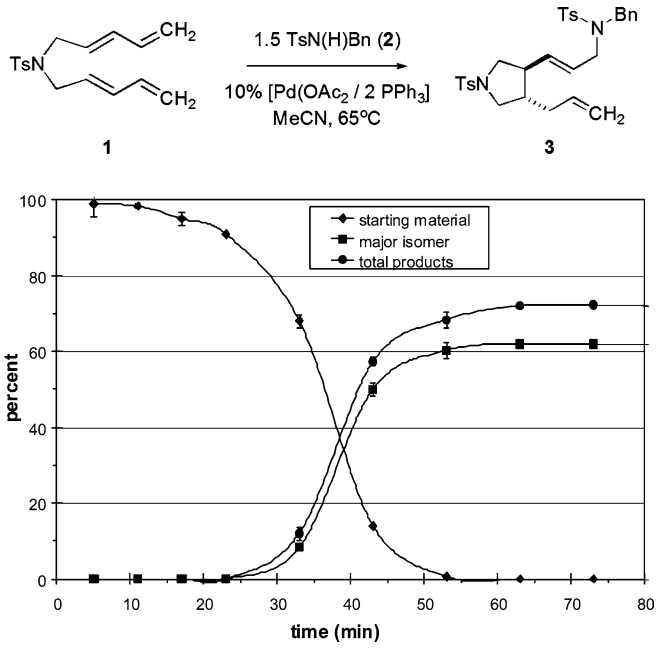
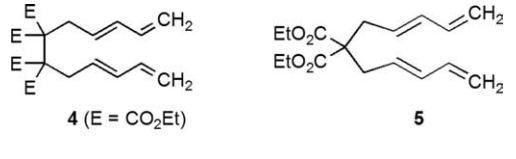


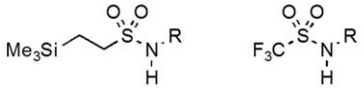
Fig. 1. The disappearance of starting materials and appearance of products in the $[Pd(OAc)_2/PPh_3]$-catalyzed cyclization of **1**.

is formed; the *trans* isomer **3** is favored and the *trans*:*cis* ratio (typically greater than 5:1) remains roughly constant over the course of the reaction.

In subsequent experiments (Table 1), the $[Pd(OAc)_2/PPh_3]$-catalyst system was successfully applied to the reaction of **2** with two other simple bisdiene substrates (i.e., **4** and **5**). Furthermore, we find that a fairly broad range of variation in the nature of the sulfonamide (i.e., **2**, **6**, and **7**) are tolerated in the cyclization-trapping reaction with **1** [9]. The successful use of sulfonamides adds another versatile set of trapping reagents to the arsenal for the palladium-catalyzed bisdiene cyclization.

Table 1
Other successful bisdiene substrate-sulfonamide trapping reagent combinations used with $[Pd(OAc)_2/2\ Ph_3P]$[a]



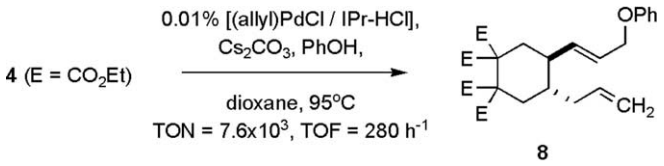


Entry	Bisdiene	Sulfonamide	R	Yield (%)[b]
1	**1**	**2**	Bn	(70)
3	**1**	**6**	Bn	73
4	**1**	**7**	Bn	83
5	**1**	**7**	*c*-C_6H_{11}	64
6	**1**	**7**	Ph	70
7	**4**	**2**	Bn	(60)
8	**4**	**6**	Bn	75
9	**5**	**2**	Bn	(72)
10	**5**	**6**	Bn	70

[a] Reactions run using 10 mol% palladium in MeCN (65 °C) for 1–2 h.
[b] Yields determined by HPLC are given in (parentheses).

During the course of this study, we became interested in exploring the use of N-heterocyclic carbene (NHC) ligands, in part, due to their potential for forming catalyst systems that exhibit higher turnover number and frequency. NHCs derived from hindered imidazolium salts mimic phosphines as sigma donors and have emerged as a useful class of ligands for a variety of metal-catalyzed reactions [10]. While there are relatively few examples of their use in metal-catalyzed carbocyclizations of α,ω-unsaturated substrates [11], the class of carbocyclizations to which the bisdiene cyclizations belong, NHC-palladium catalyst systems have been used masterfully for the linear dimerization-trapping of 1,3-butadiene with alcohols [12] and amines [13].

