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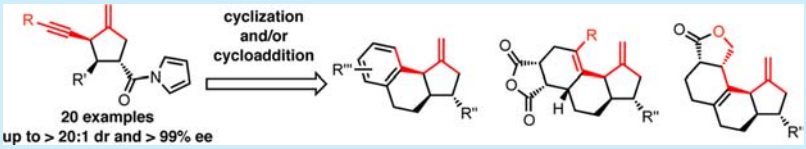
An Approach for Rapid Increase in Molecular Complexity: Atom Economic Routes to Fused Polycyclic Ring Systems

Barry M. Trost* and Veronika Ehmke

Department of Chemistry, Stanford University, Stanford, California 94305-5080, United States

Supporting Information



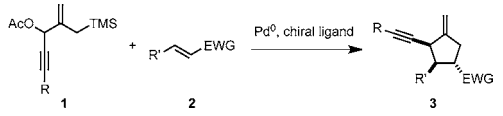
ABSTRACT: A protocol for the asymmetric trimethylenemethane (TMM) [3 + 2] cycloaddition reaction of alkynyl-substituted TMM donors and unsaturated *N*-acyl pyrroles employing a chiral bisdiamidophosphite ligand has been developed. This process generates alkynyl-substituted cyclopentanes in high yields and diastereo- and enantioselectivities. These chiral precursors are employed for the atom economic assembly of fused polycyclic hydrocarbons with hydroindene, hydroazulene, and hydrocyclopentanaphthalene scaffolds by consecutive cycloaddition reactions.

The most atom economic processes to increase molecular complexity, a constant need in the pharmaceutical and chemical industry, are those forming more than one bond at a time, as it is the case for cycloaddition reactions.[1] The performance of consecutive cycloaddition steps would thus open up new routes to rapidly assemble complex fused polycyclic ring systems. The scarcity of efficient methods for the construction of these polycondensed hydrocarbons prompted us to elaborate our palladium-catalyzed trimethylenemethane (TMM) [3 + 2] cycloaddition approach further.[2] The use of chiral phosphoramidite[3] and bisdiamidophosphite ligands[4] led to the development of enantioselective variants and of substituted TMM donors to selectively access cyano-,[3b,5] vinyl-,[4] and vinylidene-substituted[6] cyclopentanes and pyrrolidines. Despite this progress, however, the use of synthetically more valuable TMM donors has not yet been disclosed, preventing a broader application. We envisioned that the implication of an alkyne substituent on the TMM donor would represent a major advancement of this methodology for several reasons. First, an alkyne functionality is able to chemoselectively participate in metal-catalyzed processes, offering a broad scope of subsequent transformations. Second, the variation of the substituent on the alkyne group itself would, for the first time, provide access to a whole TMM donor family, whereas previous efforts concentrated only on the development of protocols for the use of one specific TMM donor. And last, alkynyl-derived TMM donors represent a highly versatile donor class, since alkynes serve as functional equivalents of alkene, saturated alkyl, or functionalized alkyl groups.

Since the beginning of our program, alkynyl-substituted TMM donors constantly failed as substrates in TMM cycloadditions. The possible interference with the active palladium species represents a major issue, and the extension of this methodology toward alkyne donors is therefore not a trivial extrapolation of our previous studies. We describe here the application of an alkynyl-substituted TMM donor family in the asymmetric TMM [3 + 2] cycloaddition reaction, and we show that the obtained alkynyl-derived cycloadducts serve as chiral precursors for the atom economic assembly of fused polycyclic hydrocarbons with hydroindene, hydroazulene, and hydrocyclopentanaphthalene scaffolds by consecutive cycloaddition reactions.

At the outset of our investigations, we focused on the reaction of suitable alkyne TMM donors **1** with electron-deficient olefins **2** (EWG = electron-withdrawing group) to obtain alkynyl-substituted cyclopentanes **3** bearing three contiguous stereocenters (Scheme 1). We were particularly

Scheme 1. Palladium-Catalyzed TMM [3 + 2] Cycloaddition Reaction with Alkynyl-Substituted TMM Donors 1



interested in the use of α,β-unsaturated *N*-acyl pyrroles as substrates, as these ester surrogates can be directly transformed into a wide range of carbonyl compounds at both the ketone and ester oxidation level.[7]

Initial experiments with alkyne donor **1a** (2.0 equiv) and α,β-unsaturated *N*-acyl pyrrole **2** in toluene were unsuccessful in the presence of $Pd(dba)_2$ and phosphoramidite ligand **L1**[3b] (Table 1, entry 1, and Figure 1). The use of *trans*-stilbene bisdiamidophosphite ligand **L2**,[6] however, afforded cycloadduct **3a** in 50% yield and moderate diastereo- and enantioselectivity (5:1 dr, 79% ee, entry 2).[8] Gratifyingly, upon changing the

