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# Access to Polyfunctionalized Diquinanes, Hydrindanes, and Decalines via $TiCl_4$ Promoted Michael–Aldol and Baylis–Hillman Reactions

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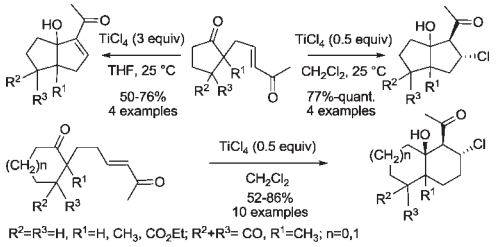
## ABSTRACT




**The addition of 0.5 equiv of $TiCl_4$ to (cyclo)alkanones tethered to $\alpha,\beta$-unsaturated ketones afforded polyfunctionalized diquinanes, hydrindanes, and decalines. These products, resulting from a Michael–aldol or a Baylis–Hillman reaction, can be obtained with high or total diastereoselectivity in moderate to high yields. These scaffolds represent interesting building blocks for the synthesis of complex natural products.**

Fused ring systems, especially diquinane and hydrindane, bearing a hydroxyl group at the ring junction represent important substructures of numerous bioactive natural products. For example, sesquiterpenes or triterpenes, belonging respectively to the capnellene[1] or to the 14$\beta$-hydroxy pregnane family,[2] are characterized by such bicyclic fused ring substructures (Figure 1).

The access to this type of substructures stimulated the development of a large panel of methodologies. Among these, the Hajos–Parrish–Eder–Sauer–Wiechert reaction

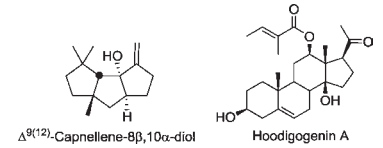



**Figure 1.** Natural products bearing diquinane, hydrindane, and decaline substructures.

is one of the most representative examples readily affording 5-5 and 5-6 fused ring systems bearing (or not) a hydroxy group at the ring junction.[3] Many other reactions were explored to afford such bicyclic ring systems including:

(1) (a) Hu, J.; Yang, B.; Lin, X.; Zhou, X.; Yang, X.; Long, L.; Liu, Y *Chem. Biodiversity* **2011**, *8*, 1011–1032 and references cited therein. (b) Chang, C.-H.; Wen, Z.-H.; Wang, S.-K.; Duh, C.-Y. *J. Nat. Prod.* **2008**, *71*, 619–662. (c) Morris, L. A.; Jaspars, M.; Adamson, K.; Woods, S.; Wallace, H. M. *Tetrahedron* **1998**, *54*, 12953–12958. (d) Kageshika, K.; Shibasaki, M. *J. Org. Chem.* **1991**, *56*, 4093–4094.

(2) (a) Kunert, O.; Simic, N.; Ravinder, E.; Rao, B. V. A.; Kumar, B. R.; Alex, R. M.; Kuehnelt, D.; Rao, A. V. N. A. *Phytochem. Lett.* **2009**, *2*, 134–138. (b) Shukla, Y. J.; Pawar, R. S.; Ding, Y.; Li, X.-C.; Ferreira, D.; Khan, I. A. *Phytochemistry* **2009**, *70*, 675–683.

(3) (a) Hajos, Z. G.; Parrish, D. R. German Patent DE 2,102,623, 1971. (b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. Eder, U.; Sauer, G.; Wiechert, R. German Patent DE 2,014,757, 1971. (c) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496.

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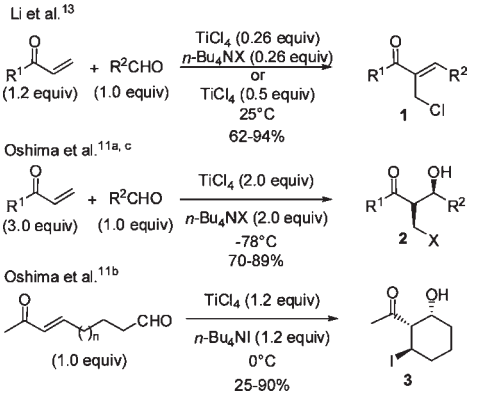
reduction–aldolization tandem reaction,[4] Lewis acid promoted cyclizations,[5] radical cyclizations,[6] TBAF promoted intramolecular cyclizations,[7] and organocatalyzed reactions.[8] On the other hand, the tandem Michael–aldol reaction promoted by Lewis acids was pioneered by Taniguchi,[9] and chalcogenide-$TiCl_4$, $TiCl_4$, or $TiCl_4$/*n*-$Bu_4NI$ mediated inter- and intramolecular reactions between aldehydes and electron-deficient alkenes were studied.[10−14] Particularly, Li[13] and Oshima[11a,c] showed respectively that the addition of $TiCl_4$/*n*-$Bu_4NI$ to a mixture of aldehyde and α,β-unsaturated ketone yielded either compound **1** or Michael–aldol adduct **2**. An intramolecular version of this reaction was also carried out by Oshima et al. starting from an aldehyde tethered to an α,β-unsaturated ketone to deliver the corresponding Michael–aldol product **3** (Scheme 1).[11b]

**Scheme 1.** Previous Michael–Aldol Reactions between Aldehydes and Enones




However, to the best of our knowledge, intramolecular Michael–aldol reactions promoted by $TiCl_4$ were never reported starting from (di)ketones tethered to α,β-unsaturated ketones. Being already involved in the synthesis of polyfunctionalized 5-5 and 5-6 fused ring systems bearing a hydroxyl group at the ring junction,[15] we report herein efficient tandem Michael–aldol and (or) Baylis–Hillman[16] intramolecular reactions promoted by $TiCl_4$. A large variety of polyfunctionalized 5-5, 5-6, and 6-6 fused ring systems were prepared starting from ketones and 1,3-diketones tethered to an α,β-unsaturated ketone. The latter are readily available via a two-step reaction sequence (Michael addition of acrolein followed by a Wittig reaction) starting from commercially available ketones.

