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# Enantioselective Palladium-Catalyzed Addition of 1,3-Dicarbonyl Compounds to an Allene Derivative

**Barry M. Trost,* Alessandro B. C. Simas, Bernd Plietker, Christoph Jäkel, and Jia Xie[a]**

**Abstract:** Enhancing atom economy of the metal-catalyzed asymmetric allylic alkylation (AAA) shifts from the usual nucleophilic displacement of a leaving group to an addition of a pronucleophile to a double bond. Using 1-alkoxyallenes as proelectrophiles, the palladium-catalyzed AAA proceeds with 1,3-dicarbonyl compounds as pronucleophiles with excellent regioselectivity and enantiomeric excess under optimized conditions. The pH of the medium proved crucial for reactivity/selectivity. By using the more acidic Meldrum's acids, the reactions required a co-catalytic amount of Brønsted acid, such as trifluoroacetic acid. Single regioisomeric products of 82–99 % *ee* were obtained. On the other hand, the less acidic 1,3-diketones failed to react under such conditions. The fact that a less acidic acid like benzoic acid sufficed, suggested the need for general base catalysis as well. Thus, a mixture of triethylamine and benzoic acid proved optimal (*ee*'s 93–99). Employment of the (*R*,*R*)-phenyl Trost ligand gave a product with *S* configuration. A model to rationalize the results has been developed.

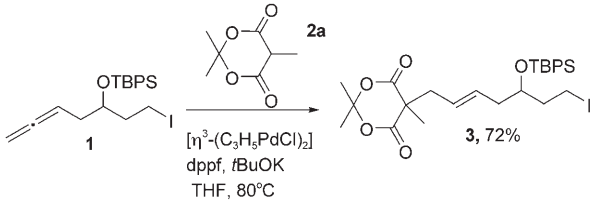
**Keywords:** alkylation · allylic compounds · asymmetric catalysis · palladium · proelectrophiles · pronucleophiles

With the current development status of synthetic methodology, there is a widespread perception that chemists are able to build "from scratch" any material at will. However, the discovery of novel natural products featuring high structural complexity and outstanding biological properties[1] as well as the demand for efficient design of large libraries of micromolecules, as required by the emerging field of chemical genetics,[2] pose new challenges to the field. Chemical selectivity[3] and atom economy,[4] as displayed by reactions featuring asymmetric induction,[5–7] are major goals in the modern chemical enterprise in its search for creativity-driven syntheses and environment-friendly processes. Invention of new reactions or improvement of known processes along these lines hold promise to remove present design constraints in the synthesis of complex molecules.[8] In this context, transition-metal catalysis[7,9] has been particularly fruitful in delivering new synthetic technology targeting such high expectations.

Allylic alkylation represents a very useful and broadly explored transformation among the so-far developed catalytic methodologies. A variety of synthetically useful nucleophiles can be introduced to generate chiral compounds, which can be further elaborated in the synthesis of more complex molecules. However, this reaction needs stoichiometric amounts of base and the starting material possesses a leaving group that is not incorporated in the product. The final goal would be the development of an asymmetric allylic alkylation without the use of stoichiometric amounts of base or of leaving groups.

Some years ago, our group[10] and others[11] disclosed the palladium-catalyzed addition of pronucleophiles to allenes, also referred to as hydrocarbonation of allenes [Eq. (1)]. These investigations showed that compounds possessing acidic hydrogen atoms (such as **2a**) add to allenes (such as **1**) under neutral conditions or in the presence of minimal amounts of base to form adducts (such as **3**) regioselectively.

Based upon experimental evidence,[10] our group proposed a mechanism involving a hydropalladation step instead of the carbopalladation alternative, as outlined in Scheme 1.

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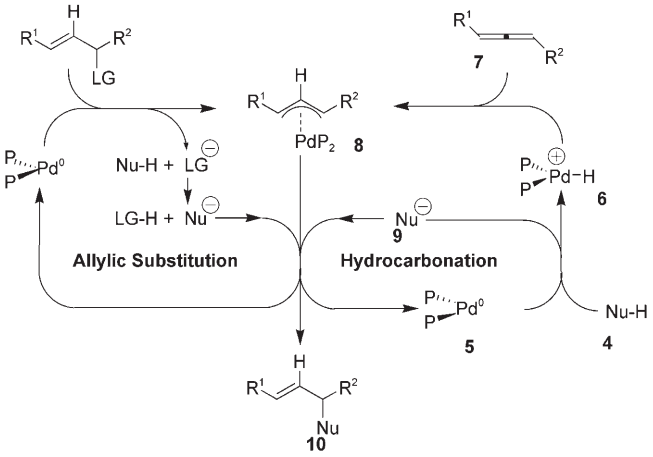
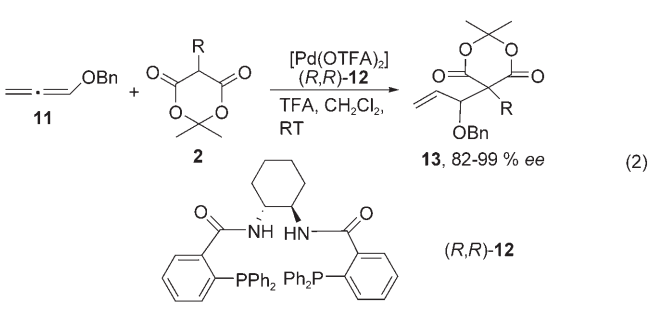



Scheme 1. Allylic alkylation: substitution versus hydrocarbonation.

The pronucleophile **4** releases its acidic proton to a palladium(0) complex **5** producing palladium hydride **6**, which in turn interacts with the allene substrate **7** affording, after hydropalladation, π-allylpalladium intermediate **8**, the common intermediate in Pd-catalyzed allylic alkylations. The nucleophile generated in the catalytic cycle (**9**) attacks this intermediate liberating the palladium complex to initiate another cycle and the product **10**. As a simple addition reaction with a high level of chemoselectivity, this methodology meets the principles of atom economy. Further studies demonstrated its usefulness in the construction of macrocyclic structures.[12]

More recently, a preliminary report of the first enantioselective version of this process from our laboratory appeared.[13] Through the use of two distinct conditions, both Meldrum's acid derivatives [Eq. (2)] and azalactones were regioselectively added to benzyloxyallene providing branched products with high regio- and enantioselectivity. Thus, compared to the highly successful palladium-catalyzed asymmetric allylic alkylations,[6,14] the hydrocarbonation of allenes might be considered a step ahead, as a highly efficient asymmetric induction is attained without the necessity to use equivalent amounts of base or electrophile activation through leaving groups.