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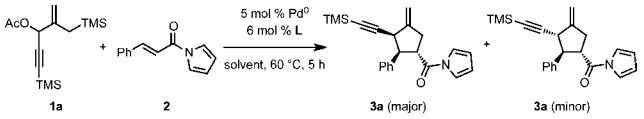
Table 1. Selected Optimization Studies[a]



entry	precatalyst	L	solvent	yield	dr	ee
1	$Pd(dba)_2$	**L1**	toluene	NR		
2	$Pd(dba)_2$	**L2**	toluene	50%	5:1	79%[b]
3	$Pd(dba)_2$	**L3**	toluene	83%	6:1	95%
4[c]	$Pd(dba)_2$	**L3**	toluene	70%	10:1	94%
5[c]	$CpPd(\eta^3\text{-}C_3H_5)$	**L3**	toluene	85%	9:1	94%
6[c]	$CpPd(\eta^3\text{-}C_3H_5)$	**L3**	dioxane	91%	12:1	99%

[a]Reactions were performed with 2.0 equiv of **1a** at 0.5 M concentration with 0.1 mmol of substrate **2**. [b]Opposite enantiomer obtained. [c]1.4 equiv of **1a**. Yields are combined isolated values; ee's were determined by chiral HPLC with a chiral stationary phase. NR = no reaction.

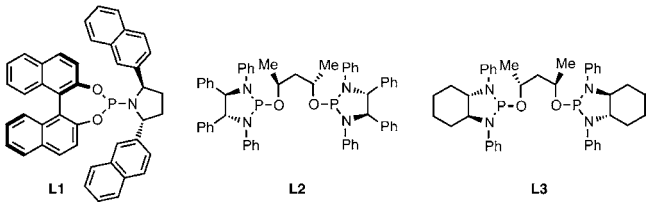
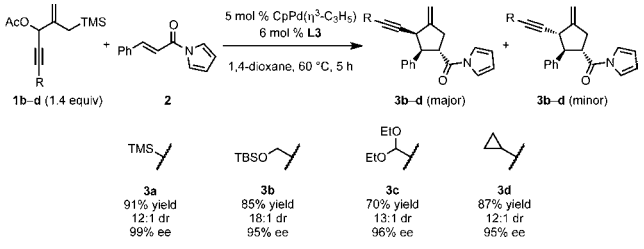


Figure 1. Chiral phosphoramidite (**L1**) and bisdiamidophosphite ligands (**L2** and **L3**) used for the optimization of reaction conditions.

ligand to the cyclohexyldiamine bisdiamidophosphite **L3**, we observed significant improvement in both yield and selectivity (83% yield, 6:1 dr, 95% ee, entry 3). Reduction of the TMM donor equivalents gave the desired product in lower yield, but proved to be beneficial in terms of diastereoselectivity (70% yield, 10:1 dr, 94% ee, entry 4). Replacement of $Pd(dba)_2$ with $CpPd(\eta^3\text{-}C_3H_5)$ provided the product in high yield and diastereo- and enantioselectivity (85% yield, 9:1 dr, 94% ee, entry 5). Finally, an additional increase in yield and selectivities was achieved by switching solvents from toluene to 1,4-dioxane (91% yield, 12:1 dr, 99% ee, entry 6).

With these optimized conditions in hand, we wanted to examine other TMM donors featuring different alkyne substituents to determine whether the alkyne substituent is a generally tolerated motif (Scheme 2). Indeed, donors with a TBS-protected methyl alcohol, an acetal group, or a cyclopropyl substituent afforded the respective cycloadducts **3b–d** in good

Scheme 2. Scope of the Palladium-Catalyzed TMM [3 + 2] Cycloaddition Reaction with Different Alkyne TMM Donors 1[a]

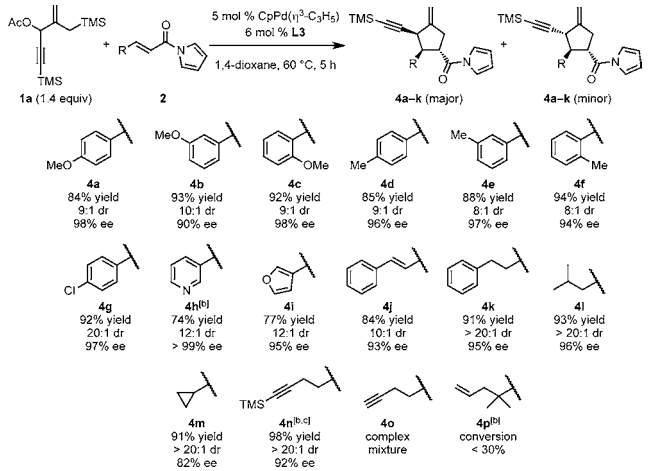


[a]Reactions were performed at 0.5 M concentration with 0.1 mmol of substrate **2**. Yields are combined isolated values; ee's were determined by chiral HPLC with a chiral stationary phase.

yields and excellent diastereo- and enantioselectivities (>70% yield, >12:1 dr, >95% ee).

