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# Palladium-Catalyzed Dearomative Trimethylenemethane Cycloaddition Reactions

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Supporting Information

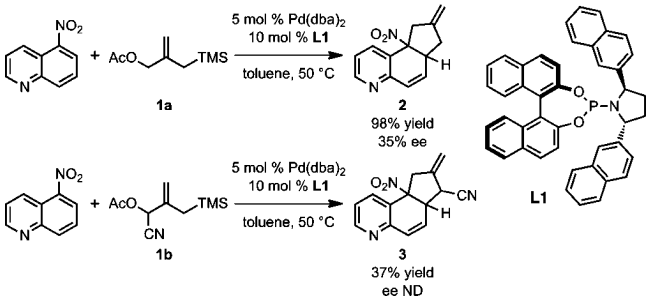
**ABSTRACT:** A general protocol for the palladium-catalyzed dearomative trimethylenemethane [3+2] cycloaddition reaction with simple nitroarene substrates is described. This methodology leads to the exclusive formation of the dearomatized alicyclic products without subsequent rearomatization. The reaction is tolerant toward a broad range of heterocyclic and benzenoid substrates. The use of chiral bisdiamidophosphite ligands enabled the development of an enantioselective variant of this transformation, representing one of the rare examples of an asymmetric catalytic dearomatization process.

Dearomatization reactions have the potential to convert structurally simple substrates into unprecedented complex structures by disruption of the aromatic $\pi$-system.[1] The available protocols, however, are often limited to non-enantioselective and stoichiometric methods.[2] Cycloaddition reactions represent an attractive atom-economic approach for the dearomatization of electron-rich aromatic systems creating polycyclic systems. Overwhelmingly in Diels–Alder reactions the aromatic ring is either the 4 $\pi$-electron partner as in the case of pyrroles or furans[2a] or part of the 4 $\pi$-electron partner as in the case of vinyl indoles.[3] Diels–Alder reactions of vinyl indoles and cycloadditions involving pyrroles and furans, mainly used as 4 $\pi$-electron reaction partners, are prominent examples. The use, however, of aromatic systems as 2 $\pi$-electron reaction partners and of benzenoid substrates is rare due to the high energy barrier resulting from loss of aromaticity.[2b] The use of nitronaphthalenes as dienophiles in Diels–Alder reactions was studied by Mancini et al.[4] The main products in these reactions were found to be the rearomatized cycloadducts, with only traces of dearomatized compounds being detected. The field of catalytic asymmetric dearomatization is even more unexplored, and there is a high demand for the improvement of catalyst efficiency, reactivity in intermolecular reactions, and chemoselectivity.

We[5] and others[6] have investigated the use of nitroarenes as substrates in palladium-catalyzed trimethylenemethane (TMM) [3+2] cycloaddition reactions.[7] However, it was consistently observed that nitroarenes as TMM acceptors exclusively lead to the formation of the rearomatized cycloadducts via release of nitrous acid. Not detecting any evidence for the formation of the presumed initial intermediate, we hypothesized that the energetically favored rearomatization occurred much more rapidly than the initial addition. This proposal drove our curiosity about the feasibility of isolation of the dearomatized species despite the unfavorable relative energetic situation. The drastic rate accelerations by our ligand system developed for asymmetric palladium-catalyzed TMM cycloadditions[8] and our experience with nitroalkene TMM acceptors[9] prompted us to examine this prospect despite the discouraging probability.

We began our studies by reacting 5-nitroquinoline as the TMM acceptor to a palladium–TMM complex generated from TMM donor **1a**, $Pd(dba)_2$, and phosphoramidite ligand **L1** (Scheme 1). In contrast to all aforementioned studies, we observed the exclusive formation of the dearomatized cycloadduct **2** in 98% yield without the elimination of nitrous acid. The induction of asymmetry with chiral ligand **L1**, however, was low (35% ee). The reaction with cyano-substituted TMM donor **1b**[8a] was rather sluggish and resulted in only low conversion but again to the dearomatized product **3**.

**Scheme 1. Dearomative TMM [3+2] Cycloaddition Reaction with 5-Nitroquinoline**[a]




[a]dba = dibenzylideneacetone, ND = not determined.

