DOI: 10.1002/adsc.201100983

Beyond the Limits: Palladium-N-Heterocyclic Carbene-Based Catalytic System Enables Highly Efficient [4+2] Benzannulation Reactions

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Received: December 27, 2011; Published online: April 13, 2012

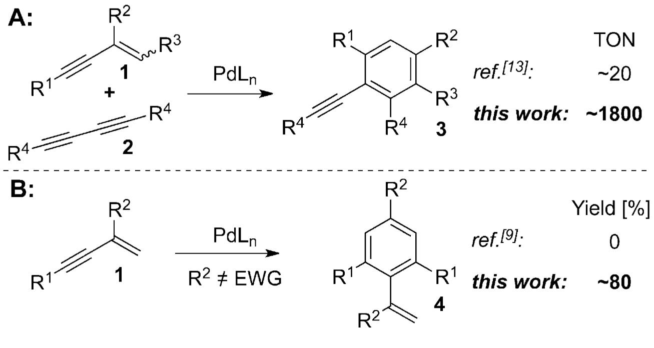
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201100983.

Abstract: A highly efficient catalytic system for the palladium-catalyzed [4+2] benzannulation reaction of enynes and enynophiles has been developed. The use of an N-heterocyclic carbene-based palladium precursor allowed us to achieve turnover numbers up to 1800. The new catalytic system has enabled an expansion of the scope of the [4+2] homo-benzannulation reaction.

Keywords: benzannulation; cycloaddition; N-heterocyclic carbenes; palladium catalysis; turnover number

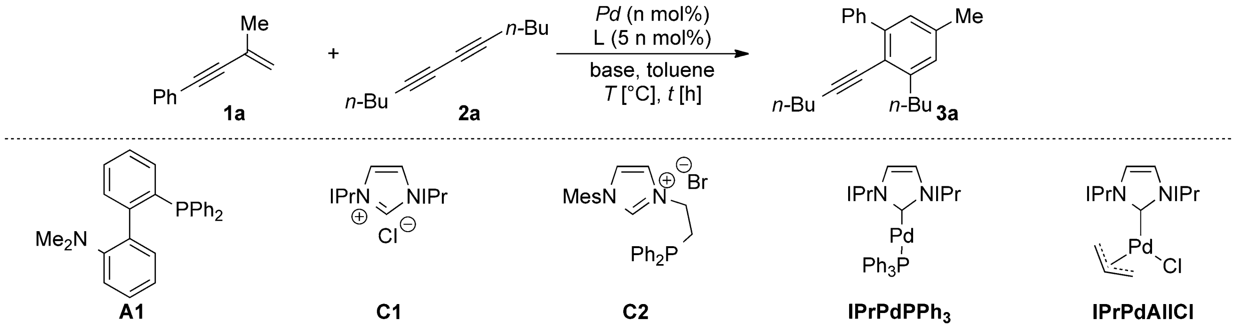
In the era of sustainable chemistry, the development of highly active catalytic systems for atom- and step-economical processes is on high demand.[1] Transition metal-catalyzed cycloaddition reactions are an example of transformations of this kind, since the construction of two or more bonds occurs in a single step without formation of by-products.[2] One of the ways to improve the activity of the catalytic system in transition metal catalysis is the stabilization of the reactive metal complex, which allows for high turnover numbers (TONs) of the catalyst. Thus, a number of ligands has been designed, employment of which resulted in efficient protocols for Rh-[3] and Cu-catalyzed[4] cycloaddition reactions. Despite the immense progress made in the development of high TON Pd-catalyzed cross-coupling reactions,[5] to the best of our knowledge, the first example of a cycloaddition reaction catalyzed by palladium complexes with high TON is yet to described.[6] Herein, we report a highly active catalytic system for the Pd-catalyzed [4+2] benzannulation reaction, which not only enabled a dramatic improvement of the TON up to 1800 (Scheme 1, **A**), but also overcame the limitations of this chemistry, thus expanding the scope of the homo-benzannulation procedure (Scheme 1, **B**).