To learn more about how the reaction conditions depend upon the nature of the pronucleophiles for good enantioselectivity and about its scope, as well as gaining some mechanistic insight, we focused our attention on the reactions of

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1,3-dicarbonyl compounds. Herein, we report a full account of our studies on the enantioselective addition of Meldrum's acid derivatives to allene **11** under the chiral catalytic system developed by our group[6] and the recent findings regarding its application to reactions in which 1,3-diketones are pronucleophiles.

## Results

Methyl Meldrum's acid (**2a**) was successfully added to benzyloxyallene **11** to afford adduct **13a**, albeit in low selectivities [Eq. (3)], in the presence of the catalyst based on the chiral ligand (*R*,*R*)-**12** and under basic conditions established in our previous work with allenes.[10] The choice of alkoxyl substituent in the allenic substrate **11** followed the precedent in the literature[15] and aimed at selecting the branched adduct (**13a**) over the linear one (**14**). Decreasing the catalyst load[16] improved the *ee*, but left the regioselectivity unaltered (Table 1, entries 1,2). Moreover, addition of tetrabutyl ammonium bromide (TBAB)[17] improved both the branched/linear product ratio and enantioselectivity (entry 3). Substituting THF by dimethyl sulfoxide (DMSO) as solvent allowed the reaction to be conducted at room temperature (entries 4,5). Under such conditions, a dramatic enhancement of reaction efficiency was observed. Further experimentation showed that tetraalkylammonium halides did not have a significant effect on the *ee* for reactions run in DMSO (entries 6–8). Unfortunately, when different batches of **2a** were employed, the best yield and *ee* obtained before could not be reproduced. Purification of these materials was not able to restore the stereoselectivity, which then ranged well below the previous level (45–56%). As a matter of fact, we observed that higher stereoselectivities were obtained with impure samples of **2a**. Variation of the base as well as employment of additives were tried with no success.

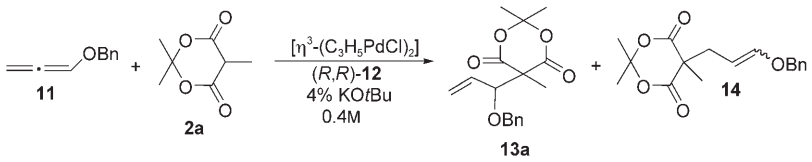
Table 1. Addition of methyl Meldrum's acid **2a** to allene **11** under basic conditions.[a]

| Entry | Conditions[a] | Ratio | Yield [%] | *ee* [%] |
|---|---|---|---|---|
| 1 | THF, 80°C, 12 h[b] | 3.0:1.0 | 69 | 38 |
| 2 | THF, 80°C, 12 h | 2.8:1.0 | 62 | 55 |
| 3 | THF, 4% TBAB, 80°C, 12 h | 7.3:1.0 | 67 | 72 |
| 4 | THF, 4% TBAB, RT, 48 h | – | – | – |
| 5 | DMSO, 4% TBAB, RT, 12 h | >99:1 | 86 | 83 |
| 6 | DMSO, 6% TBAB, RT, 12 h | >99:1 | 90 | 84 |
| 7 | DMSO, 8% TBAB, RT, 12 h | >99:1 | 89 | 84 |
| 8 | DMSO, RT, 12 h | >99:1 | 89 | 83 |

[a] Catalyst: 1.0% $[\eta^3\text{-}(C_3H_5PdCl)_2]$, 2.5% (*R*,*R*)-**12**, unless otherwise stated. [b] 2.0% $[\eta^3\text{-}(C_3H_5PdCl)_2]$, 5.0% (*R*,*R*)-**12**.

As methylmalonic acid is an important contaminant in commercial samples of **2a**, the effect of acid on this reaction was investigated. Experiments using malonic acid as additive demonstrated that, up to a certain level, an increase in acid

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content resulted in an improvement of *ee* (Table 2, entries 1–3) although, an excess of the additive led to a lower yield (entry 4). While use of *t*BuOK at low concentration

Table 2. Addition of methyl Meldrum's acid 2a to allene 11 under acidic conditions.[a]

| Entry | Acid (%) | Yield [%] | *ee* [%] |
|---|---|---|---|
| 1 | malonic (10) | 75 | 57 |
| 2 | malonic (40) | 90 | 77 |
| 3 | malonic (100) | 96 | 87 |
| 4 | malonic (400) | 66 | 85 |
| 5 | malonic (100)[b] | 87 | 86 |
| 6 | malonic (100)[c] | 80 | 71 |
| 7 | AcOH (100) | 81 | 72 |
| 8 | TFA (100) | 34 | – |
| 9 | TsOH (100) | 18 | – |

[a] 2.0% $[Pd(OTFA)_2]$, 2.5% (*R*,*R*)-**12**, 2% *t*BuOK, additive, DMSO, RT, 16 h. [b] No base was added. [c] 20% *t*BuOK instead.

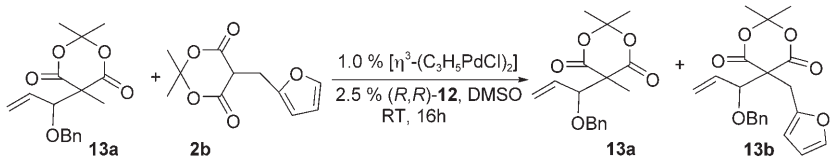
(with 1.0 equiv of malonic acid) had no effect on reaction efficiency (entry 5), a tenfold increase of this additive caused a substantial drop in stereoselectivity (entry 6). Use of AcOH brought about a lower *ee* (entry 7), whereas use of stronger acids had a deleterious effect on both yield and regioselectivity, such that substantial amounts of the linear regioisomer were formed (entries 8,9). The beneficial effect of acid in this case may be related to the nature of the pronucleophile. Under such conditions, the enol form of methyl Meldrum's acid would probably act as nucleophile. Its lower reactivity relative to that of the conjugate base of **2a** would slow down the nucleophilic addition step, enabling a more effective π–σ–π equilibration of the π-allyl–Pd intermediate.[18]

Nonetheless, the following crossover experiments indicated an additional role of acid additives [Eq. (4)]. When

Table 3. Reaction reversibility determined by cross-experiments involving **13a** and **2b**.

