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Bicatalytic Allylation-Cross Metathesis Reactions as γ -Carbonyl Cation Equivalents.

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Abstract: The products corresponding to the reactions of arenes and γ -carbonyl cations may be obtained by a one pot, bicatalytic process involving InCl_3 catalyzed arene allylation and cross metathesis with electron deficient alkenes. The process is success with electronically neutral and electron rich arenes, and modestly Lewis basic donor groups are tolerated with an increase in InCl_3 loading from 10 mol% to 15 mol%, and in one case, 20 mol%.

Key words allylation; electrophilic aromatic substitution; indium; metathesis; Umpolung

The creation of γ -carbonyl cation equivalents (or 1,5-homo-Michael equivalents) (**1**, Figure 1) is a tactic of increasing importance for functionalizing carbonyl systems by way of umpolung synthons.¹ Among methods not involving rearrangement of the carbon framework,² there has been considerable success in the generation and use of γ -carbonyl cationic species stabilized as propargyldicobalt complexes (**2**)^{3,4} or iron allyl complexes (**3**, $\text{ML}_n = \text{Fe}(\text{CO})_4$),^{5,6} however, these methods require stoichiometric complexation and decomplexation steps.⁷ A number of metal catalyzed allylation (**3**, $\text{M} = \text{Pd}, \text{Mo}, \text{Ir}$) and propargylation reactions are known, which have been⁸ or could be in principle be extended to γ -carbonyl cation equivalents. Unfortunately, these have limited electrophilicity and as such are insufficiently reactive with most arenes.⁹ Phosphine catalyzed γ -nucleophilic attack reactions are known for electron deficient alkynes or allenes,¹⁰ but these also require strong nucleophiles for successful reaction. Recently, 3,4-allenoates have shown the capability of undergoing Au^{I} or Pd^{II} catalyzed reactions with nucleophiles to give γ -functionalized alkenoates; based on a limited number of cases, strongly activated arene nucleophiles may be employed.¹¹ In contrast, there have been a number of recent strong Lewis acid catalyzed allylation and propargylation protocols.¹² By far most of these and a few of metal catalyzed systems¹³ require substrates in which the allyl cation is additionally stabilized, rather than being capable of bearing strongly electron withdrawing groups.

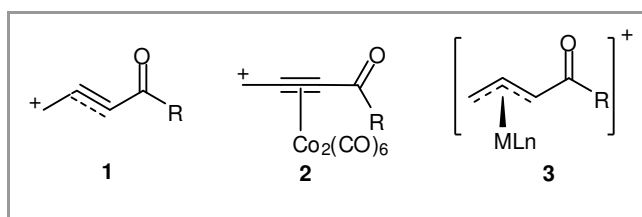
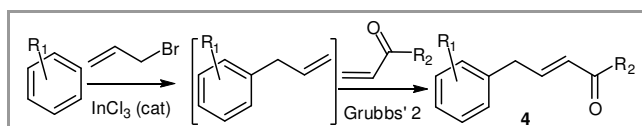


Figure 1 γ -Carbonyl Cations

Among the Lewis acid allylation catalysts, In^{III} has been demonstrated recently to be among the most reactive, as they have the ability to induce allylation from substrates with no additional cation stabilizing groups.¹⁴ Fortunately, allylbenzene is an excellent partner in cross metathesis (CM) for carbonyl substituted alkenes,¹⁵ which are in turn type 2 alkenes with the Grubbs' 2nd generation (G2) precatalyst.¹⁶ As at result, we considered it possible that the products corresponding reaction of γ -carbonyl cations with arenes (**4**, Scheme 1) could be realized by a one pot, bicatalytic allylation-cross metathesis process involving In^{III} . Herein we report our efforts towards this goal.



Equation 1 Allylation-Cross Metathesis Protocol

Initial experimentation began with 1,3,5-trimethoxybenzene (**5a**, 3 equiv, Figure 2) as test nucleophile. In the presence of allyl bromide and 4 Å molecular sieves, 10 mol% InCl_3 gave conversion to 2-allyl-1,3,5-trimethoxybenzene at reflux in CH_2Cl_2 (20 h), but ceased at 90% conversion. Consequently, 15 mol% InCl_3 was employed, to give complete conversion over the same period.¹⁷ At this point, addition of Grubbs' 2 precatalyst and methyl acrylate (**6a**, 3 equiv) showed complete conversion to **4a** at 10 mol% catalyst loading. Unfortunately, the analogous experiments employing methyl vinyl ketone (**6b**) as CM partner afforded no indication of cross metathesis, but rather ¹H NMR spectral analysis revealed the presence of extensive amounts of the product of conjugate addition of 1,3,5-trimethoxybenzene to methyl vinyl ketone (**7**, Figure 3).