Building upon the very successful work of Beller and Nolan [14] on the linear dimerization-trapping of 1,3-butadiene, we recently carried out a study of the bisdiene cyclization-trapping reaction of bisdiene **4** with phenol [15]. In that study we reported that a variety of (NHC)Pd complexes catalyze the cyclization-trapping reaction, giving the same product as the traditional phosphine-promoted reactions but with significantly higher turnover number. Among the NHC-precursors screened, the commercially available IMes · HCl and IPr · HCl imidazolium salts proved to be particularly effective. For example, at 0.01% catalyst loading, the (IPr)Pd(η^3-C_3H_5)Cl in situ generated catalyst gave a turnover number of 7.6×10^3 with turnover frequency of 280 h^{-1} for the cyclization-trapping of **4** with phenol to give product **8**. These values are significantly higher than usually seen in this and related carbocyclization reactions and almost identical to those obtained by Beller and co-workers in the linear dimerization-trapping of butadiene with phenol.



From our prior studies of bisdiene cyclizations, we know that many palladium-catalyst systems are quite sensitive to the nature of the bisdiene and the trapping reagent. We are therefore interested in exploring the scope of the NHC-palladium catalysts and now report its successful use with sulfonamides as the trapping reagent.

Table 2 summarizes the data obtained from the in situ generated (NHC)Pd-catalyzed cyclization-trapping of bisdiene **1** with sulfonamide **2** in acetonitrile. Two common, commercially available NHC-precursors (IMes · HCl and IPr · HCl) were screened in combination with a series of catalyst precursors (Pd_2dba_3, $Pd(acac)_2$, $Pd(OAc)_2$ and

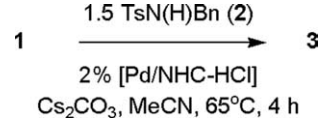
[(η^3-C_3H_5)PdCl]$_2$). In addition, combinations of [(η^3-C_3H_5)PdCl]$_2$ with $NaBF_4$, $NaSbF_6$ and $NaPF_6$ were screened in a attempt to probe whether the presence of a presumed associated (e.g., Cl) or dissociated (e.g., BF_4, SbF_6 or PF_6) counterion influences the reaction. The base (Cs_2CO_3) presumably serves a dual role in the reaction. It is needed to generate the NHC from its precursor, and for [(η^3-C_3H_5)PdCl]$_2$-derived catalyst systems, it likely promotes the addition of sulfonamide to the η^3-allylpalladium complex to generate the (NHC)Pd(0) catalyst.

All experiments in Table 2 were run using 2% palladium at 65 °C for 4 h. The yields shown are determined by HPLC analysis of the crude reaction mixtures. By screening all combinations at same catalyst loading, reaction temperature and reaction time, the yields, in part, reflect the relative rates of the various catalyst combinations. Excellent yields are obtained for all of the combinations screened with the exception of [Pd(acac)$_2$/IMes · HCl]; it gives a surprisingly poor yield. The latter was repeated several times, and at this point, we have no explanation for its poor performance, especially in contrast to [Pd(acac)$_2$/IPr · HCl]. We do not see a pronounced difference in the reactions run under ion exchange conditions, [(η^3-C_3H_5)PdCl/NaX]. We further compared those latter reactions to ones run with the corresponding silver salts. The yields obtained using the AgX salts were generally somewhat lower (results not shown).

Having established the viability of the reaction, we decided to compare the (IMes)- and (IPr)Pd catalysts derived from [(η^3-C_3H_5)PdCl]$_2$ at lower catalyst loading. Using a 0.1% Pd loading we find that the cyclization is efficient for both NHCs, but the (IMes)Pd catalyst appears to react slightly faster. At this lower catalyst loading, the in situ prepared catalyst, [(η^3-C_3H_5)PdCl/IMes · HCl] (Cs_2CO_3, MeCN), promotes the cyclization-trapping of bisdiene **1** with TsN(H)CH_2Ph (**2**) in good yield (75%, 75 °C, 9 h).

