



Trip Report for

“89th Canadian Chemistry Conference and Exhibition”

Halifax, Nova Scotia

May 27-31, 2006

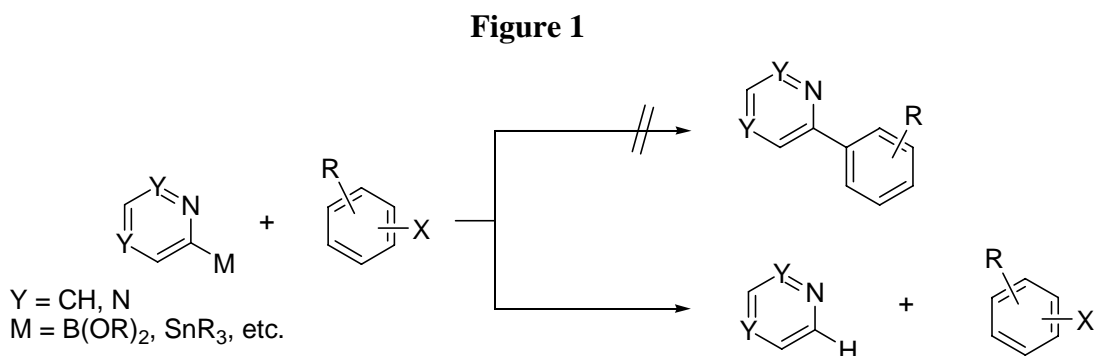
Andrew Zych, Ph.D.

Abstract: *Abstract copy* The 89th Canadian Chemistry Conference and Exhibition was held in Halifax, Nova Scotia May 27-31, 2006. A summary of selected lecture and poster presentations concerning synthetic methodologies is presented.

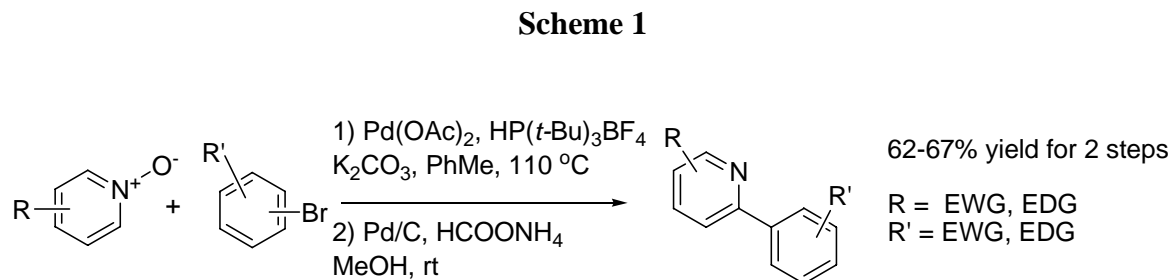
“Direct Arylation of Diazine *N*-Oxides: An Alternative to Problematic Suzuki Cross-Coupling Reactions”

Jean-Phillippe Leclerc and Keith Fagnou, Department of Chemistry, University of Ottawa.

The synthesis of biaryl compounds via transition metal-catalyzed cross-couplings has become ubiquitous in organic chemistry in the past few decades. However, some substrate classes continue to present serious difficulties in these reactions. In particular, 2-pyridyl organometallics and related heterocyclic species are often poor partners for cross-coupling reactions, probably due to their inherent instability towards proto-deboronation and proto-demetalation (Figure 1).

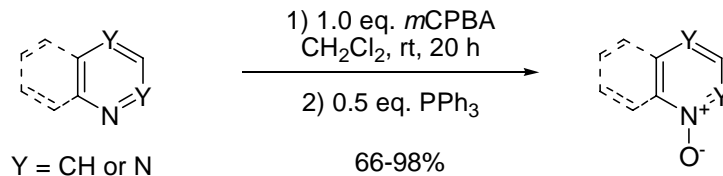


Although coupling reactions of 2-halopyridines and related heterocycles are well precedented, in many instances it would be advantageous to reverse the coupling partners. Therefore a reliable surrogate for 2-pyridyl organometallics and boronic acids would be of considerable utility. A recent report (JACS **2005**, *127*, 18020) presented pyridine-*N*-oxide as an inexpensive, stable synthetic equivalent to these unstable species. Direct coupling with aryl bromides of the *N*-oxides followed by reduction was demonstrated as a viable route to 2-aryl pyridines (Scheme 1).