In view of the apparent limitations of this protocol, a number of additives were screened in order to minimize the conjugate addition side reactions caused either by residual In^{III} or by the HBr liberated in the allylation process. It was found that addition of NaHCO_3 (3 equiv), prior to the addition of the electron deficient alkene and G2 precatalyst, enabled the CM reaction with methyl vinyl ketone to proceed to give **4b** with 7.5 mol% G2, and with methyl acrylate allowed a reduction in the required amount of Grubbs' 2 precatalyst for conversion to **4a** to 5 mol%.

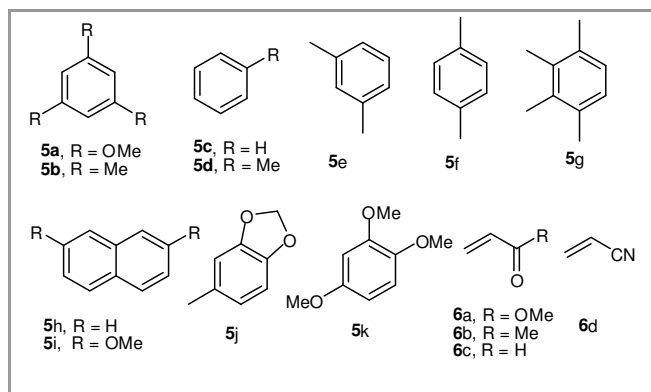


Figure 2 Selected Arenes and Electron Poor Alkenes.

Experimentation moved at this point to mesitylene (**5b**), chosen as a nucleophile representative of arenes without Lewis basic groups. In our hands, and consistent with the work of Cook,^{14a} complete consumption of allyl bromide now occurred with 10 mol% at room temperature in CH_2Cl_2 (20 h), but instead of simple allylation, only the products of allylation followed by HBr addition to the alkene (**8**, Figure 3) were observed in the ^1H NMR spectrum of the reaction mixture. Fortunately, a simple switch in protocol to the addition of solid NaHCO_3 (3 equiv, in addition to the 4 Å molecular sieves) prior to the addition of allyl bromide reduced the amount of **8** to at most trace levels, and did not appear to interfere substantially with the allylation rate. As a result, this protocol was adopted as the general one, with modifications in InCl_3 and G2 loadings to give complete conversions. In most cases, the amount of nucleophile was fixed at 3 equiv, except in the cases of arene nucleophiles sufficiently volatile to be removed readily under vacuum. In those instances larger excesses were employed. Under these conditions the 1,3,5-trimethoxybenzene (**5a**) / methyl acrylate (**6a**) combination afforded **4a** in 67% yield, the 1,3,5-trimethoxybenzene/methyl vinyl ketone (**6b**) combination afforded **4b** in 71% yield, and the mesitylene/methyl acrylate combination gave **4c** in 72% yield (Table 1). Chromatographic separation of each allylation-cross metathesis product was readily accomplished; this is in contrast to the simple allylation intermediates, which were difficult to separate from the arene nucleophile. Each of **4a-n** was isolated as exclusively the *E*- isomer, while ^1H NMR

spectra of the crude reaction products showed pre-purification *E*:-*Z*- ratios of ≥ 96 :4.

One other side product could be observed during this process, during the reactions involving methyl acrylate, which was the formation of small amounts of β -arylalkenoate (cinnamate) **9**. This material was believed to stem from Ru-H induced isomerization of the alkene function of the allylated arene into conjugation with the arene, followed by its cross metathesis.¹⁸ In most cases this was quite minimal in amount ($\leq 4\%$ relative to the intended product), and decreased with increasing ortho- substitution, but was a substantial byproduct in the case of benzene (**5c**, 10 equiv) as nucleophile and methyl acrylate (10% of **8** relative to **4d**). For this case 12 mol% of 1,4-benzoquinone¹⁹ was added to the reaction mixture immediately prior to the 5 mol% G2 precatalyst; this modification reduced the amount of cinnamate byproduct to trace amounts (1-1.5 % relative to **4d**) and allowed the formation of **4d** in good yield (75%).