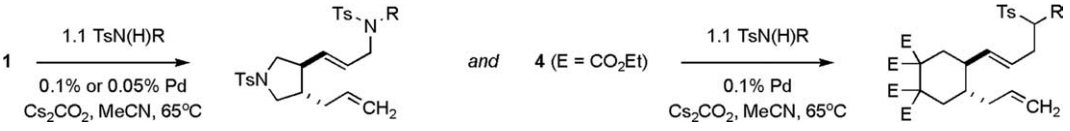
In an effort to further improve the efficiency of the cyclization, we prepared and isolated the known (IPr)Pd(allyl)Cl and (IMes)Pd(allyl)Cl complexes [16] and examined their use in the cyclization-trapping reaction. The results are summarized in Table 3. The reaction time required and yield of product obtained using the preformed (IMes)Pd(η^3-C_3H_5)Cl complex (Table 3, entry 2, 74%) at 0.1% catalyst loading are comparable to those of the corresponding in situ generated (IMes)-catalyst system (entry 1, 75%). The preformed (IPr)Pd(η^3-C_3H_5)Cl complex gave a slightly lower yield (entry 3, 68%). The *N*-methyl and *N*-phenyl TsN(H)R derivatives (entries 4 and 5) and a 2-naphthyl sulfonamide (entry 6) give excellent yields (81–92%) for the cyclization-trapping of **1**. The cyclization of bisdiene **4** leading to the formation of a six-membered ring system also proceeds readily using the preformed (IMes)Pd(η^3-C_3H_5)Cl complex (entries 7 and 8).

Table 2
The yield of cyclized product **3** as a function of catalyst- and NHC-precursor



Entry	Catalyst precursor	IMes · HCl	IPr · HCl
1	Pd_2dba_3	91	
2	$Pd(acac)_2$	20	100
3	$Pd(OAc)_2$	100	99
4	[(η^3-C_3H_5)PdCl]$_2$	98	94
5	[(η^3-C_3H_5)PdCl]$_2$/$NaBF_4$	98	87
6	[(η^3-C_3H_5)PdCl]$_2$/$NaSbF_6$	92	95
7	[(η^3-C_3H_5)PdCl]$_2$/$NaPF_6$	86	92

Table 3
(NHC)Pd-catalyzed cyclization-trapping reactions of bisdienes **1** and **4** (E = CO_2Et) with sulfonamides (TsN(H)R)[a]



Entry	Catalyst	Mol% Pd	Bisdiene	TsN(H)R, R=	Time (h)	Yield (%)
1[b]	(allyl)PdCl/IMes · HCl	0.1	**1**	$PhCH_2$	9	75
2	(IMes)Pd(allyl)Cl	0.1	**1**	$PhCH_2$	9	74
3	(IPr)Pd(allyl)Cl	0.1	**1**	$PhCH_2$	9	68
4	(IMes)Pd(allyl)Cl	0.1	**1**	Me	24	91
5	(IMes)Pd(allyl)Cl	0.1	**1**	Ph	9	92
6	(IMes)Pd(allyl)Cl	0.1	**1**	$PhCH_2$[c]	9	81
7	(IMes)Pd(allyl)Cl	0.1	**4**	$PhCH_2$	9	77
8	(IMes)Pd(allyl)Cl	0.1	**4**	Me	9	62
9	(IPr)Pd(allyl)Cl	0.05	**1**	$PhCH_2$	18	71
10	(IMes)Pd(allyl)Cl	0.05	**1**	$PhCH_2$	18	78
11	(allyl)PdCl/2 Ph_3P	0.05	**1**	$PhCH_2$	18	50

[a] All reactions use 1.1 equivalents of sulfonamide (TsN(H)R) and catalytic Cs_2CO_3 and are run in MeCN at 75 °C for the indicated time.
[b] The in situ generated catalyst is used in this entry.
[c] 2-Naphthylsulfonamide is used in place of **2** in this entry.

It was gratifying to see that, unlike the corresponding catalysts prepared in situ, the cyclization-trapping of **1** with $TsN(H)CH_2Ph$ (**2**) at the yet lower 0.05% catalyst loading level readily proceeds to completion (75 °C, 18 h) using either preformed complex, (IPr)Pd(η^3-C_3H_5)Cl or (IMes)Pd(η^3-C_3H_5)Cl (Table 3, entries 9 and 10). The yield obtained with (IMes)Pd(η^3-C_3H_5)Cl is again slightly higher (78% versus 71%), but both are superior to a triphenylphosphine-modified catalyst (entry 11, 50%) under these low catalyst loading conditions.