It was envisioned that the same strategy could also be applied to diazines such as pyrazines, quinoxalines, pyridazines, and pyrimidines. *N*-Oxides of the various the diazines were easily synthesized using *m*CPBA (Scheme 2). Notably, these *N*-oxides show no sign of decomposition after several months of storage and no exothermic decomposition up to 250 °C in calorimetry studies.

Scheme 2



The *N*-oxides of pyrazines, quinoxalines, and pyridazines all gave good results in the optimized direct arylation reaction (Tables 1-3).

Table 1

ArX	Yield (%)	ArX	Yield (%)	ArX	Yield (%)
	75		70		60
	75		75		89
	77		72		70
	76		82		

Table 2

ArX	Yield (%)	ArX	Yield (%)	ArX	Yield (%)
	84		68		57

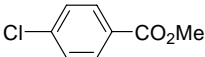
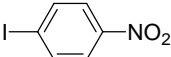
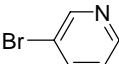
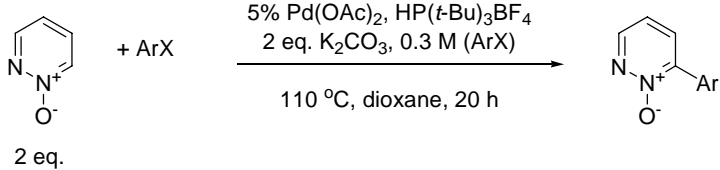
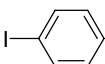
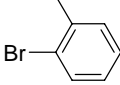
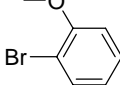
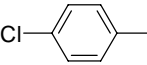
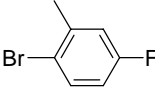
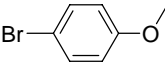
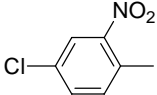
	84		70		50
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Table 3

					
ArX	Yield (%)	ArX	Yield (%)	ArX	Yield (%)
	92		76		44
	73		74		60
	47				

Pyrimidine *N*-oxide gives only a 15% yield when coupled with 4-bromotoluene under the standard conditions. Poisoning studies suggest that the pyrimidine *N*-oxide may become a ligand leading to catalyst sequestration. However, use of the preformed catalyst Pd(P(*t*-Bu)₃)₂ improves the yield to 56%.

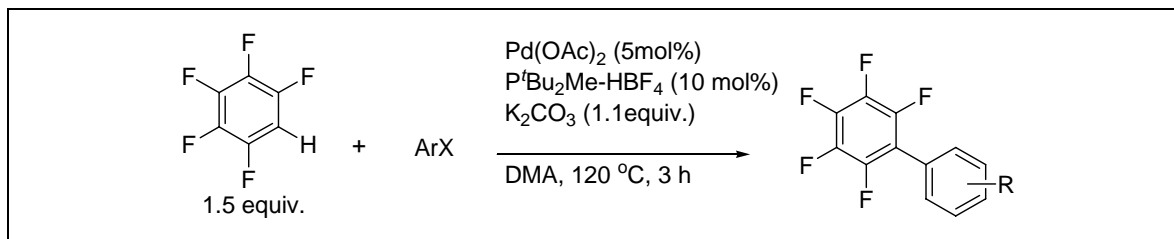
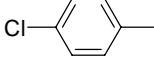
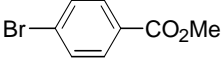

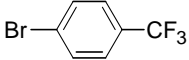
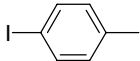
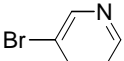
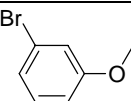
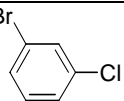
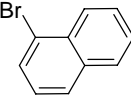
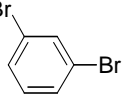
The *N*-oxide diazine products are all easily deoxygenated using transfer hydrogenation over palladium on carbon in 98-70% yield, as demonstrated previously for the pyridine analog series (Scheme 1).