| Entry | Additive (%) | Ratio **13a**:**13b** | Yield [%] |
|---|---|---|---|
| 1 | KO*t*Bu (2) | 1.0:1.1 | 99 |
| 2 | – | 1:0 | 80 |
| 3 | malonic acid (100) | 1:0 | 93 |

occur when the same experiment was run under neutral conditions or in the presence of malonic acid (entries 2,3). Therefore, at least part of the selectivity erosion in the reaction run in basic medium could result from oxidative addition to the formed adduct reforming the π-allyl–Pd intermediate. In the presence of acid, such an unproductive pathway was possibly shut off by protonation of palladium. The protonation of palladium(0) complexes to afford the corresponding hydridopalladium(II) species requires relatively strong acids[20] with respect to their nickel or platinum counterparts. Amatore and co-workers demonstrated that complete protonation of the palladium species in the $Pd/PPh_3$/DMF system only occurred when an excess of acetic acid was employed.[21] Thus, considering the lower basicity of ligand **12**, an equilibrium involving the palladium hydride intermediate probably occurs. Unfortunately, under the most effective protocol identified so far, the addition of different Meldrum's acid derivatives to allene **11** displayed high variability with regard to enantioselectivity. These results indicated the need for further development, that is, the definition of a more consistent catalytic system. Moreover, it was clear to us that by using stoichiometric amounts of acid, the full potential of this reaction concerning atom economy had been compromised. We reasoned that the *ee* inconsistency could be aided by using less coordinating solvents (i.e., nonpolar solvents). Furthermore, by using less basic solvents than DMSO, less buffering by the solvent would allow greater effectiveness of the acid at lower concentrations.

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adduct **13a** was treated with Meldrum's acid derivative **2b** under basic conditions, group exchange was observed (Table 3, entry 1). It had previously been shown that carbon-based substituents in allylic positions can serve as leaving groups in palladium-catalyzed reactions if the generated anion is sufficiently stabilized.[19] The crossover did not

As anticipated, changing the solvent to $CH_2Cl_2$ or THF led to high *ee*'s even when smaller quantities of malonic acid were employed (Table 4, entries 1,2). Experiments with the more sensitive substrate **2b** showed that, with 1% of malonic acid as additive, $CH_2Cl_2$ is a better solvent for this reaction (entries 3,4). Furthermore, we learned that the

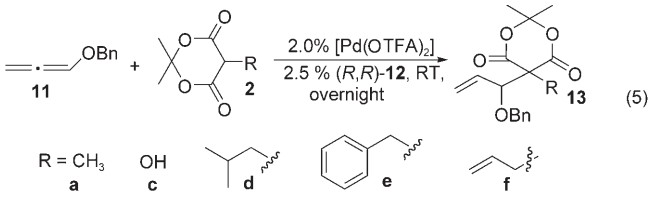
Table 4. Addition of methyl Meldrum's acid **2a** or **2b** to allene **11** in nonpolar solvents under acidic conditions.[a]

| Entry | Meldrum's acid | Acid (mol%) | Solvent | Yield [%] | *ee* [%] |
|---|---|---|---|---|---|
| 1 | **2a** | malonic (10) | THF | 43[b] | 97 |
| 2 | **2a** | malonic (10) | $CH_2Cl_2$ | 46[b] | 98 |
| 3 | **2b** | malonic (1) | THF | 81 | 66 |
| 4 | **2b** | malonic (1) | $CH_2Cl_2$ | 78 | 85 |
| 5 | **2b** | – | $CH_2Cl_2$ | 78 | 86 |
| 6 | **2b** | TFA (1) | $CH_2Cl_2$ | 81 | 94 |
| 7 | **2b** | TFA (2) | $CH_2Cl_2$ | 78 | 91 |
| 8 | **2b** | TFA (4) | $CH_2Cl_2$ | 40 | 88 |

[a] 2.0 mol% $[Pd(OTFA)_2]$, 2.5 mol% (*R*,*R*)-**12**, RT, overnight. [b] Reaction halted after 5 h.

same level of efficiency could be achieved in the absence of malonic acid (entry 5). Gratifyingly, higher *ee*'s could be attained by employment of 1% trifluoroacetic acid (TFA), confirming the decisive role of acid in the reaction under study (entry 6). Raising the TFA concentration, however, decreased both the *ee* and yield as other acid-catalyzed reactions become significant (entries 7,8).

Taking the conditions of entry 6, Table 4, as optimal, the reaction was extended to other Meldrum's acid derivatives as summarized in Equation (5) and Table 5.

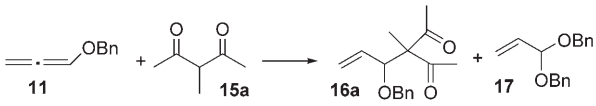


(5)

Table 5. Addition of methyl Meldrum's acid derivatives **2** to allene **11** under optimized conditions.

| Entry | Meldrum's acid | Yield [%] | *ee* [%] |
|---|---|---|---|
| 1 | **2a** | 75 | 99 |
| 2 | **2c** | 63 | 82 |
| 3 | **2d** | 61 | 88 |
| 4 | **2e** | 90 | 91 |
| 5 | **2f** | 82 | 96 |

After the encouraging results obtained for palladium-catalyzed addition of Meldrum's acid derivatives to allene **11**, we set out to investigate the use of 1,3-diketones as pronucleophiles. Their addition to allene **11** would reveal any differences in reactivity and selectivity between cyclic and noncyclic substrates. We started with reactions of 3-methylpentane-2,4-dione (**15a**) using the same chiral catalyst system [Eq. (6), Table 6]. Interestingly, the successful conditions designed for Meldrum's acid derivatives completely failed when applied to diketone **15a** (entry 1). Acetal **17** was the only observed product. Byproduct **17** is supposedly formed after partial degradation of allene **11** under the reaction conditions followed by catalyzed addition of released BnOH to **11**.[22] In fact compound **17** was found to be a common side product in sluggish additions to **11**. Fortunately, we found that in the absence of TFA, compound **15a** reacts to afford adduct **16a** in very high *ee*, albeit rather slowly (entry 2). A higher catalyst load substantially increased chemical yield, but the formation of **16a** was still sluggish (entry 3). Moreover, this modification in the reaction conditions did not lead to a decrease in *ee*, as previously observed with other systems.[16]



(6)