The use of phosphoramidite ligand **L2**[10] (Scheme 2a) led to a reactivity similar to that observed with ligand **L1** but with a slight erosion of enantioselectivity. Changing to the diamidophosphite ligand **L3** resulted in a lower conversion and formation of considerable amounts of the rearomatized byproduct. The enantioselectivity was unfortunately not improved. The applicability of the diamidophosphite ligand class was further put into question due to the unsatisfying performance of bisdiamidophosphite ligands **L4** and **L5**.[11] To contrast a 6-membered ring aromatic to a 5-membered one, we used 3-nitroindole derivative **4** as a TMM acceptor in combination with ligand **L2** (Scheme 2b). Gratifyingly, the desired dearomatized cycloadduct **5** could be isolated in

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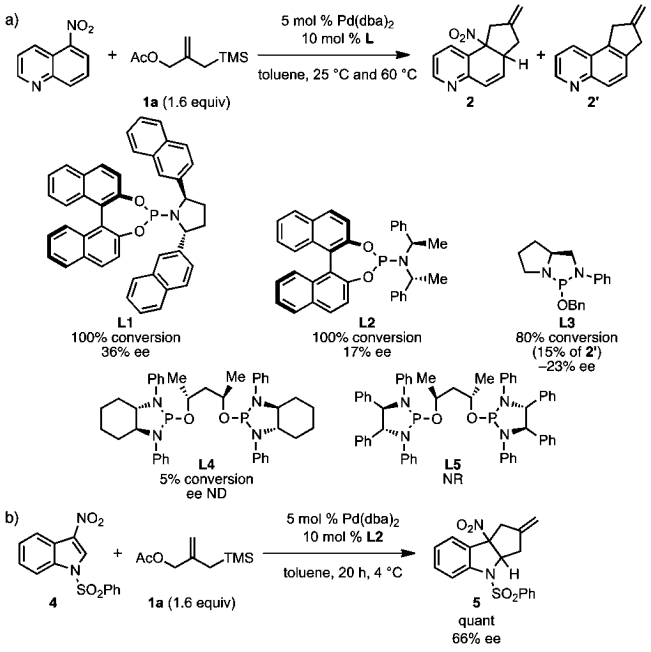
**Scheme 2. Chiral Ligands in Dearomative TMM [3+2] Cycloaddition Reactions**[a]

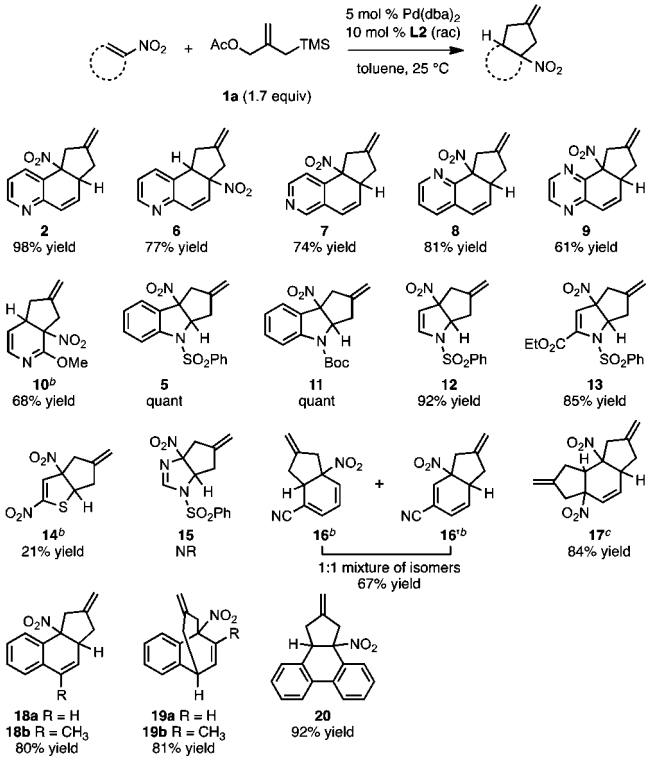



[a]NR = no reaction, quant = quantitative yield.

quantitative yield with significant improvement in enantioselectivity (66% ee).