“Catalytic Intermolecular Direct Arylation of Perfluoroarenes”

Marc Lafrance, Christopher N. Rowley, Tom K. Woo and Keith Fagnou, Department of Chemistry, University of Ottawa.

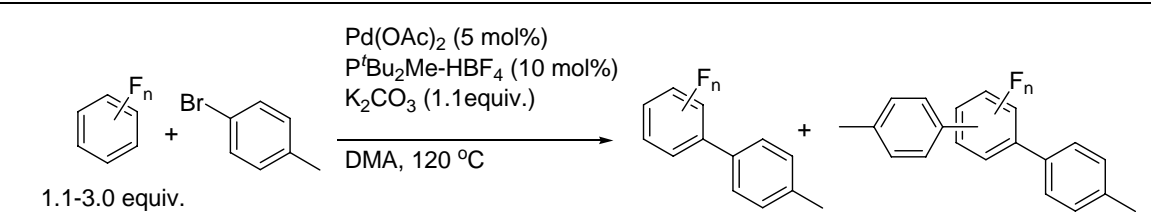
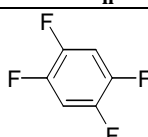
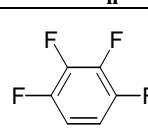
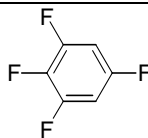
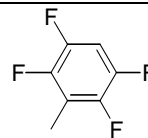
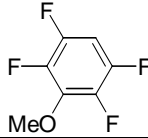
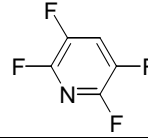
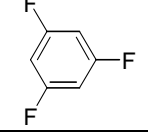
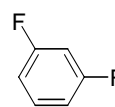
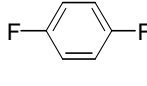
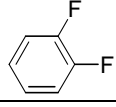
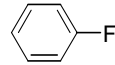
As noted in the previous talk, the synthesis of biaryl compounds via transition metal catalyzed cross-couplings has become one of the most common, reliable reactions in organic synthesis, although some substrate classes continue to present challenges. Another problematic substrate class, in addition to the diazines discussed above, includes highly electron deficient arylboronic acids such as pentafluorophenyl boronic acid. This species is an inactive cross-coupling partner under most conditions although it will react in specially optimized conditions (OL **2005**, 7, 4915). Considering the importance of perfluorinated biphenyls in medicinal chemistry and materials science it was recognized

Table 4

			
ArX	Yield (%)	ArX	Yield (%)
	57		83
	83		89
	95 (0.5 eq. AgOTf)		78
	85		96 (3-chlorobiphenyl)
	91		76 (triaryl product)