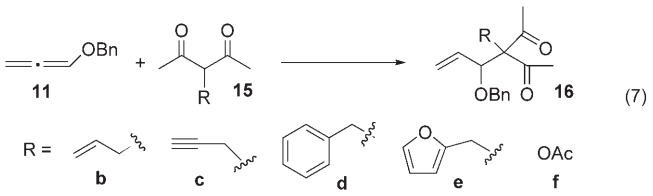
It is worth noting that in contrast to the reactions with Meldrum's acid derivatives, reaction of diketone **15a** proceeded under neutral conditions in high *ee* (Table 6, entries 2 and 3). The reactivity problem should nonetheless be tackled. It might stem from this compound's lower acidity relative to that of **2a** ($pK_{a\,DMSO}$: Meldrum's acid: 7.3; 2,4-pentanedione: 13.3).[23] Addition of acid would facilitate protonation of palladium, but make the conjugate base of the pronucleophile unavailable. Thus, it appeared to us that a buffered system should be applied here. We chose 2:1 $PhCO_2H/Et_3N$ mixtures to probe the acid–base combination effect on the reaction rate. The following results showed that the buffer system indeed made the addition of **15a** to **11** more efficient (2% Pd). Whereas stereoselectivity was maintained, the reaction rate was dramatically improved (Table 6, entry 4). Decrease of additive concentration helped to uniformly increase chemical yield (entries 5,6). Further decrease made its effect irrelevant. Additional experiments were carried out to clarify partial contributions of acid ($PhCO_2H$ and $Et_3NH^+$) and base ($PhCO_2^-$) components of the buffer. They disclosed that both $PhCO_2H$ and $PhCO_2^-$ had a positive effect on reaction rate (entries 7–9).

Table 6. Effect of additives on the addition of diketone **15a** to allene **11**.

| Entry | Conditions[a] | Additive (%) | *T* [h] | Yield of **16a** [%] | *ee* [%] |
|---|---|---|---|---|---|
| 1 | A | TFA (2) | 15 | – | – |
| 2 | B | – | 36–40 | 48[b] | 98 |
| 3 | C | – | 36 | 63 | 98 |
| 4 | B | $PhCO_2H$ (20); $Et_3N$ (10) | 12–15 | 59 | 96 |
| 5 | B | $PhCO_2H$ (10); $Et_3N$ (5) | 12–15 | 65 | 96 |
| 6 | B | $PhCO_2H$ (5.0); $Et_3N$ (2.5) | 12–15 | 73 | 96 |
| 7 | C | $Bu_4NOBz$ (3) | 24 | 65 | 96 |
| 8 | C | $PhCO_2H$ (3) | 24 | 71 | 97 |
| 9 | C | $PhCO_2H$ (3); $Et_3N$ (3) | 24 | 68 | 97 |
| 10 | C | TFA (3); $Et_3N$ (3) | 24 | 36[b] | 97 |

[a] A: 2% $[Pd(OTFA)_2]$, 4% ligand (*R*,*R*)-**12**. B: 1% $[\eta^3\text{-}(C_3H_5PdCl)_2]$, 2.5% ligand (*R*,*R*)-**12**. C: 1.5% $[\eta^3\text{-}(C_3H_5PdCl)_2]$, 3.75% ligand (*R*,*R*)-**12**. [b] Not complete.

The same did not apply to $Et_3NH^+/CF_3CO_2^-$ (entry 10). We applied the optimum conditions to the additions of a series of pentane-2,4-dione derivatives to allene **11** [Eq. (7), Table 7]. To obtain higher yields, 3% Pd and a small excess




(7)

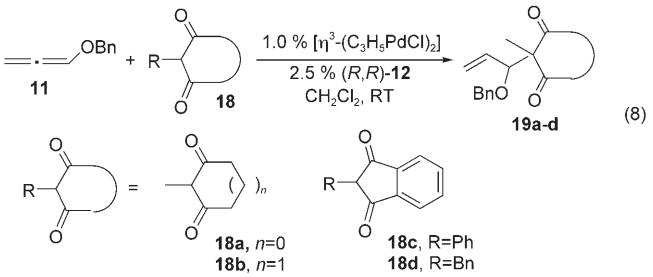
Table 7. Generality of the addition of pentane-2,4-dione derivatives **15** to allene **11**.

| Entry | Pronucleophile | Yield [%][a] | *ee* [%] |
|---|---|---|---|
| 1 | **15b** | 86 | 99 |
| 2 | **15c** | 83[b] | 98 |
| 3 | **15d** | 91 | 99 |
| 4 | **15e** | 97 | 98 |
| 5 | **15f** | 95[c] | 93 |

[a] Optimized conditions: 1.5% $[\eta^3\text{-}(C_3H_5PdCl)_2]$, 3.75% ligand (*R*,*R*)-**12**, allene **11** (1.3 mol equiv), 5% $PhCO_2H$, 2.5% $Et_3N$, RT, 15 h. [b] The same as [a], except for: 1.0% Pd dimer, 2.5% ligand (*R*,*R*)-**12**, allene **11** (1.0 mol equiv). [c] Reaction time: 1 h.

of allene (0.3 mol equiv) was used. Excellent yields and stereoselectivities in the formation of adducts **16** resulted. Interestingly, derivative **15f** reacted very quickly and resulted in a slightly lower enantioselectivity (entry 5). It is possible that in the absence of buffer, a higher efficiency in the formation of **16f** could be accomplished.

Performance of cyclic 1,3-diketones as pronucleophiles was investigated [Eq. (8), Table 8]. A marked difference in reactivity compared to acyclic diketones **15** was observed.




(8)

Table 8. Addition of cyclic 1,3-diketones **18** to allene **11**.

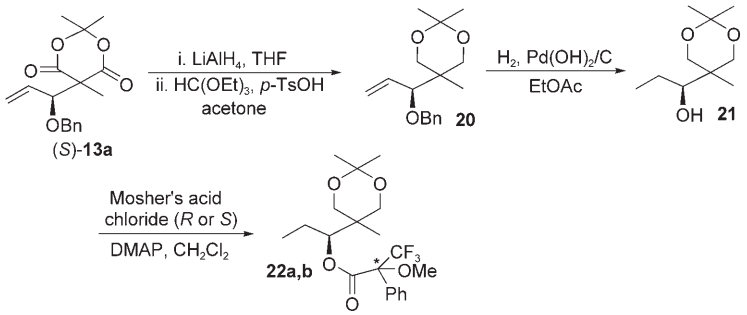
| Entry | Pronucleophile | Conditions[a] | Yield [%] | *ee* [%] |
|---|---|---|---|---|
| 1 | **18a** | A | 67 | 93 |
| 2 | **18a** | B | 66 | 78 |
| 3 | **18b** | A | 90 | 77 |
| 4 | **18b** | B | 70 | 77 |
| 5 | **18c** | A | 88 | <8 |
| 6 | **18d** | A | 77 | 81 |

[a] A: no additive. B: 20% $PhCO_2H$, 10% $Et_3N$.