The use of microwave irradiation in organic synthesis has recently attracted a great deal of attention [17], although there are relatively few examples of its use to promote the reactions with NHC-metal catalysts [18]. Preliminary screening studies using the in situ generated (IMes)Pd-catalyst indicate that the cyclization proceeds more readily under microwave heating than the corresponding thermal reaction. For example using 0.1% catalyst loading, we obtain the cyclized product **3** from the reaction of bisdiene **1** with $TsN(H)CH_2Ph$ (**2**) in 86% yield after only 2.5 h of microwave heating at 75 °C [19].

In summary, we find that the NHC catalyst derived in situ from the combination of [(η^3-C_3H_5)PdCl/IMes · HCl] or the preformed (IMes)Pd(η^3-C_3H_5)Cl complex (Cs_2CO_3, MeCN) is effective for the cyclization-trapping of bisdienes with sulfonamides. The (IMes)Pd-catalyst appears to be slightly faster than the (IPr)Pd-catalyst, and the reaction is somewhat faster and affords higher yield with microwave rather than thermal heating under conditions where the measured temperature is approximately the same. Further studies on the application of (NHC)Pd catalysts with other bisdiene substrates and trapping reagents and on the apparent differences between the thermal and microwave-heated reactions are planned.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2005.08.048.

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[19] (*Note*. Microwave-assisted reactions were carried out in a Milestone START, multimode microwave lab station operated at 200–400 W. Temperature control for the microwave assisted reactions was accomplished using a built-in IR sensor.) The reaction was set up in a dry, nitrogen-filled glovebox using a glass reactor. To a mixture of Cs_2CO_3 (3 mg) in MeCN (2.75 mL) was sequentially added IMes · HCl (1.01 mL of a 0.99 μM solution, 1.0 μmol) and $[(allyl)PdCl]_2$ (0.38 mL of a 0.655 μM solution, 0.50 μmol Pd). After stirring at room temperature for 1 h, a mixture of bisdiene **1** (153.5 mg, 0.506 mmol) and $TsN(H)CH_2Ph$ (**2**, 158.0 mg, 0.605 mmol) in MeCN (2.0 mL) was added. The glass reactor was sealed with a pressure-relief valve, placed in the microwave cavity, and irradiated at 75 °C for 2.5 h; the desired temperature was maintained by modulation of power (<250 W). After cooling, the reaction was filtered through a short (~2 cm) plug of silica (DCM), the solvent evaporated, and the residue chromatographed on silica (25:75 EtOAc:Hex) to afford the product **3** as a pale yellow oil (245.8 mg, 86%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75–7.62 (m, 5 H), 7.35–7.15 (m, 8H), 5.6–5.45 (m, 1H), 5.12 (ddd, $J = 15.3$, 6.5, 6.5 Hz, 1H), 5.05–4.87 (m, 3H), 4.35 (d, $J = 14.9$ Hz, 1H), 4.19 (d, $J = 14.9$ Hz, 1H), 3.63 (dd, $J = 6.5$, 5.7 Hz, 2H), 3.37 (dd, $J = 10.0$, 7.3 Hz, 1H), 3.27 (dd, 10.0, 7.8 Hz, 1H), 2.78 (dd, $J = 10.0$, 8.8 Hz, 1H), 2.73 (dd, $J = 10.0$, 9.5 Hz, 1H), 2.42 (s, 6H), 1.95–2.10 (m, 2H), 1.55–1.7 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 135.30, 133.19, 129.85, 129.76, 128.54, 128.28, 127.45, 127.13, 52.55, 52.42, 51.03, 49.05, 46.64, 43.41, 35.38, 21.55; IR (neat) 3057, 3030, 2974, 2915, 1912, 1813, 1639, 1600, 1493, 1441, 1342, 1144, 1089, 1029, 927; HRMS (FAB, *m*/*z*) calcd for $C_{31}H_{37}N_2O_4S_2$ $(M + H)^+$ 565.2195, found 565.2186.