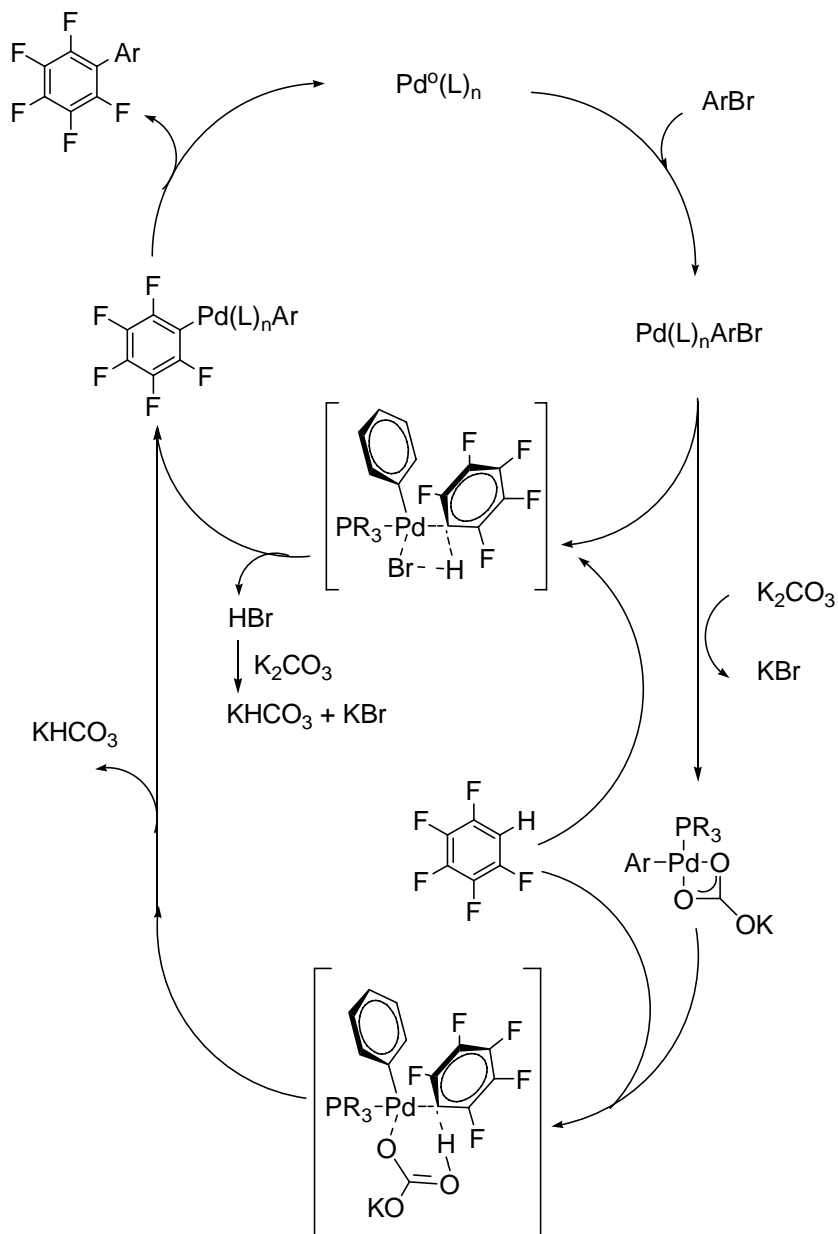
Tetra-, tri- and difluoroarenes also give biaryl products in good to excellent yields (Table 5). Note that mono arylation can be favored by using an excess of the fluoroarene when there is more than one C-H acidic site present. Despite being less electron-deficient, difluoroarenes are also productive substrates for the reaction. Even fluorobenzene is active although the biaryl yield is rather low.

Table 5

			
ArF_n	Yield (%)	ArF_n	Yield (%)
	79 (mono) 20 (di)		68 (mono) 10 (di)
	75 (mono) 24 (di)		86
	92		86
	69 (mono) 24 (di)		85 (1,2,3-tri-substitution)
	43 (mono) 13 (di, regioisomers)		29 (1,2,3-tri-substitution) 9 (di)
	9		

Competition experiments established that the relative reactivity of different fluoroarenes parallels their relative acidities. Likewise, the most acidic proton of any given substrate is the most reactive position for that species. A significant kinetic isotope effect of 3.0 was observed indicating that C-H bond cleavage is a significant event in the catalytic cycle. Two catalytic pathways were proposed as consistent with the experimental data and density functional theory calculations (Figure 3). Both involve concerted metalation of the fluoroarene and then proton transfer to either a Br ligand or carbonate ligand on the catalyst.

Figure 3



Note: This work was published during preparation of the manuscript (JACS **2006**, *128*, 8754).