Cyclopentanedione **18a** reacted with **11** very quickly under neutral conditions to give adduct **19a** in high *ee*. Conversely, analogous diketone **18b** added to allene **11** in moderate *ee*. The reactions of both pronucleophiles resulted in very different behavior towards the buffered system successfully used before. A significant drop in *ee* resulted when the buffer system was employed in the reaction of five-membered diketone **18a**, while no effect on the *ee* was observed with cyclohexanedione **18b**. However, in the latter case, the yield was higher when the reaction was additive-free. Indanediones **18c** and **18d** also reacted under neutral conditions. Although both compounds underwent fast additions, their performance regarding stereoselectivity was very different, with benzyl-substituted derivative **18d** showing a far better enantioselectivity. As a matter-of-fact, substance **18c** was expected to react more selectively than **18d** as its conjugate base is more stable. A slower rate in the nucleophilic addition should lead to higher *ee*. A co-addition experiment showed that indanedione **18c** is nonetheless more reactive than the counterpart **18d**. Such a result indicates that either palladium atom protonation or hydropalladation of allene **11** is the rate-limiting step. In other words, enantioselection occurs in the fast step of these reactions. The low selectivity in the reaction of pronucleophile **18c** may be accounted for by the nucleophile's steric hindrance, which would disrupt molecular recognition by the catalyst. No effort was made to optimize the results obtained with cyclic 1,3-diketones by means of controlling the rate of the nucleophilic addition.[16,17c,d,18]

To determine the enantiodirection of the process under study, we chose to use adduct **13a**, the absolute configuration of which was disclosed by Mosher's NMR method.[24] Thus, this compound was transformed into the saturated secondary alcohol **21**, which upon reaction with the two enantiomeric Mosher's acid chlorides, led to diastereomers **22a** and **22b** (Scheme 2).

According to the accepted model, shielding effects by the phenyl substituent (some of which are shown in Figure 1) indicated the relative configuration shown by diastereomers **22a** and **22b** to be as depicted. Thus, in reactions of pronucleophiles and allene **11** in the presence of the catalyst based on the (*R*,*R*)-**12** ligand, adducts possessing the *S* configuration are formed.




Scheme 2. Derivatization of adduct **13a** to form distereomeric esters **22a**,**b**.

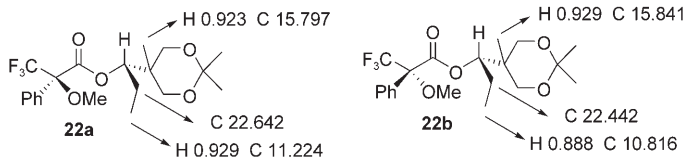



Figure 1. Difference in chemical shifts ($^1$H and $^{13}$C NMR spectra) shown by diastereomers **22a**,**b**.

## Discussion

Our work has shown that hydrocarbonation of allene **11** with Meldrum's acid derivatives **2** becomes more efficient when acid additives are employed in the reaction. As briefly discussed earlier, this finding suggested that the enol form of the pronucleophile, instead of its conjugate base, must take part for higher stereoselectivities to occur. When base was employed, a lower *ee* resulted. Such observations pointed out the need of efficient π–σ–π equilibration in the π-allyl–Pd intermediate (Curtin–Hammett conditions). A less reactive nucleophile would allow a more effective equilibration and, thus, the "matched" π-allyl–Pd intermediate could be more efficiently selected. The observed effect of TBAB on the addition of Meldrum's acid derivatives in THF in the presence of base furnished additional evidence for such an assertion. It has been proposed that this halide effect originates from halide binding to palladium that favors a change of hapticity.[17a,b] Conversely, a higher concentration of the nucleophilic species, which may be the case for reactions run in DMSO and in the presence of acid additives, accelerates the rate of nucleophilic addition. As pointed out previously, insuring that equilibration of the chiral π-allyl–Pd complexes is fast relative to nucleophilic attack is necessary for high *ee*—a requirement that may not be met when nucleophilic addition is very fast.

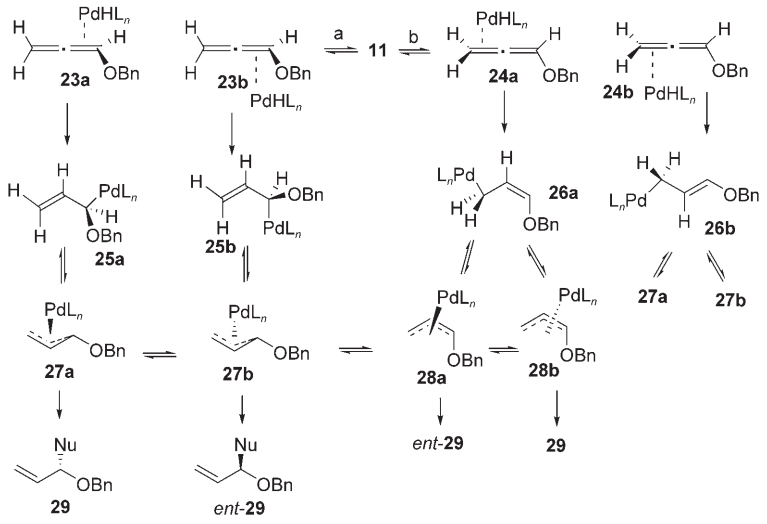
The experiments involving pentane-2,4-dione derivatives **15** indicated a different role for additives in the reaction under study. We reasoned that with less acidic pronucleophiles, the use of acidic additives would be necessary to attain satisfactory rates. However, under such conditions, the pronucleophile's conjugate base would be unavailable and, thus, an effective concentration of its enol form is necessary. We assumed that use of a buffer, such as the $PhCO_2H/Et_3N$ system, might ensure both palladium protonation and efficient formation of the enol tautomer. Naturally, the π-allyl–Pd species involved must be reactive enough towards such a nucleophile. Our results showed that this is, in fact, the best additive system for reactions of pentane-2,4-diones **15**. Conversely, TFA completely inhibited addition of **15a** to allene **11**, whereas its conjugate base apparently had no effect on this reaction. Thus, the formation of a palladium hydride species does not solely guarantee adduct formation. It is clear that the reactivity of the 1,3-diketone's enol form plays an important role here. Pentane-2,4-dione derivatives are known to form enols, as easily detected by $^1$H NMR spectroscopy, and are able to add to **11** under neutral conditions, albeit slowly. Therefore, the observed additive effect may be mainly related to the nucleophilic addition step, possibly by general base catalysis. As an indication of that, we point out that both $PhCO_2H$ and $PhCO_2^-$ species (in the form of $Bu_4N^+$ or $Et_3NH^+$ salts) were equally effective additives. With the former, $PhCO_2^-$ is made available after formation of the palladium hydride intermediate. Thus, co-catalysis by the $PhCO_2H/PhCO_2^-$ additive system afforded the best results (even with lower catalyst loading) by simultaneously providing activation of the pre-catalyst by protonating palladium and generation of the requisite nucleophile, presumably the 1,3-diketone enolate.