We were interested in improving efficacy of the palladium-catalyzed [4+2] benzannulation reaction,[7] a catalytic version of the Danheiser benzannulation.[8] This cycloaddition reaction of conjugated enynes with enynophiles opens a straightforward access to densely substituted aromatic compounds. Since the first reports on the homo-benzannulation of enynes[9] with the formation of styrenes and cross-benzannulation with diynes[10] toward arylalkynes, the scope of this useful transformation has been systematically investigated.[11] Thus, phenols,[11a] aryl ethers,[11b] anilines,[11c] coumaranones,[11a] benzylphosphine oxides,[11d] arylstannanes,[11e] cyclophane-type compounds,[11f–i] 2,6-diarylstyrenes,[11j] as well as precursors for 4-arylphenanthrenes,[11k,l] have been synthesized *via* this methodology. Combination of this process with alkyne dimerization[12a] or Sonogashira cross-coupling[12b] protocols led to the development of multicomponent cascades. However, the reaction often requires high catalyst loading (5 mol% or more) and long reaction times, which significantly limits its synthetic applicability. Although a substantial improvement of catalytic activity has been achieved by introduction of a Lewis



Scheme 1. The Pd-catalyzed [4+2] benzannulation reaction.

Table 1. Optimization of the reaction conditions for the Pd-catalyzed [4+2] benzannulation reaction.[a]



Entry	Pd, n [mol%]	Ligand	Base	T [°C], t [h]	C [M]	Yield [%][b]
1	Pd_2dba_3, 1.5	PPh_3	–	80, 80	1.0	74
2	Pd_2dba_3, 1.5	**A1**	–	80, 80	1.0	69
3	Pd_2dba_3, 1.5	DPPF	–	80, 80	1.0	0[c]
4	Pd_2dba_3, 1.5	**C1**	Cs_2CO_3	80 120	1.0	0[c]
5	Pd_2dba_3, 1.5	**C1**, PPh_3	Cs_2CO_3	80, 66	1.0	82
6	Pd_2dba_3, 1.5	**C2**	Cs_2CO_3	120, 20	1.0	58
7	IPrPdPPh$_3$, 1.5	–	–	80, 40	1.0	67
8	IPrPdAllCl, 1.5	PPh_3	Cs_2CO_3	80, 40	1.0	77
9	IPrPdAllCl, 0.5	PPh_3	Cs_2CO_3	80, 100	1.0	75
10	IPrPdAllCl, 0.1	PPh_3	Cs_2CO_3	80, 100	1.0	21[d]
11	IPrPdAllCl, 1.0	TFP	Cs_2CO_3	100, 25	1.0	80
12	IPrPdAllCl, 1.0	**A1**	Cs_2CO_3	100, 25	1.0	83
13	IPrPdAllCl, 1.0	**A1**	CsOPiv	100, 8	1.0	85
14	IPrPdAllCl, 1.0	**A1**	CsOPiv	120, 15	1.0	39[d]
15	IPrPdAllCl, 1.0	**A1**	CsOPiv	120, 15	2.5	74
16	**IPrPdAllCl, 0.1**	**TFP**[e]	**CsOPiv**	**120, 15**	**10**	**86**
17	**IPrPdAllCl, 0.05**	**TFP**	**CsOPiv**	**120, 40**	**20**	**85**

[a] *Reaction conditions:* **1a** (0.1 mmol), **2a** (0.11 mmol), Pd (n mol%), ligand (5n mol%), base (10n mol%) in dry toluene.

[b] GC/MS yield at 100% conversion of enyne.

[c] No reaction was observed.

[d] Conversion was not complete.

[e] TFP = tris(2-furyl)phosphine.

acid or a Brønsted base[13] to the reaction media, the turnover number of the palladium catalyst remains limited to 20.