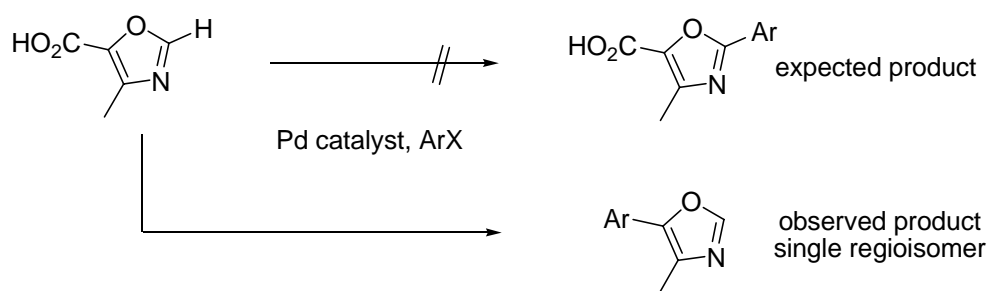
“An Unprecedented Regioselective Intermolecular Pd-Catalyzed Cross-Coupling Reaction Employing Heterocyclic Carboxylic Acids and Aryl Halides”

F. Bilodeau, M.C. Brochu, M. St. Onge, and P. Forgie; Boehringer Ingelheim (Canada) Ltd. Research and Development; Laval, QC.

Aryl substituted heterocycles are widely utilized throughout drug discovery and materials science. These compounds are often synthesized through cross-coupling reactions of aryl halides with heterocyclic organometallics, such as boronic acids, Grignard reagents, and tin compounds. However, alternative approaches such as direct arylation are garnering increased attention for their application to difficult substrate classes and expanded range of substrates.

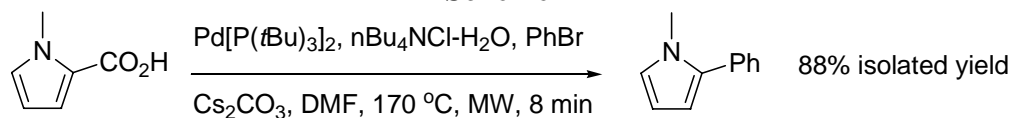
The direct arylation approach to aryl substituted heterocycles has been successfully applied to a number of systems such as furans and thiazoles (OL, **2001**, 3, 1677; BCSJ **1998**, 71, 467). In this work oxazole carboxylic acids were explored as the heterocyclic component for direct arylation (Figure 4). However, none of the expected product was obtained. Interestingly, a single isomer product was isolated in which the carboxylate group had been replaced by an aryl substituent.

Figure 4



Optimization of this new arylation process was performed on *N*-methyl-2-carboxypyrole (Scheme 4). A number of bases and solvents gave good results, but the highest yield and cleanest product were obtained using tetrabutylammonium chloride monohydrate in dimethylformamide. Other aryl halides and sulfonates gave comparable results.

Scheme 4



A variety of heterocyclic carboxylic acids successfully participate in the reaction (Table 6). Note, however, that the best results are obtained when the carbon adjacent to the carboxylate is substituted.

Table 6

RCO₂H	Yield (%)	RCO₂H	Yield (%)
	86		41
	63		decomposed
	74		23
	54		86

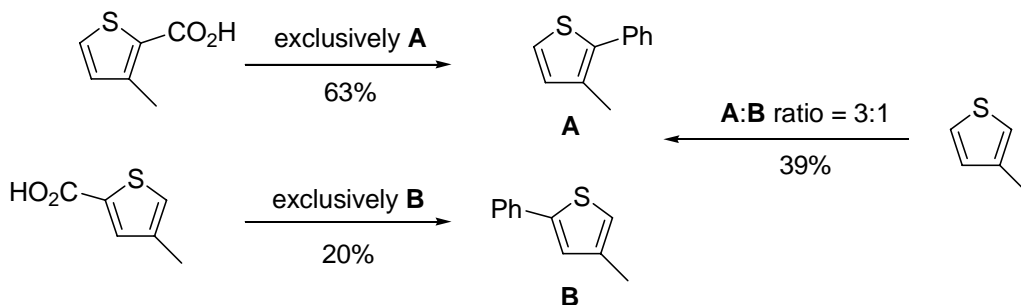
The reaction also exhibits a good scope of the aryl halide coupling partners (Table 7). Electron-rich aryl halides, electron-deficient aryl halides, and heterocyclic halides give good results in most cases.