The reactions of pentane-2,4-dione derivatives **15** were surprisingly robust with regard to stereoselectivity. The *ee* remained virtually constant over very different conditions. Under neutral conditions, after the hydropalladation step, the nucleophilic species in the nucleophilic addition would naturally be the pronucleophile's conjugate base. It is worth noting that in such a medium, the same degree of enantioselection is obtained as that under acidic or buffered conditions; the enol form of the pentane-2,4-dione derivative likely takes part in this step. It should be noted that acetylacetonate (acac) functions as a ligand to $Pd^{II}$. At a minimum, a pH-dependent equilibrium wherein the acac is bound to $Pd^{II}$ exists under the conditions of the reaction. Since such coordination inhibits alkylation, the more favorable this equilibrium the poorer the reaction rate.

The cyclic 1,3-diketones showed dramatically different effects. First, the reactions are considerably faster which may relate to the fact that they cannot serve as bidentate ligands to Pd in contrast to the acyclic 1,3-diketones. Furthermore, their reactions may be more sensitive to additives resulting in lower enantioselectivities. The source of the effect may derive from an increase in rate of nucleophilic addition in the presence of the additive. On the other hand, by running under neutral conditions, the slower rate of alkylation allows the intermediate π-allyl complexes to equilibrate faster than they can react and thus give higher *ee*. Similar effects have previously been noted.[25]

In general, our results herein affirm the need for nucleophilic addition to be slow in order to obtain good stereoselectivity. In fact, we have shown that additives and steric hindrance at the nucleophile have such an effect on the mechanism that allows an efficient π–σ–π equilibration of the π-allyl–Pd intermediate. Allenes, such as **11**, give rise to this species through hydropalladation according to the accepted mechanism. Allene **11** can undergo hydropalladation through pathways a and b, which would be initiated by a palladium complexation to either the C–C double bond in the allenic system generating either species **23** or **24**, respectively (Scheme 3). Whereas complexes **23a**, **23b**, and **24b** preferentially form the *syn*-π-allyl–Pd intermediates **27a** and **27b** (via **25** and **26b**) after hydropalladation, complex **24a** necessarily affords the *anti*-π-allyl–Pd intermediates **28** (via **26a**). As complex **24b** would be disfavored by steric interaction between the catalyst and the *syn* benzyloxy group, pathway b is likely to produce **24a** preferentially. Although hydropalladation of **11** via complexes **23a**,**b** is electronically



Scheme 3. Mechanistic pathways in the hydropalladation of allene **11**.

favored over complexes **24a**,**b** due to π-basicity, sterically the opposite is true. Thus, pathways a and b are expected to compete leading to formation of both complexes **27** and **28**. Reductive elimination converts intermediates **27a** and **28b** into product **29** and **27b** and **28a** into *ent*-**29**. Previous work showed that, under the catalytic system employed herein, efficient π-facial discrimination occurs in some processes.[26,27] Selection of either **25a** or **25b** could involve diastereoselection in the formation of either complexes **23** or lowering of the energy of one of the involved transition states. The fact that the product obtained corresponds to *ent*-**29** when using the *R*,*R* ligand requires that **27b** and/or **28a** be the reactive intermediates in this ligand-controlled reaction. Nevertheless, considering that our results suggests that high stereoselectivities depend on efficient equilibration of the π-allyl–Pd intermediate, such initial π-facial diastereoselectivity could explain the substantial formation of minor enantiomer **29** in some reactions. Furthermore, structural studies[6a,18] do not support the possibility of *syn* and *anti* intermediates **27b** and **28a**, respectively, converging to the same product *ent*-**29**. The allyl systems thereof would not fit equally well in the chiral catalyst pocket.

## Experimental Section

**Representative procedure for addition of Meldrum's acid derivatives 2 to allene 11**

**5-(1-Benzyloxy-allyl)-2,2,5-trimethyl-[1,3]-dioxa-4,6-dione (13a)**:[13] In a 4 mL Minivert pressure vial, a mixture of $[Pd(OTFA)_2]$ (6.7 mg), ligand (*R*,*R*)-**12** (17 mg) and methyl Meldrum's acid **2a** (316.3 mg, 2.0 mmol) was evacuated and flushed with Ar three times and then diluted with $CH_2Cl_2$ (4.5 mL). Then, a freshly prepared 1 M solution of TFA in $CH_2Cl_2$ (20 μL) was added by syringe. After 30 min of stirring at RT, allene **11** (2.0 mmol) was added by syringe. After stirring overnight, the product was purified by direct flash chromatography on silica gel (3:2 petroleum ether/$Et_2O$) to yield **13a**[13] (527.7 mg, 87%) as a colorless oil, which solidified upon standing, with an *ee* of 97%. Enantiomeric excess was determined by chiral HPLC (Chiralcel AD, heptane/2-propanol (99:1), flow: 1 mL min$^{-1}$, 254 nm): $t_1 = 11.47$, $t_2 = 12.78$). $[\alpha]_D$ ($c = 0.92$ in $CHCl_3$): +22.98; $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 7.37$–$7.20$ (m, 5H), 6.11 (ddd, $J = 19.8$, 10.5, 9.3 Hz, 1H), 5.53 (dd, $J = 9.5$, 1.5 Hz, 1H), 5.38 (dd, $J = 18.7$, 1.2 Hz, 1H), 4.55 (d, $J = 10.8$ Hz, 1H), 4.29 (m, 2H), 1.70 (s, 3H), 1.67 (s, 3H), 1.46 ppm (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 132.0$, 128.2, 123.5, 123.3, 123.1, 118.3, 101.1, 81.8, 66.1, 48.1, 24.8, 23.9, 17.0 ppm; IR (film): $\tilde{\nu} = 1741.5$, 1379, 1290, 1204, 1069 cm$^{-1}$; elemental analysis calcd (%) for $C_{17}H_{20}O_5$ (304.34): C 67.09, H 6.62; found: C 66.91, H 6.47.