Given the novel structures available via this unexpected simple addition and the difficulties to efficiently induce enantioselectivity at this point, we examined the nitroarene scope using racemic **L2** as the ligand of choice due to its synthetic accessibility (Scheme 3). 6-Nitroquinoline, 5-nitroisoquinoline, and 8-nitroquinoline were excellent substrates in the presence of 5 mol% $Pd(dba)_2$ and 10 mol% **L2** in toluene even at ambient temperature, and cycloadducts **6**−**8** were isolated in greater than 74% yield. In addition, 6-nitroquinoxaline performed well in the reaction, affording cycloadduct **9** in 61% yield. The reaction seems to be tolerant toward the position and number of nitrogen atoms in 6-membered heterocyclic substrates. In addition, the use of 2-methoxy-3-nitropyridine as acceptor gave cycloadduct **10** as a single regioisomer in 68% yield. Phenylsulfonyl- and Boc-protected 3-nitroindoles were the best substrates in this series and provided cycloadducts **5** and **11** in quantitative yield. Moving to an intrinsically more electron-rich 5-membered heterocycle, pyrrole, did not impact the reactivity, affording the compounds **12** and **13** in excellent yields (>85%). Reactions with 2,4-dinitrothiophene or 4-nitro-1-(phenylsulfonyl)-1*H*-imidazole, however, were rather difficult. The thiophene-derived cycloadduct **14** was only obtained in low yield (21%), and the imidazole cycloadduct **15** was not formed at all. Lastly, we investigated benzenoid acceptors, arguably the most challenging substrates in dearomatization reactions. We were pleased to see that the reaction of *m*-nitrobenzonitrile led to a 1:1 mixture of the regioisomeric adducts **16** and **16′** (67% total yield). When 1,3-dinitrobenzene was subjected to our reaction conditions with 2.4 equiv of TMM donor **1a**, the tricyclic bisadduct **17** formed exclusively (84% yield). 1-Nitronaphthalene proved to be quite interesting, giving rise to a 1:1 mixture of the [3+2] and [4+3] cycloadducts **18a** and **19a**. Upon placing a methyl group at C-4, exclusive [3+2] cycloaddition occurred to give cycloadduct **18b**. On the other hand, the [4+3] cycloadduct **19b** became the exclusive product upon placing a methyl group at C-2. The reaction with 9-nitrophenanthrene led to the corresponding [3+2] cycloadduct **20** in excellent yield.

**Scheme 3. Dearomative TMM [3+2] Cycloaddition Reactions with Nitroarenes**[a]

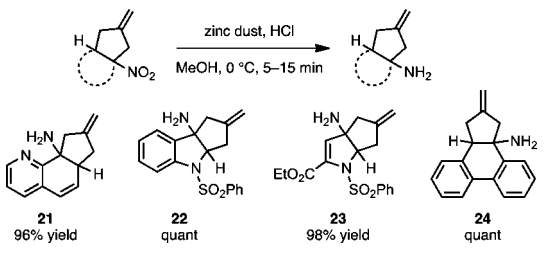



[a]Reactions were performed at 0.5 M concentration with 0.1 mmol of the nitroarene. Racemic (rac) **L2** was used. Yields are isolated values. [b]Reaction temperature 60 °C. [c]Reaction performed with 2.4 equiv of **1a**.

The benefit of this method clearly lies in the simplicity concerning the accessibility of the substrates and the avoidance of protecting groups. The nitro group serves as a useful synthetic handle allowing for numerous subsequent reactions. As an example, for the reduction of the nitro group to the respective amine, zinc dust in a methanolic hydrogen chloride solution can be used (Scheme 4). This protocol, exemplarily applied in reactions with cycloadducts **2**, **5**, **13**, and **20**, afforded the corresponding amines **21**−**24** in excellent yields (>96%).

Very recently, we developed a protocol for TMM [3+2] cycloadditions with alkynyl-substituted TMM donors leading to high levels of enantioselectivity.[12] This success motivated us to revisit the asymmetric dearomative cycloaddition reactions at

**Scheme 4. Reduction of the Nitro Group**





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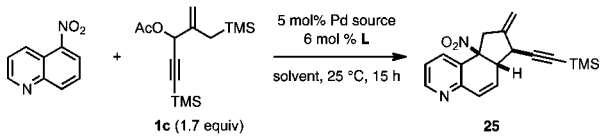
this point despite the poor enantioinduction using TMM donors **1a** and **1b** (*vide supra*). Reactions of TMS-alkyne donor **1c** with 5-nitroquinoline using our optimized conditions (5 mol % $Pd(dba)_2$, 6 mol% **L2**, toluene, 25 °C) led to the formation of the desired alkynyl-substituted cycloadduct **25**, albeit in only 20% conversion (Table 1, entry 1). Upon changing the precatalyst to CpPd(allyl), a significant increase in conversion was observed (entry 2). Interestingly, phosphoramidite ligand **L1** completely shut down the reactivity (entry 3). In contradiction to the results with the parent TMM donor, the use of CpPd(allyl) in combination with bisdiamidophosphite ligand **L4**, the optimal catalyst system for alkynyl-substituted TMM [3+2] cycloadditions,[12] led to full conversion (entry 4). Cycloadduct **25** was isolated in 77% yield and with excellent levels of enantioselectivity (95% ee) and good diastereoselectivity (4:1). Efforts to further increase the diastereoselectivity, however, by switching either solvent (1,4-dioxane, entry 5) or ligand (**L5**, entry 6) did not have any beneficial effects. The reduction of TMM donor equivalents (from 1.7 to 1.4 equiv) led to a decrease in conversion and did not significantly impact the diastereo- or enantioselectivity (entry 7).