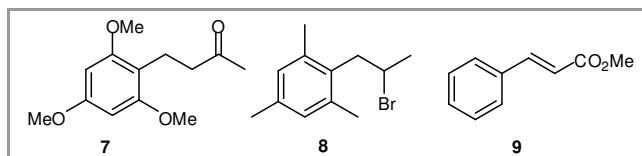


Figure 3 Reaction Side-Products.

The general trends with mesitylene also applied to other arenes lacking Lewis basic functions, in that the 10 mol% InCl_3 , 3 equiv NaHCO_3 , CH_2Cl_2 , RT conditions were sufficient for complete allyl bromide consumption (Table 1, Figure 4). Toluene (**5d**, 10 equiv) ultimately afforded **4e** (82% yield) as a mixture of regioisomers (*o*:-*p*:-*m*- [**4e**:**4e'**:**4e''**] = 60:30:10), while *m*-xylene (**5e**, 10 equiv) gave a mixture of 1,2,4- and 1,2,3- substitution products **4f** (1,2,4:-1,2,3- [**4f**:**4f'**] = 70:30) in 72% yield. While *p*-xylene (**5f**, 5 equiv) and 1,2,3,4-tetramethylbenzene (**5g**, 10 equiv) gave **4g** (65% yield) and **4h** (61% yield) in straightforward fashion, naphthalene (**5h**) gave **4i** with a small amount of the C-2 substitution isomer (**4i'**) along with the C-1 isomer (C-1:C-2 [**4i**:**4i'**] = 87:13, 61% yield).

Table 1 Allylation-Cross Metathesis Results.

Arene (equiv)	InCl_3 (mol%)	T ($^\circ\text{C}$)	6	G2 (mol%)	4	Yield (%)
5a (3)	15	40	6a	5.0	4a	67
5a (3)	15	40	6b	7.5	4b	71
5b (3)	10	22	6a	4.6	4c	72
5c (10)	10	22	6a	5.0 ^a	4d	75
5d (10)	10	22	6a	5.4	4e	82 ^b
5e (10)	10	22	6a	5.0	4f	72 ^c
5f (5)	10	22	6a	5.0	4g	65
5g (10)	10	22	6a	5.0	4h	61
5h (3)	10	22	6a	2.8	4i	61 ^d
5i (3)	15	40	6a	2.4	4j	73
5j (3)	15	40	6a	3.2	4k	61 ^e
5k (3)	20 ^f	61	6a	5.0	4l	60
5b (3)	10	22	6b	3.7	4m	68

5b (3)	10	22	6c	8.9	4n	61
5b (3)	10	22	6d	7.3 ^g	4o	63 ^h

^a 12 mol% 1,4-benzoquinone added

^b **4e**:**4e'**:**4e''** = 60:30:10

^c **4f**:**4f'** = 70:30

^d **4i**:**4i'** = 87:13

^e **4k**:**4k'** = 85:15

^f CHCl₃, reflux, 2 d

^g Hoveya-Grubbs 2 catalyst employed

^h *Z*:*E* = 71:29

The other alkoxyarenes employed as nucleophiles showed significant similarities to 1,3,5-trimethoxybenzene, in that a higher InCl₃ loading (15 mol%) in CH₂Cl₂ at reflux (with 3 equiv NaHCO₃) was required for complete consumption of allyl bromide. Under such conditions, 3,4-methylenedioxytoluene (**5i**) and 2,6-dimethoxynaphthalene (**5j**) were converted into **4j** (73% yield) and **4k** (60% yield) following cross metathesis, the latter case predominantly as the C-1 isomer (C-1:C-3 [**4k**:**4k'**] = 85:15). 1,2,4-Trimethoxybenzene (**5k**) reacted more sluggishly, possibly due to the presence of methoxy groups capable of chelation to In^{III}, but the use of 20 mol% InCl₃ in CHCl₃ at reflux (2 d) slowly gave complete consumption of allyl bromide, and ultimately product **4l** (60% yield).