**Representative procedure for addition of 1,3-diketones to allene 11**

**3-(1-Benzyloxy-allyl)-3-furan-2-yl-methyl-pentane-2,4-dione (16e)**: Degassed $CH_2Cl_2$ (0.7 mL) was added to a mixture of ligand (*R*,*R*)-**12** (8.85 mg, 3.75 mol%), $(allyl)_2Pd_2Cl_2$ (1.87 mg, 1.5 mol%) and $PhCO_2H$ (2.09 mg, 5.0 mol%), and the resulting mixture was allowed to stir at RT for ≥30 min under inert atmosphere. Then, neat 3-furylmethyl-2,4-pentanedione, (**15e**; 61.6 mg, 57.0 μL, 0.342 mmol), $Et_3N$ (0.86 mg, 2.5 mol%; added as a freshly prepared solution in degassed $CH_2Cl_2$), and neat allene **11** (65 mg, 66.7 μL, 0.445 mmol), in this order, were added by syringe, and the resulting mixture was stirred for 15 h at RT. The reaction mixture was then filtered through a short plug of silica gel and eluted with EtOAc/petroleum ether (1:1). After evaporation of the volatiles, the crude product was purified by flash chromatography to give compound **16e** as a colorless oil (108 mg, 97%) with an *ee* = 98% (HPLC: Daicel OD-H, heptane/2-propanol (90:10), 254 nm; 1 mL min$^{-1}$; 13.76 min (minor) 17.85 min (major)). $[\alpha]_D^{22.2} = +8.75$ ($c = 1.12$ in $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 7.36$–$7.28$ (m, 5H), 6.25 (m, 1H), 6.01 (d, $J = 3.0$ Hz, 1H), 5.59 (m, 1H), 5.47–5.41 (m, 3H), 4.62 (d, $J = 11.1$ Hz, 1H), 4.45 (d, $J = 7.5$ Hz, 1H), 4.33 (d, $J = 11.1$ Hz, 1H), 3.28 (d, $J = 15.4$ Hz, 1H), 3.08 (d, $J = 15.4$ Hz; 1H), 2.21 (s, 3H), 2.09 ppm (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 207.5$, 205.4, 150.3, 141.6, 137.5, 132.6, 128.3, 127.6, 127.4, 121.4, 110.5, 108.8, 81.7, 72.4, 70.9, 30.5, 30.3, 28.0 ppm; IR (neat): $\tilde{\nu} = 1699.1$, 1421.5, 1355.4, 1193.4, 1146.1, 1068.4, 1010.9, 939.3, 735.9, 698.7 cm$^{-1}$; elemental analysis calcd (%) for $C_{20}H_{22}O_4$: C 73.60, H 6.79; found: C 73.72, H 6.70; HRMS (EI): *m*/*z* calcd: 326.1518; found: 326.1517.

**Mosher's ester 22a**: A mixture of alcohol **21** (18.5 mg, 98.3 mmol) (*S*)-MTPA chloride (15.0 μL, 80.3 mmol), and DMAP (12.0 mg, 98.2 mmol) in $CH_2Cl_2$ (0.5 mL) was stirred at room temperature for 2 h ((*S*)-MPTA = α-methoxy-α-(trifluoromethyl)phenylacetic acid; DMAP = 4-dimethylamino pyridine). Then, it was concentrated and purified by flash chromatography to give ester **22a** (24.9 mg, 77%). $[\alpha]_D = +27.96$ ($c = 1.0$ in $CH_2Cl_2$); $^1$H NMR (500 MHz, $CDCl_3$): $\delta = 7.59$–$7.58$ (m, 2H), 7.42–7.40 (m, 3H), 5.30 (dd, $^1J = 10$ Hz, $^2J = 2.5$ Hz, 1H), 3.69 (d, $J = 11.5$ Hz, 1H), 3.60 (d, $J = 12$ Hz, 1H), 3.56 (s, 3H), 3.45 (d, $J = 11.8$ Hz, 1H), 3.37 (d, $J = 12$ Hz, 1H), 1.73–1.69 (m, 1H), 1.64–1.59 (m, 1H), 1.38 (s, 3H), 1.35 (s, 3H), 0.93 (t, $J = 7.5$ Hz, 3H), 0.92 ppm (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta = 166.2$, 132.0, 129.7, 128.5, 127.5, 98.2, 79.9, 66.5, 66.4, 55.5, 37.3, 23.7, 22.6, 15.8, 11.1 ppm; IR (neat): $\tilde{\nu} = 2977$, 2940, 2877, 1746, 1451, 1393, 1374, 1257, 1207, 1189, 1166, 1121, 1085, 1017, 908, 826, 768, 713 cm$^{-1}$; elemental analysis calcd (%) for $C_{20}H_{27}O_5F_3$: C 59.40, H 6.75; found: C 59.18, H 6.86.

**Mosher's ester 22b**: The procedure was the same as the one employed in the preparation of compound **22a**, except for the use of (*R*)-MTPA chloride. The yield was 56% (83% based on recovered starting material). $[\alpha]_D = -10.96$ ($c = 1.0$ in $CH_2Cl_2$); $^1$H NMR (500 MHz, $CDCl_3$): $\delta = 7.57$–7.55 (m, 2H), 7.42–7.41 (m, 3H), 5.26 (dd, $^1J = 10$ Hz, $^2J = 2.5$ Hz, 1H), 3.70 (d, $J = 12$ Hz, 1H), 3.64 (d, $J = 12$ Hz, 1H), 3.50 (s, 3H), 3.45 (d, $J =$

11.8 Hz, 1H), 3.38 (d, $J=12$ Hz, 1H), 1.68–1.64 (m, 1H), 1.61–1.56 (m, 1H), 1.39 (s, 3H), 1.37 (s, 3H), 0.93 (s, 3H), 0.89 ppm (t, $J=7.5$ Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta=166.4$, 131.7, 129.8, 128.6, 127.9, 98.2, 80.0, 66.6, 66.5, 55.2, 37.3, 23.9, 23.6, 22.4, 15.8, 10.8 ppm; IR (film): $\nu=$ 2977, 2940, 2877, 1746, 1451, 1393, 1374, 1257, 1207, 1189, 1166, 1121, 1085, 1017, 908, 826, 768, 713 cm$^{-1}$; elemental analysis calcd (%) for $C_{20}H_{27}O_5F_3$: C 59.40, H 6.75; found: C 59.18, H 6.86.