**Table 1. Selected Optimization Studies toward an Enantioselective Dearomative TMM [3+2] Cycloaddition Reaction**[a]

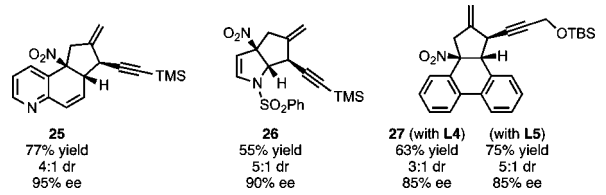



**1c** (1.7 equiv) **25**

| entry | Pd source | ligand | solvent | conv (%)/ yield (%) | ee (%)/ dr |
|---|---|---|---|---|---|
| 1 | $Pd(dba)_2$ | **L2** | toluene | 20 | – |
| 2 | CpPd($\eta^3$-$C_3H_5$) | **L2** | toluene | 50 | – |
| 3 | CpPd($\eta^3$-$C_3H_5$) | **L1** | toluene | NR | – |
| 4 | CpPd($\eta^3$-$C_3H_5$) | **L4** | toluene | 100/77 | 95/4:1 |
| 5 | CpPd($\eta^3$-$C_3H_5$) | **L4** | dioxane | 90 | 80/3:1 |
| 6 | CpPd($\eta^3$-$C_3H_5$) | **L5** | toluene | 85 | 93/4:1 |
| 7[b] | CpPd($\eta^3$-$C_3H_5$) | **L4** | toluene | 75 | 96/4:1 |

[a]Reactions were performed at 0.5 M concentration with 0.1 mmol of nitroarene. Yields are combined isolated values; enantiomeric excess determined by chiral HPLC with a chiral stationary phase. [b]1.4 equiv of **1c**.

Having demonstrated the feasibility of an asymmetric dearomative TMM [3+2] cycloaddition reaction, we wanted to see if alkyne TMM donors are able to more generally induce enantioselectivity. A phenylsulfonyl-protected 3-nitropyrrole is a suitable substrate in reactions with alkyne donor **1c** as well, affording cycloadduct **26** in satisfying yield (55%) and high selectivities (5:1 dr, 90% ee). Additionally, this procedure seems to be suitable for other alkyne-based TMM donors. Reactions of 9-nitrophenanthrene with a TMM donor with a TBS-protected methyl alcohol as alkyne substituent provided compound **27** in good yield and enantioselectivity (85% ee), but with lower diastereoselectivity (3:1 dr). This issue could be circumvented by the use of stilbene-derived bisdiamidophosphite ligand **L5**, which led to an increase in both yield (75%) and diastereoselectivity (5:1 dr) with no loss in ee. Nuclear Overhauser experiments for **27** were used to determine the relative stereochemistry of the cycloadduct (see the Supporting Information). The stereochemistry of all other cycloadducts was assigned by analogy.




**25** 77% yield 4:1 dr 95% ee | **26** 55% yield 5:1 dr 90% ee | **27** (with **L4**) 63% yield 3:1 dr 85% ee | (with **L5**) 75% yield 5:1 dr 85% ee

**Figure 1.** Current scope of the enantioselective dearomative TMM [3+2] cycloaddition reaction.

Notably, the current set of chiral phosphoramidite or diamidophosphite ligands was not able to induce high levels of enantioselectivity in reactions with the unsubstituted TMM donor **1a** despite extensive experimentation. The contrast with the alkynyl-substituted donor is striking, with respect to both reactivity and enantioselectivity. The differential reactivity may derive from the competing oligomerization of the TMM donor since the donor disappears in all cases. The parent TMM donor undergoes oligomerization much faster than any substituted donor. The fact that nitroarenes have a high barrier for addition allows oligomerization to outcompete addition—a situation which does not occur with substituted TMM donors. Regarding enantioselectivity, in the transition state, the carbon bearing the substituent is more tightly bonded to the $\beta$-carbon of the nitroarene, creating more steric congestion which accounts for the higher degree of differentiation for the two prochiral faces.

To conclude, we have developed a protocol for the palladium-catalyzed dearomative TMM [3+2] cycloaddition reaction with simple nitroarene substrates. The isolated polycyclic cycloadducts are isolatable compounds with no significant rearomatization being observed. This methodology represents a powerful entry to stable, dearomatized compounds. The synthetic accessibility of the nitroarene substrates and the lack of a complex protecting group strategy further illustrate the utility of this methodology. A most unusual pairing of reactivity/enantioselectivity of ligand choice with TMM donor structure has been observed for the first time. This reaction can be performed in an asymmetric fashion by using alkynyl-substituted TMM donors and a chiral bisdiamidophosphite ligand, which enables the induction of high levels of enantioselectivity for several substrates. This methodology represents a rare example of catalytic enantioselective dearomatization reactions in an intermolecular fashion starting from simple aromatic substrates.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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