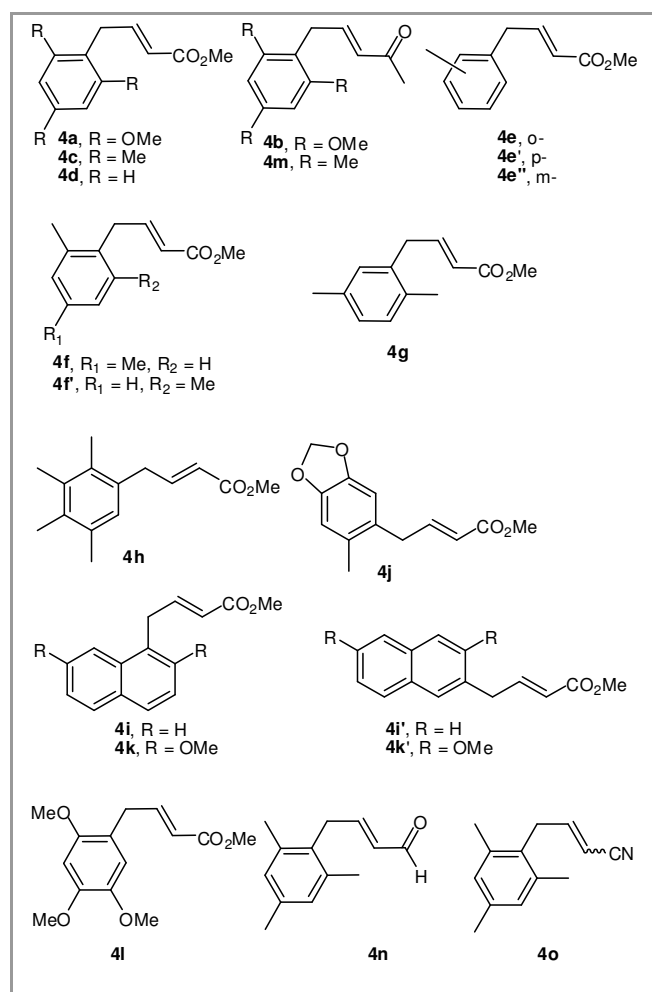


Figure 4 Allylation-Cross Metathesis Products.

Finally, a small number of electron deficient alkenes other than methyl acrylate were investigated in conjunction with mesitylene (**5b**) for the allylation-cross metathesis protocol. Use of methyl vinyl ketone (**6b**) gave **4m** (68% yield) readily, and in contrast to the case employing 1,3,5-trimethoxybenzene, required only 4 mol% of G2 for completion of the CM step. Acrolein (**6c**) also served as suitable partner in the allylation-cross metathesis process, although an increased amount of G2 (9 mol%) was required to obtain **4n** in 61% yield. Finally, the use of acrylonitrile (**6d**) and Hoveyda-Grubbs 2 precatalyst (HG2) (7 mol%) enabled the formation of **4o** (63% yield). As is established in CM reactions with acrylonitrile with HG2, the *Z*-isomer of **4o** predominated (*Z*:*E* = 71:29).²⁰

In summary, we have demonstrated that a bicatalytic, one-pot In^{III} allylation – cross metathesis protocol can afford the products corresponding to the reaction of γ -carbonyl cations with arene nucleophiles. Relative to the complementary Nicholas reaction chemistry, arenes of somewhat more modest nucleophilicity, including benzene, may be employed in the current work. In comparison to other catalytically generated γ -carbonyl cation equivalents, the current protocol may employ far less reactive nucleophiles. Moderately Lewis basic substituents are tolerated in the allylation step, although somewhat more aggressive conditions are required.

Future work will be concerned with the use of substituted allyls for the goal of creating products with γ -substitution, and with other nucleophiles compatible with the bicatalytic allylation-CM protocol.

Experimental Section

To a suspension of InCl₃ (0.0216 g, 0.098 mmol, 15 mol%) and 4 Å molecular sieves (ca. 0.4 g) in CH₂Cl₂ (6 mL) was added 1,3,5-trimethoxybenzene (0.328 g, 1.95 mmol), NaHCO₃ (0.164 g, 1.95 mmol), and allyl bromide (55.0 μ L, 0.650 mmol). The mixture was heated to reflux for 20 h. The mixture was removed from the heating source, at which time methyl acrylate (0.18 mL, 2.0 mmol) and Grubbs 2 precatalyst (0.0143 g, 0.0168 mmol, 2.6 mol%) were added. Following heating to reflux for 10 h, removal of the volatiles under reduced pressure and preparative TLC (2:1 petroleum ether : Et₂O) afforded **4a** as a colourless solid; yield: 0.1167 g (0.438 mmol, 67%). IR (neat) ν = 3000 (m), 2949 (m), 1716 (s), 1652 cm⁻¹ (s); ¹H NMR (500 MHz) δ = 7.05 (dt, *J* = 15.6, 6.4, 1H), 6.14 (s, 2H), 5.72 (dt, *J* = 15.6, 1.6, 1H), 3.82 (s, 3H), 3.79 (s, 6H), 3.69 (s, 3H), 3.46 (dd, *J* = 6.4, 1.6, 2H); ¹³C (125 MHz) δ = 167.5, 160.0, 158.7, 148.4, 120.1, 106.4, 90.5, 55.6, 53.3, 51.2, 25.5; MS *m/z* = 266 (M⁺); HR-MS (EI): *m/z* = 266.1144, calcd. for C₁₄H₁₈O₅; 266.1154.