To this end, the cross-benzannulation reaction of enyne **1a** and diyne **2a** toward arylalkyne **3a** was tested (Table 1).[14] We turned our attention to those ligands which show superior performance in high TON Pd-catalyzed cross-coupling reactions and related processes. Thus, biphenylphosphine ligands **A**,[15] multidentate ferrocene-based ligands **B**,[16] and N-heterocyclic carbene (NHC) ligands **C**[17] (Figure 1) were examined. It was found that the employment of 2-diphenylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl (PhDavePhos, **A1**) did not provide any improvement compared to the standard reaction conditions (Table 1, entries 1 and 2). Disappointingly, no reaction was observed in the presence of 1,1′-bis(diphenylphosphino)ferrocene (DPPF) (entry 3). Several commercially available bidentate ligands were also tested to mimic the highly active multidentate analogs **B**. However, ferrocene-based phosphines, as well as other bidentate ligands, were ineffective in this reaction.[14] Likewise, employment of 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (IPr·HCl, **C1**) as an NHC-ligand precursor did not promote the reaction (entry 4). On the other hand, a combination of NHC and phosphine ligands resulted in an improvement of the reaction yield (entry 5).[18] Utilization of mixed ligand **C2**[19] or defined IPrPdPPh$_3$ catalyst[20] was not beneficial (entries 6 and 7). Gratifyingly, employment

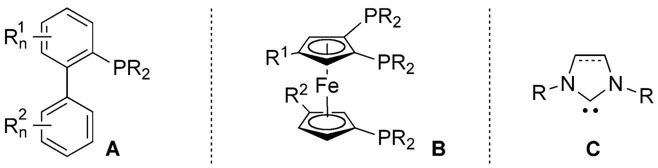
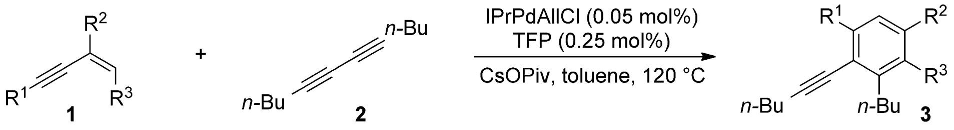
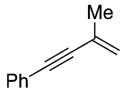
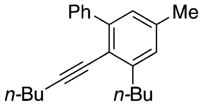
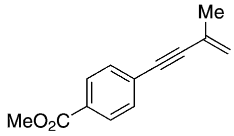
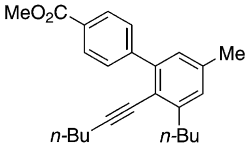
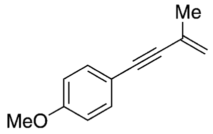
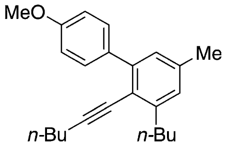
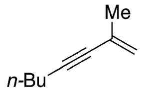
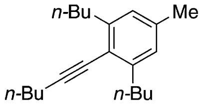
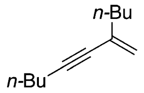
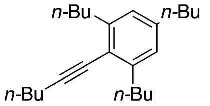
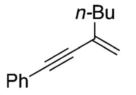
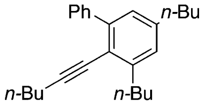
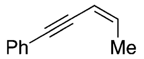
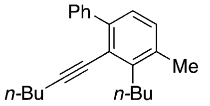
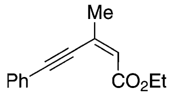
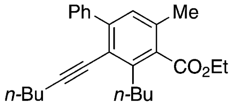
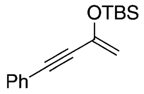
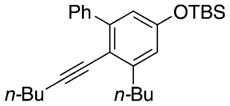
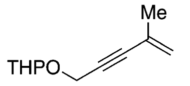
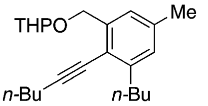
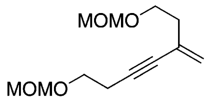
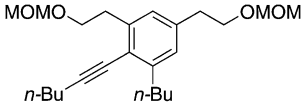
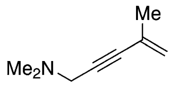
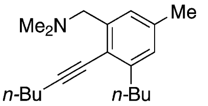


Figure 1. Typical ligands for high TON catalytic systems for the Pd-catalyzed transformations.