These results encouraged us to explore the scope of the cycloaddition reaction with TMS-alkyne donor **1a** (Scheme 3).

Scheme 3. Substrate Scope of the Palladium-Catalyzed TMM [3 + 2] Reaction with Alkyne TMM Donor 1a[a]



[a]Reactions were performed at 0.5 M concentration with 0.1 mmol of substrate **2**. Yields are combined isolated values; ee's were determined by chiral HPLC with a chiral stationary phase. [b] Reaction time 15 h. [c] Scale 0.9 mmol.

In general, good to excellent yields and diastereo- and enantioselectivities were achieved with a large variety of *α,β*-unsaturated *N*-acyl pyrroles **2**. The reaction is tolerant toward different aromatic groups regardless of the substitution pattern and the nature of the substituent. Methoxy-, methyl-, and chloro-substituted cycloadducts **4a–g** were obtained in good yields and selectivities (>84% yield, >8:1 dr, >90% ee). Heterocycles, such as pyridine and furan, are well tolerated and provided the respective products **4h** and **4i** with excellent enantioselectivities. The reaction is highly chemoselective with respect to the more electron-deficient double bond, and styryl derivative **4j** was isolated as a single isomer (84% yield, 10:1 dr, 93% ee). We were furthermore pleased to find that reactions with various alkyl-substituted *α,β*-unsaturated *N*-acyl pyrroles proceeded with excellent yields and selectivities as well (**4k–4n**). Only cyclopropyl derivative **4m** showed a somewhat reduced enantioselectivity (82% ee). Notably, substrates with a free alkyne group or increased steric bulk next to the reaction center drastically affected the reaction and led to a complex mixture (for **4o**) or low conversion (for **4p**). Nuclear Overhauser experiments for **4c** and X-ray crystal structure analysis of a functionalization product (*vide infra*) were used to determine the relative and absolute stereochemistry of the cycloadducts.[8] The stereochemistry of all other cycloadducts was assigned by analogy.

With a reliable protocol in hand, we wanted to illustrate the versatility of the accessible cycloadducts. We were intrigued by the possibility of intramolecular cyclization reactions of the alkyne group with proximal functionalities to efficiently construct fused polycondensed ring systems. The ruthenium-catalyzed [2 + 2 + 2] cyclotrimerization of alkynes is a convenient approach for the synthesis of benzene systems, especially since the development of catalytic and chemo- and regioselective methods.[9] To apply this strategy to our diyne

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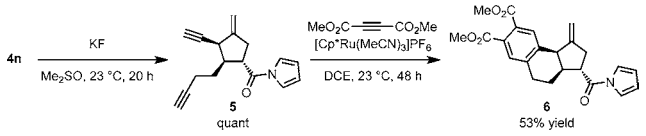
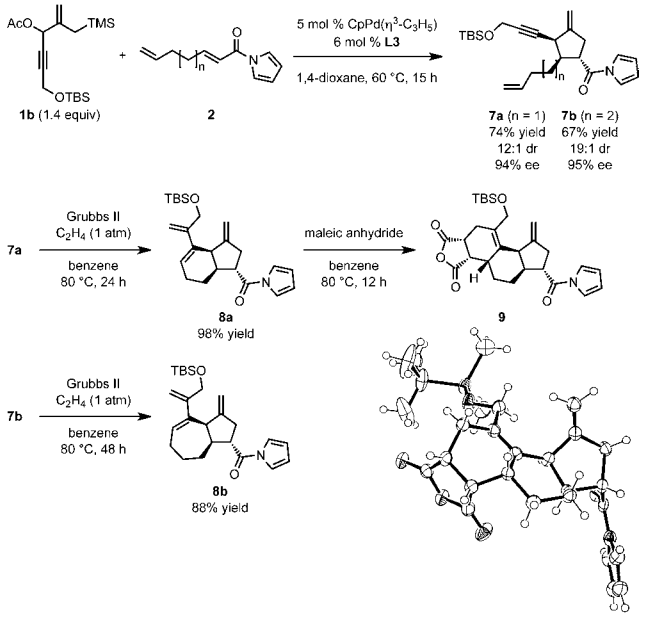
cycloadduct **4n**, the TMS-alkynes were first deprotected using potassium fluoride in dimethyl sulfoxide to quantitatively provide the free 1,7-diyne **5** (Scheme 4). Subsequent exposure of **5** to dimethyl acetylenedicarboxylate in 1,2-dichloroethane in the presence of $[Cp^*Ru(MeCN)_3]PF_6$ furnished tricyclic diester **6** in 53% yield.