Supporting Information for this article is available online at <http://www.thieme-connect.com/ejournals/toc/synlett>.

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References

- (1) (a) Hase, T.A. In *Unpoled Synthons*; Hase, T. A.; Ed.; Wiley: New York, **1987**, 292. (b) Green, J. R. *Synlett* **2012**, 23, 1271.
- (2) For selected papers on carbonyl- or donor-acceptor substituted cyclopropanes, see: (a) Qu, J.-P.; Deng, C.; Zhou, J.; Sun, X.-L.; Tang, Y. *J. Org. Chem.* **2009**, *74*, 7684. (b) Lifchits, O.; Alberico, D.; Zakharian, I.; Charette, A. B. *J. Org. Chem.* **2008**, *73*, 6838, and references therein. (c) Hu, B.; Xing, S.; Wang, Z. *Org. Lett.* **2008**, *10*, 5481. (d) Tang, J.; Ren, J.; Wang, Z. *Tetrahedron Lett.* **2008**, *49*, 6659. (e) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321. (f) Harrington, P. A.; Kerr, M. A. *Tetrahedron Lett.* **1997**, *38*, 5949. (g) Danishefsky, S. *Acc. Chem. Res.* **1979**, *12*, 66.
- (3) (a) Taj, R. A.; Green, J. R. *J. Org. Chem.* **2010**, *75*, 8258. (b) Green, J. R.; Tjeng, A. A. *J. Org. Chem.* **2009**, *74*, 7411. (c) Green, J. R. *Chem. Commun.* **1998**, 1751. (d) Vizniowski, C. S.; Green, J. R.; Breen, T. L.; Dalacu, A. V. *J. Org. Chem.* **1995**, *60*, 7496.
- (4) For recent reviews on the Nicholas reaction, see: (a) Diaz, D. D.; Betancort, J. M.; Martin, V. S. *Synlett* **2007**, 343. (b) Teobald, B. J. *Tetrahedron* **2002**, *58*, 4133. (c) Green, J. R. *Curr. Org. Chem.* **2001**, *5*, 809. (d) Fletcher, A. J.; Christie, S. D. R. *J. Chem. Soc., Perkin Trans 1* **2000**, 1657. (e) Welker, M. E. *Curr. Org. Chem.* **2001**, *5*, 785. (f) Müller, T. J. J. *Eur. J. Org. Chem.* **2001**, 2021. (g) Omae, I. *Appl. Organometal. Chem.* **2007**, *21*, 318. (h) Bromfield, K. M.; Gradén, H.; Ljungdahl, N.; Kann, N. *Dalton Trans.* **2009**, 5051.
- (5) (a) Green, J. R.; Carroll, M. K. *Tetrahedron Lett.* **1991**, *32*, 1141. (b) Zhou, T.; Green, J. R. *Tetrahedron Lett.* **1993**, *34*, 4497. (c) Enders, D.; Finkham, M. *Synlett* **1993**, 401. (d) Charlton, M. A.; Green, J. R. *Can. J. Chem.* **1997**, *75*, 965. (e) Enders, D.; Jandeleit, B.; Von Berg, S. *Synlett* **1997**, 421, and references therein. (f) Enders, D.; Jandeleit, B.; von Berg, S.; Raabe, G.; Runsink, J. *Organometallics* **2001**, *20*, 4312.
- (6) For reviews including γ -carbonyl cation equivalents and their vinylogous homologs by way of iron dienyl cations, see: (a) Pearson, A. J. *Adv. Met.-Org. Chem.* **1988**, *1*, 1, and references therein. (b) Pearson, A. J. *Iron Compounds in Organic Synthesis*; Academic: London, **1994**, Chapter 5. (c) Donaldson, W. A.; Chaudhury, S. *Eur. J. Org. Chem.* **2009**, 3831. (d) Donaldson, W. A. *Curr. Org. Chem.* **2000**, *4*, 837.
- (7) For stoichiometric allylmolybdenum cases, see: (a) Zhang, Y.; Liebeskind, L. *J. Am. Chem. Soc.* **2005**, *127*, 11258. (b) Coombs, T. C.; Zhang, Y.; Garnier-Ambland, E. C.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2009**, *131*, 876.