Table 2. The scope of enynes in the Pd-catalyzed [4+2]benzannulation reaction.[a]



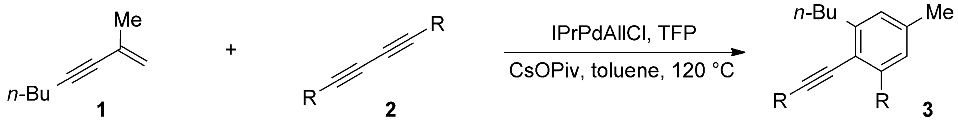
Entry	Enyne		Product		Yield [%][b]	TON[c]
1		**1a**		**3aa**	83	1660 (20)[13]
2		**1b**		**3ba**	86	1720
3		**1c**		**3ca**	71	1420
4		**1d**		**3da**	85	1700
5		**1e**		**3ea**	87	1740 (17)[12a]
6		**1f**		**3fa**	84	1680
7		**1g**		**3ga**	53	1060
8		**1h**		**3ha**	75	1480 (15)[13]
9		**1i**		**3ia**	41	820 (15)[13]
10		**1j**		**3ja**	77	1540
11		**1k**		**3ka**	69	1380 (11)[12a]
12		**1l**		**3la**	90	1800

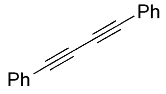
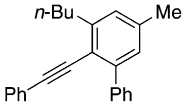
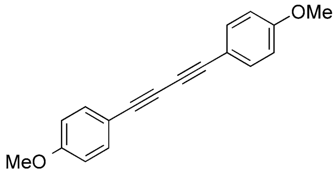
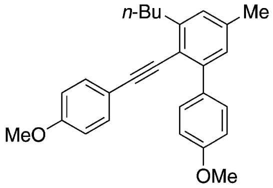
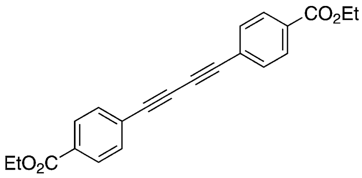
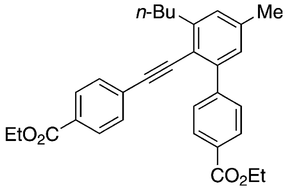
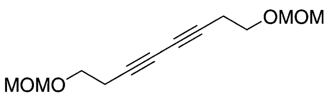
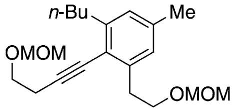
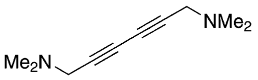
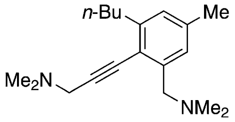
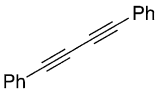
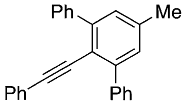
[a] *Reaction conditions:* **1** (1 equiv.), **2a** (1.1 equiv.), IPrPdAllCl (0.05 mol%), TFP (0.25 mol%), CsOPiv (0.5 mol%) in dry toluene (20 M).

[b] Isolated yield.

[c] TON is equal to [(product mol) × (catalyst mol)$^{-1}$], previously reported TON values are given in parentheses.

Table 3. The scope of diynes in the Pd-catalyzed [4+2] benzannulation reaction.[a]



Entry	Diyne		Product		Yield [%][b]	TON[c]
1		2b		3db	41	820
2					62[d]	620
3					84[e]	168
4		2c		3dc	77[e]	154
5		2d		3dd	88[e]	196
6		2e		3de	59	1180
7		2f		3df	32	620
8		2b		3ab	55[d,f]	550 (17)[10c]

[a] *Reaction conditions:* **1d** (1 equiv.), **2** (1.1 equiv.), IPrPdAllCl (0.05 mol%), TFP (0.25 mol%), CsOPiv (0.5 mol%) in dry toluene (20M).

[b] Isolated yield.

[c] TON is equal to [(product mol) × (catalyst mol)$^{-1}$], the previously reported TON value is given in parentheses.

[d] IPrPdAllCl (0.1 mol%), TFP (0.5 mol%), CsOPiv (1.0 mol%) in dry toluene (10M).

[e] IPrPdAllCl (0.5 mol%), TFP (2.5 mol%), CsOPiv (2.5 mol%) in dry toluene (2M).

[f] (3-Methylbut-3-en-1-ynyl)benzene **1a** was used.