Table 7

RX	Yield (%)	RX	Yield (%)
	76		80
	0		77
	78		71
	86		18

Significantly, the decarboxylative coupling can give complete control over regioselectivity while direct arylation often gives a mixture of products (Scheme 5).

Scheme 5

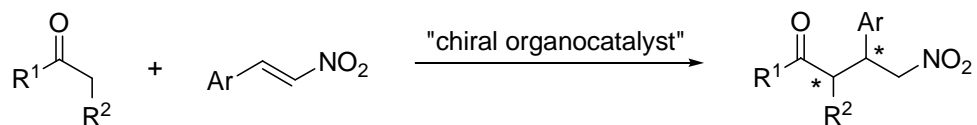


Conditions: PhBr, Pd[P(*t*Bu)₃]₂, *n*-Bu₄NCl·H₂O, Cs₂CO₃, DMF, 170 °C, MW, 8 min

“Organocatalytic Asymmetric Michael Addition of Cyclic Ketones to Nitro-Olefins”
Sunil V. Pansare and Keyur Pandya; Department of Chemistry, Memorial University of Newfoundland.

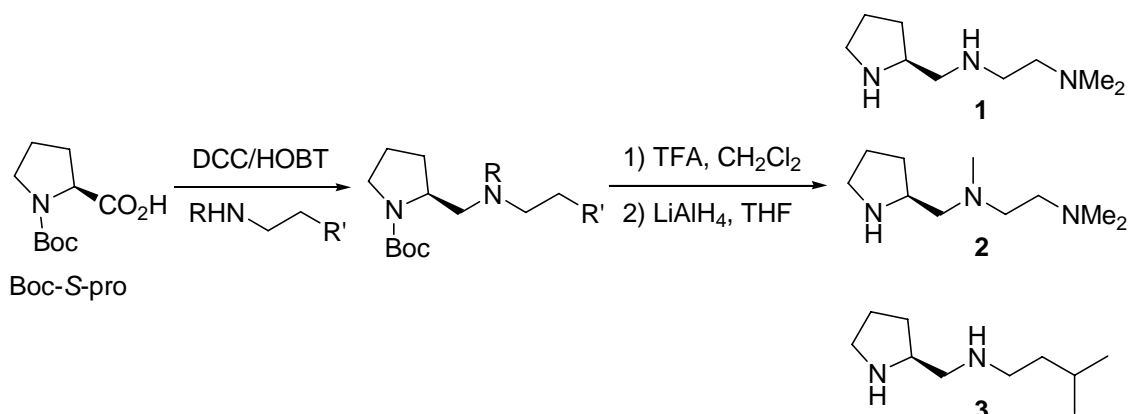
An active area of asymmetric catalysis research is devoted to the development of organocatalytic systems. These systems are attractive due to several advantages over traditional metal-based catalysts. They are more economical, they can tolerate aerobic conditions, and their products are free of metal contaminants. Organocatalysis has been applied toward a wide range of asymmetric reactions in recent years including the conjugate addition of ketones to nitro alkenes. This reaction is of significant interest since the process creates useful synthetic intermediates, γ -nitro ketones, with two contiguous stereocenters in one step (Scheme 6). Chiral pyrrolidine derivatives have been employed in asymmetric Michael reactions with moderate success. However these catalysts required use of low temperatures and a large excess of ketone. Development of a catalyst without these limitations would be desirable.

Scheme 6



Towards this goal a series of pyrrolidine catalysts were synthesized from an inexpensive, readily available proline derivative (Scheme 7). The design incorporated additional amine functionality to potentially provide rate enhancements and to allow for the possibility of conformationally modified, protonated forms of the catalyst.