- (8) (a) Pd: Jackson, W. R.; Strauss, J. U. G. *Tetrahedron Lett.* **1975**, 2591. (b) Tsuji, J.; Ueno, H.; Kobayashi, Y.; Okumoto, H. *Tetrahedron Lett.* **1981**, *21*, 2573. (c) Nemoto, T.; Fukuda, T.; Matsumoto, T.; Hitomi, T.; Hamada, Y. *Adv. Synth. Catal.* **2005**, *347*, 1504. (d) Mo: Trost, B. M.; Lautens, M. *Organometallics* **1983**, *2*, 1687. (e) Ir: Baeza, A.; Casas, J.; Nájera, C.; Sansano, J. M. *J. Org. Chem.* **2006**, *71*, 3837.
- (9) (a) Kuhn, O.; Mayr, H. *Angew. Chem. Int. Ed.* **1999**, *38*, 342. (b) Troshin, K.; Mayer, P.; Mayr, H. *Organometallics* **2012**, *31*, 2416.
- (10) For selected papers, see: (a) Trost, B. M.; Li, C. *J. Am. Chem. Soc.* **1994**, *116*, 3167. (b) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535.
- (11) (a) Zhang, Z.; Widenhoefer, R. A. *Org. Lett.* **2008**, *10*, 2079. (b) Tarselli, M. A.; Liu, A.; Gagné, M. R. *Tetrahedron* **2009**, *65*, 1785. (c) Fang, Z.; Fu, C.; Ma, S. *Chem.—Eur. J.* **2010**, *16*, 3910. (d) Fang, Z.; Fu, C.; Ma, S. *Eur. J. Org. Chem.* **2011**, 1227. (e) see also Zhang, M.; Jiang, H.; Dixneuf, P. H. *Adv. Synth. Catal.* **2009**, *351*, 1488.
- (12) (a) Bandini, M.; Tragni, M. *Org. Biomol. Chem.* **2009**, *7*, 1501. (b) Detz, R. J.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2009**, 6263.
- (13) Miyake, Y.; Uemura, S.; Nishibayashi, Y. *ChemCatChem* **2009**, *1*, 342.
- (14) (a) Kaneko, M.; Hayashi, R.; Cook, G. R. *Tetrahedron Lett.* **2007**, *48*, 7085. (b) Lim, H. J.; Keum, G.; Kang, S. B.; Kim, Y.; Chung, B. Y. *Tetrahedron Lett.* **1999**, *40*, 1547. (c) For a Rh^{I} or Ir^{I} based catalyst, see: Tsukada, N.; Yagura, Y.; Sato, T.; Inoue, Y. *Synlett* **2003**, 1431. (d) For cases via Ru^{IV} allyl intermediates, see: Fernández, I.; Hermatschweiler, R.; Breher, F.; Pregosin, P. S.; Veiros, L. F.; Calhorda, M. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 6386. (e) For Mo catalysis, see: Shimizu, I.; Sakamoto, T.; Kawaragi, S.; Maruyama, Y.; Yamamoto, A. *Chem. Lett.* **1997**, 137.
- (15) For recent reviews, see: (a) Prunet, J.; Grimaud, L. In *Metathesis in Natural Product Synthesis*; Cossy, J.; Arseniyadis, S.; Meyer, C., Eds.; Wiley-VCH: Weinheim, **2010**, 287–312. (b) Waetzig, J. D.; Hanson, P. R.; *Chemtracts* **2006**, *19*, 157. (c) Connon, S. J.; Blechert, S. *Angew. Chem. Int. Ed.* **2003**, *42*, 1900.
- (16) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.*, **2003**, *125*, 11360.
- (17) In the absence of molecular sieves, lower conversions occurred.
- (18) Alcaide, C.; Almendros, P.; Luna, A. *Chem. Rev.* **2009**, *109*, 3817.
- (19) Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160.
- (20) (a) Vehlow, K.; Maechling, S.; Blechert, S. *Organometallics* **2006**, *25*, 25. (b) Ledoux, N.; Linden, A.; Allaert, B.; Vander Mierde, H.; Verpoort, F. *Adv. Synth. Catal.* **2007**, *349*, 1692.

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