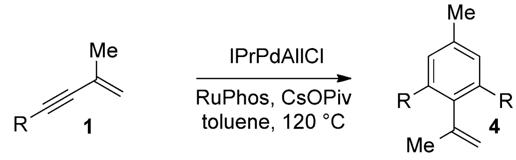
of the Pd NHC-based pre-catalyst IPrPdAllCl resulted in a shortened reaction time (entry 8). It also allowed us to reduce the amount of catalyst to 0.5 mol% (entry 9). Further decreasing the catalyst loading led to the termination of the reaction at about 20% conversion (entry 10). Among phosphine co-ligands, electron-rich phosphines were the most efficient (entries 11 and 12). Cesium carboxylates were found to be superior compared to other inorganic bases tested. Thus, the reaction was completed within 8 h in 85% yield in the presence of CsOPiv (entry 13), although a high TON was still illusionary (entry 14). Expectedly, an increase of the concentration gave a reasonable improvement of the reaction yield (entry 15). Finally, in the presence of tris(2-furyl)phosphine (TFP) ligand under nearly neat conditions, a *TON higher than 1600* has been achieved (Table 1, entry 17)!

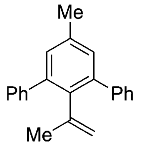
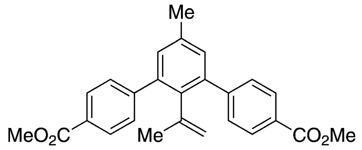
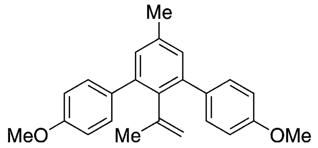
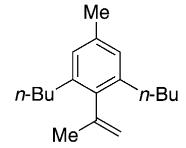
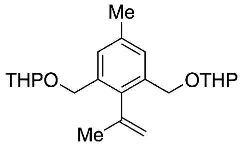
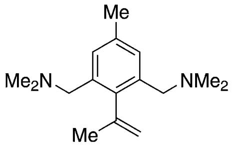
Next, the enyne generality in this highly efficient [4+2] cross-benzannulation reaction, catalyzed by IPrPdAllCl/TFP/CsOPiv system, was investigated (Table 2). It was found that arylenynes possessing electron-poor aromatic substituents were slightly more efficient compared to their electron-rich counterparts (entries 1–3). Enynes bearing 1,3-dialkyl substitution smoothly underwent benzannulation reaction regardless of the substituent size at the C-3 position (entries 4 and 5). The least reactive 1,4-disubstituted substrate **1g** gave the product in diminished yield (entry 7), however 1,3,4-trisubstituted enyne **1h** reacted well (entry 8). Enynes bearing a masked hydroxy group provided access to phenol **3ia**, benzyl **3ja**, and homobenzyl alcohol **3ka** derivatives (entries 9–11). A substrate possessing a tertiary amine group reacted smoothly to give the corresponding *ortho*-alkynylbenzylamine **3la** (entry 12).

The scope of diynes is presented in Table 3. Due to low solubility of 1,4-diphenylbutadiyne under the reaction conditions, the benzannulation proceeded to about 50% conversion, thus providing a poor yield of the product (entry 1). However, decreasing the concentration allowed us to obtain the corresponding biarylalkyne **3db** in 84% yield, although a higher catalyst loading was required under more dilute conditions (entries 2 and 3). Analogously to the reactivity trend observed for enynes, electron-deficient diaryldiyne **2d** gave a better yield of the corresponding product compared to that for electron-rich compound **2c** (entries 4 and 5). The diyne possessing a protected alcohol moiety underwent benzannulation in slightly diminished yield (entry 6). Unlike the corresponding enyne **1l**, diyne **2f** bearing an amine functionality gave an unsatisfactory yield due to its decomposition (entry 7).