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[1] a) D. A. Spiegel, J. T. Njardarson, I. M. McDonald, J. L. Wood, *Chem. Rev.* **2003**, *103*, 2691–2727; b) S. J. Mickel, D. Niederer, R. Daeffler, A. Osmani, E. Kuesters, E. Schmid, K. Schaer, R. Gamboni, W. Chen, E. Loeser, F. R. Kinder Jr., K. Konigsberger, K. Prasad, T. M. Ramsey, O. Repic, R.-M. Wang, *Org. Process Res. Dev.* **2004**, *8*, 122–130 and preceding papers; c) C. H. Heathcock, M. McLaughlin, J. Medina, J. L. Hubbs, G. A. Wallace, R. Scott, M. M. Claffey, C. J. Hayes, G. R. Ott, *J. Am. Chem. Soc.* **2003**, *125*, 12844–12849; d) J. L. Hubbs, C. H. Heathcock, *J. Am. Chem. Soc.* **2003**, *125*, 12836–12843.
[2] a) S. L. Schreiber, *Chem. Eng. News* **2003**, *81*(9), 51–61; b) See also: S. Borman, *Chem. Eng. News* **2004**, *82*(9), 32–40.
[3] B. M. Trost, *Pure Appl. Chem.* **1979**, *51*, 787–800.
[4] B. M. Trost, *Science* **1991**, *254*, 1471–1477.
[5] R. Noyori, M. Kitamura, *Angew. Chem.* **1991**, *103*, 90; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 49–69.
[6] a) B. M. Trost, *Acc. Chem. Res.* **1996**, *29*, 355–364; b) B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395–422.
[7] a) R. Noyori, M. Kitamura, T. Ohkuma, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5356–5362; b) B. M. Trost, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5348–5355; c) *Comprehensive Asymmetric Catalysis, Vols. I–III* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Spring, Berlin, **2000**.
[8] T. Hudlicky, *Chem. Rev.* **1996**, *96*, 3–30.
[9] a) B. M. Trost, *Angew. Chem.* **1995**, *107*, 285; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259–281; b) B. M. Trost, *Acc. Chem. Res.* **2002**, *35*, 695–705.
[10] B. M. Trost, V. J. Gerusz, *J. Am. Chem. Soc.* **1995**, *117*, 5156–5157.
[11] Y. Yamamoto, M. Al-Masum, N. Asao, *J. Am. Chem. Soc.* **1994**, *116*, 6019–6020.
[12] B. M. Trost, P.-Y. Michellys, V. J. Gerusz, *Angew. Chem.* **1997**, *109*, 1837–1839; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1750–1753.
[13] B. M. Trost, C. Jäkel, B. Plietker, *J. Am. Chem. Soc.* **2003**, *125*, 4438–4439.
[14] a) B. M. Trost, *J. Org. Chem.* **2004**, *69*, 5813–5837; b) B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921–2943.
[15] Y. Yamamoto, M. Al-Masum, *Synlett* **1995**, 969–970.
[16] a) I. J. S. Fairlamb, G. C. Lloyd-Jones, *Chem. Commun.* **2000**, 2447–2448; b) B. M. Trost, J.-P. Surivet, *J. Am. Chem. Soc.* **2000**, *122*, 6291–6292.
[17] a) M. P. T. Sjogren, S. Hansson, B. Åkermark, A. Vitagliano, *Organometallics* **1994**, *13*, 1963; b) U. Burckhardt, M. Baumann, A. Togni, *Tetrahedron: Asymmetry* **1997**, *8*, 155; c) B. M. Trost, R. C. Bunt, *J. Am. Chem. Soc.* **1998**, *120*, 70–79; d) B. M. Trost, G. M. Schroeder, *J. Org. Chem.* **2000**, *65*, 1569–1573.
[18] B. M. Trost, F. D. Toste, *J. Am. Chem. Soc.* **1999**, *121*, 4545–4554.
[19] Y. I. M. Nilsson, P. G. Andersson, J. E. Bäckvall, *J. Am. Chem. Soc.* **1993**, *115*, 6609–6613; N. Vicart, J. Gore, B. Cazes, *Synlett* **1996**, 850–852.
[20] V. V. Grushin, *Chem. Rev.* **1996**, *96*, 2011–2033.
[21] a) C. Amatore, A. Jutand, G. Meyer, I. Carelli, I. Chiarotto, *Eur. J. Inorg. Chem.* **2000**, 1855–1859; for recent findings on the importance of palladium hydride species, see: b) I. D. Hills, G. C. Fu, *J. Am. Chem. Soc.* **2004**, *126*, 13178–13179.
[22] a) F. P. J. T. Rutjes, T. M. Kooistra, H. Hiemstra, H. E. Schoemaker, *Synlett* **1998**, 192–194; b) H. Ovaa, M. A. Leeuwenburgh, G. A. van de Marcel, J. H. van Boom, *Tetrahedron Lett.* **1998**, *39*, 3025–3028.
[23] F. Bordwell, *Acc. Chem. Res.* **1988**, *21*, 456–463.
[24] S. K. Latypov, J. M. Seco, E. Quiñoá, R. Riguera, *J. Org. Chem.* **1996**, *61*, 8569–8577.
[25] G. Giambastiani, G. Poli, *J. Org. Chem.* **1998**, *63*, 9608–9609.
[26] a) B. M. Trost, F. D. Toste, *J. Am. Chem. Soc.* **1998**, *120*, 9074–9075; b) B. M. Trost, M. J. Krische, R Radinov, G. Zanoni, *J. Am. Chem. Soc.* **1996**, *118*, 6297–6298.
[27] For cases in which π-facial discrimination does not seem to operate efficiently, see: a) reference [18]; b) B. M. Trost, H. C. Shen, L. Dong, J. -P. Surivet, C. Sylvain, *J. Am. Chem. Soc.* **2004**, *126*, 11966–11983.

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