Scheme 7



Initial experiments were performed in various solvents using cyclohexanone and β -nitrostyrene as the Michael donor/acceptor pair (Table 8). The effect of acid additives was also examined. In these studies the bis secondary amines **1** and **3** proved to be better catalysts than the mono secondary amine **2**. Addition of catalytic *p*TsOH gave considerable improvement in yields and diastereoselectivity (Entries 4/5 and 11/12). Poor solubility of **2**/*p*TsOH in some solvents precluded further study.

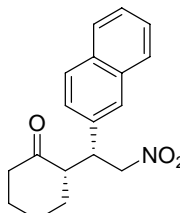
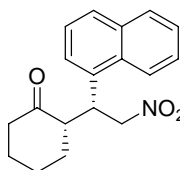
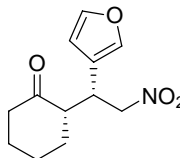
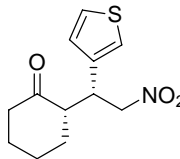
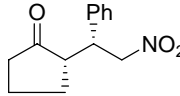
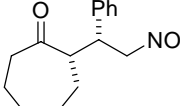
Table 8

Entry	Catalyst	Solvent	Additive	Yield (%)	syn/anti	ee (%) syn
1	1	Toluene	-	40	19/1	90
2	1	<i>i</i> PrOH	-	8	2/1	25
3	1	CH ₂ Cl ₂	-	57	30/1	85
4	1	DMF	-	30	3/1	73
5	1	DMF	<i>p</i> TsOH (20 mol%)	78	5/1	91
6	1	DMF	TFA (20 mol%)	0	-	-
7	2	Toluene	-	21	4/1	47
8	2	Ethanol	-	51	1/1	48
9	2	DMF	-	29	4/1	56
10	3	Toluene	-	90	19/1	87
11	3	DMF	-	51	20/1	76
12	3	DMF	<i>p</i> TsOH (20 mol%)	86	19/1	>99

With optimized conditions for the organocatalyzed Michael reaction available, the scope of the reaction with various ketones and nitroalkenes was then examined. In general, good to excellent diastereoselectivities and enantioselectivities were observed (Table 9). Enantioselectivities for nitroalkenes with 2-substituted phenyl moieties were somewhat lower perhaps due to crowding in the transition state. Note that the sterically less demanding acid, MsOH, gave improved results (Table 9, entry 6). For thiophene and furan substituted olefins MsOH was also found to be a superior additive compared to *p*TsOH (Table 9, entries 9-10). Other cycloketones, such as cyclopentanone and cycloheptanone, gave rather poor results compared to cyclohexanones (Table 9, entries 11-12).

Table 9

Entry	Product	Cat./additive	Yield (%)	syn/anti	ee (%) syn
1		1 / <i>p</i> TsOH	78	19/1	99
2		1 / <i>p</i> TsOH	99	19/1	85
		3 / <i>p</i> TsOH	90	20/1	92
3		1 / <i>p</i> TsOH	95	50/1	86
		3 / <i>p</i> TsOH	97	50/1	88
4		1 / <i>p</i> TsOH	75	3/1	>99
		3 / <i>p</i> TsOH	88	3/1	>99
5		1 / <i>p</i> TsOH	83	19/1	99
6		1 / <i>p</i> TsOH 1 /MsOH	99 93	5/1 50/1	86 99

7		1/pTsOH	90	19/1	>99
8		1/pTsOH	86	12/1	87
9		1/pTsOH 1/MeSO₃H	76 82	19/1 15/1	80 88
10		1/pTsOH 1/MeSO₃H	87 74	8/1 19/1	78 85
11		1/pTsOH 3/pTsOH	51 33	7/1 2/1	29 49
12		3/pTsOH	79	10/1	56

Note: This work was published during preparation of the manuscript (JACS **2006**, *128*, 9624).