Next, we turned our attention to the Pd-catalyzed [4+2] homo-benzannulation reaction. Although the [4+2] homo-benzannulation of 1- or 3-monosubstituted enynes is well elaborated[9] (Scheme 1, **B**), the homo-benzannulation of disubstituted enynes was limited to electron-deficient substrates only.[9b,12b] Notably, during the initial optimization of the cross-benzannulation reaction the formation of a trace amount of the enyne dimer was observed. We found this result quite surprising, as 1,3-disubstituted electron-neutral enynes did not undergo homo-dimerization reaction before.[9] We decided to investigate the potential homo-benzannulation reaction of disubstituted enyne **1a**. It was found that in the presence of 1.5 mol% of IPrPdAllCl, 3 mol% of tris(*p*-methoxyphenyl)phosphine and 3 mol% of Cs_2CO_3 in toluene (1 M) enyne **1a** underwent homo-benzannulation providing the corresponding styrene derivative **4a** in 65% unoptimized yield. Brief optimization of the reaction conditions revealed that the catalyst loading could be reduced to 0.5 mol% with enhanced yield by employment of 2-dicyclohexylphosphino-2′,6′-diisopropoxy-1,1′-biphenyl (RuPhos) ligand and CsOPiv (Table 4, entry 1).[14] The scope of this transformation was also examined. Expectedly, electron-deficient substrate **1b** provided the desired product in higher yield (entry 2), whereas the reactivity of electron-rich enyne **1c** was lower (entry 3). Bis-1,3-dialkyl substituted enyne **1d** reacted efficiently to afford styrene **4d** (entry 4). Likewise, styrenes **4j** and **4l** with alkoxy and alkylamine moieties were effectively synthesized in good yields from the corresponding alkoxymethyl- and aminomethylenynes (entries 5 and 6).

Table 4. The scope in the Pd-catalyzed [4+2] homo-benzannulation of 1,3-disubstituted enynes.[a]



Entry	Enyne	Product		Yield [%][b]
1	**1a**		**4a**	80
2	**1b**		**4b**	89
3	**1c**		**4c**	47
4	**1d**		**4d**	77
5	**1j**		**4j**	73
6	**1l**		**4l**	76

[a] *Reaction conditions:* **1** (1 equiv.), IPrPdAllCl (0.5 mol%), RuPhos (2.5 mol%), CsOPiv (2.5 mol%) in dry toluene (5 M).

[b] Isolated yield.

In summary, a highly efficient catalytic system for the palladium-catalyzed [4+2] benzannulation reaction of enynes with enynophiles has been developed. The newly found conditions enabled the synthesis of a variety of densely substituted arylacetylenes with high turnover numbers of the palladium catalyst. Moreover, the new catalytic system allowed us to expand the scope of this transformation, as previously unreactive 1,3-disubstituted enynes underwent smooth homo-benzannulation to afford multisubstituted styrenes. The development of the pre- and post-benzannulation cascades employing this highly active catalytic system is underway in our laboratory.

Experimental Section

General Procedure for the Palladium-Catalyzed [4+2] Cross-Benzannulation Reaction

Enyne **1** (1.0 mmol, 1 equiv.) and diyne **2** (1.1 mmol, 1.1 equiv.) were placed in an oven-dried 0.5-mL V-vial, equipped with a stirring bar. CsOPiv (1.2 mg, 0.005 mmol, 0.5 mol%) was added under an N_2 atmosphere. Stock solution (50 μL) of IPrPdAllCl (0.0005 mmol, 0.05 mol%) and $(2\text{-furyl})_3P$ (0.0025 mmol, 0.25 mol%) in toluene were added *via* a microsyringe under an N_2 atmosphere and the reaction vessel was capped with a syringe valve. The reaction mixture was stirred at 120 °C for 40–120 h. The reaction was monitored by GC/MS analysis. Upon completion the resulting mixture was cooled down to room temperature, diluted with dichloromethane, and filtered through a celite plug. The filtrate was concentrated under a reduced pressure. The crude product was purified by column chromatography on silica gel to afford **3**.

General Procedure for the Palladium-Catalyzed [4+2] Homo-Benzannulation Reaction of Enynes

Enyne **1** (0.5 mmol, 1 equiv.) was placed to an oven-dried 0.5-mL V-vial, equipped with a stirring bar. IPrPdAllCl (1.4 mg, 0.0025 mmol, 0.5 mol%), RuPhos (5.8 mg, 0.0125 mmol, 2.5 mol%), CsOPiv (2.4 mg, 0.0125 mmol, 2.5 mol%) and toluene (100 μL) were added under an N_2 atmosphere and the reaction vessel was capped with a syringe valve. The reaction mixture was stirred at 120 °C for 15–48 h. The reaction was monitored by GC/MS analysis. Upon completion the resulting mixture was cooled down to room temperature, diluted with dichloromethane and filtered through a celite plug. The filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel to afford styrene **4.**

Acknowledgements

The support of the National Science Foundation (CHE-1112055) is gratefully acknowledged.

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