Scheme 4. Functionalization of Cycloadduct 4n



In addition, we sought to apply cyclization strategies leading to conjugated 1,3-dienes with hydroindene or hydroazulene skeletons suitable for subsequent Diels–Alder reactions (Schemes 5 and 6). Enynes **7a** and **7b** were envisaged as substrates for ring-closing enyne metatheses[10] and palladium-catalyzed enyne cyclizations.[11] The TMM [3 + 2] cycloaddition reaction of alkyne donor **1b** and the respective α,β-unsaturated *N*-acyl pyrroles afforded enynes **7a** and **7b** in satisfying yields and excellent selectivities (>67% yield, >12:1 dr, >94% ee). Treatment of **7a** and **7b** with Grubbs' second-generation catalyst in benzene under an ethylene atmosphere gave the desired hexahydroindene **8a** (98% yield) and octahydroazulene **8b** (88% yield), respectively. The subsequent Diels–Alder reaction of **8a** with maleic anhydride in benzene afforded the tetracyclic anhydride **9** in 61% yield as a single isomer. Crystals of **9** suitable for X-ray crystal structure analysis unambiguously confirmed its proposed structure and the relative and absolute stereochemistry (Scheme 5).

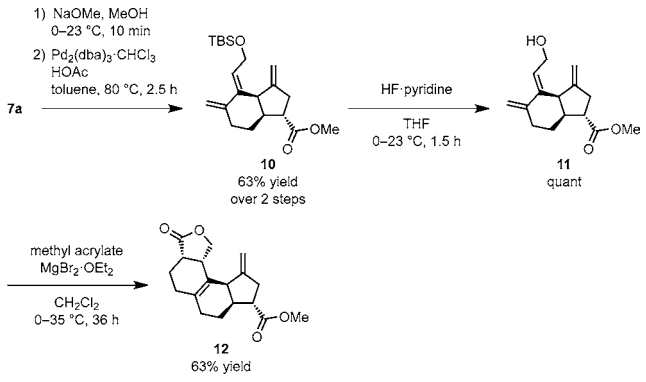
Scheme 5. Functionalizations of Cycloadducts 7a and 7b and ORTEP Plot of the X-ray Crystal Structure of Anhydride 9[a]



[a]Atomic displacement parameters obtained at 120 K are shown at the 50% probability level.

The intramolecular palladium-catalyzed enyne cyclization[11] of cycloadduct **7a** should give rise to an isomeric dialkylidene system (Scheme 6). To avoid undesired side reactions of the *N*-acyl pyrrole substituent, cycloadduct **7a** was first treated with sodium methoxide in methanol to give the corresponding methyl ester in 97% yield. The subsequent enyne cyclization reaction proceeded with $Pd_2(dba)_3{\cdot}CHCl_3$ and acetic acid furnishing 1,3-diene **10** in 65% yield. Careful control of the reaction time was essential in order to avoid migration of the exocyclic double bond. The TBS-group was quantitatively cleaved upon treatment with HF·pyridine to allow for a directed intermolecular Diels–Alder reaction.[12] Exposure of alcohol **11** to methyl acrylate in the presence of $MgBr_2{\cdot}OEt_2$ as a Lewis acid afforded the desired tetracylic lactone **12** in 63% yield.

Scheme 6. Functionalization of Cycloadduct 7a



To conclude, we have developed an asymmetric palladium-catalyzed [3 + 2] cycloaddition reaction with alkynyl-substituted TMM donors to furnish highly functionalized cyclopentane systems with three contiguous stereocenters in good yields and high diastereo- and enantioselectivity. This methodology allowed the employment of a TMM donor family consisting of different alkynyl-substituted donors for the first time, in contrast to our previous studies where mostly only one TMM donor could be used. Moreover, the alkynyl-substituted cycloaddition reaction was found to have the broadest substrate tolerance as compared to any other substituted TMM donor class. The proximity of the alkyne substituent to other functional groups makes the obtained cycloadducts unique chiral precursors for the rapid synthesis of fused polycyclic ring systems with diverse hydrocarbon skeletons. The synthetic utility of this TMM donor family is the key aspect of these studies, and this new strategy allows access to structural complexity in an overall atom economic and convergent fashion.

■ ASSOCIATED CONTENT

Supporting Information

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

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: bmtrost@stanford.edu.

Notes

The authors declare no competing financial interest.

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(8) All products were isolated as single diastereoisomers. The relative and absolute stereochemistry of the cycloadducts were assigned by nuclear Overhauser effect experiments (for **4c**) and X-ray crystal structure analysis (for **9**). The stereochemistry of all other cycloadducts was assigned by analogy. For details see the Supporting Information.

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