The tandem Michael–aldol reaction was first studied starting from the triketone derivative **4**. Our first trial was carried out according to the conditions developed by Oshima et al.,[11] which is the addition of a combination of $TiCl_4$/*n*-$Bu_4NI$ to **4** in dichloromethane at 0 °C. Thus, the iodo derivative was isolated in 75% yield (entry 1). Indeed, according to Oshima et al., the addition of ammonium halide was essential because, in its absence, the Michael–aldol product was only isolated in poor yield (< 10%). However, we observed that the Michael–aldol reaction readily took place at rt when $TiCl_4$ was utilized alone, leading to the chloro derivative **6**, isolated in 89% yield (entry 2). Moreover, the reaction smoothly took place in the presence of 0.5 equiv of $TiCl_4$ (**6**: 74% yield; entry 3) and in the presence of 0.25 equiv of $TiCl_4$ (**6**: 44% yield; entry 4). This result differs also from the observation made by Li et al.: indeed, these authors obtained always the halo α,β-unsaturated keto derivative **1** and not the corresponding Michael–aldol product. Switching to THF as solvent did not improve the yield when less then 3 equiv of $TiCl_4$ were utilized (entries 5–7). However, in the presence of 3 equiv of $TiCl_4$, the yield of **6** increased to 84% (entry 8). The Michael–aldol reaction could also be carried out in ether or dioxane, but the yields were moderate (entries 9–10). The formation of **5** and **6** took place with total diastereoselectivity (Table 1). The structure of **6** was confirmed by X-ray analysis.[17]

These results prompted us to extend the Michael–aldol reaction to other substrates by focusing first of all on the formation of diquinanes. Compounds **7**–**10** were respectively treated with 0.5 or 1.2 equiv of $TiCl_4$ in dichloromethane (Table 2). As indicated by TLC

(4) (a) Chiu, P.; Szeto, C.-P.; Geng, Z.; Cheng, K.-F. *Org. Lett.* **2001**, *3*, 1901–1903. (b) Chiu, P.; Leung, S. K. *Chem. Commun.* **2004**, 2308–2309. (c) Chiu, P. *Synthesis* **2004**, 2210–2215. (d) Huddleston, R. R.; Krische, M. J. *Org. Lett.* **2003**, *5*, 1143–1146. (e) Koech, P. K.; Krische, M. J. *Org. Lett.* **2004**, *6*, 691–694. (f) Deschamp, J.; Riant, O. *Org. Lett.* **2009**, *11*, 1217–1220. (g) Katoh, T.; Mizumoto, S.; Fudesaka, M.; Takeo, M.; Kajimoto, T.; Node, M. *Tetrahedron: Asymmetry* **2006**, *17*, 1655–1662.

(5) (a) Balog, A.; Geib, S. V.; Curran, D. P. *J. Org. Chem.* **1995**, *60*, 345–352. (b) Macdonald, T. L.; Delahunty, C. M.; Mead, K.; O'Dell, D. E. *Tetrahedron Lett.* **1989**, *30*, 1473–1476. (c) Schinzer, D.; Panke, G. *J. Org. Chem.* **1996**, *61*, 4496–4497. (d) Xu, T.; Yu, Z.; Wang, L. *Org. Lett.* **2009**, *11*, 2113–2116. (e) Davis, C. E.; Coates, R. M. *Angew. Chem., Int. Ed.* **2002**, *114*, 509–511. Kang, S.-K.; Kim, Y.-M.; Ha, H-y.; Yu, C.-M.; Yang, H.; Lim, Y. *Tetrahedron Lett.* **2002**, *43*, 9105–9108.

(6) Molander, G. A.; Le Huérou, Y.; Brown, G. A. *J. Org. Chem.* **2001**, *66*, 4511–4516.

(7) (a) Schinzer, D.; Blume, T.; Jones, P. G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2500–2502. (b) Kuroda, C.; Ito, K. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2297–2303.

(8) (a) Lathrop, S. P.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 13628–13630. (b) Vo, N. T.; Pace, R. D. M.; O'Hara, F.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 404–405.

(9) Taniguchi, M.; Hino, T.; Kishi, Y. *Tetrahedron Lett.* **1986**, *27*, 4767–4770.

(10) Kataoka, T.; Kinoshita, H. *Eur. J. Org. Chem.* **2005**, 45–58.

(11) (a) Uehira, S.; Han, Z.; Shinokubo, H.; Oshima, K. *Org. Lett.* **1999**, *1*, 1383–1385. (b) Yagi, K.; Turitani, T.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2002**, *4*, 3111–3114. (c) Han, Z.; Uehira, S.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2001**, *66*, 7854–7857.

(12) Shi, M.; Jiang, J.-K. *Tetrahedron* **2000**, *56*, 4793–4797.

(13) (a) Li, G.; Wei, H.-X.; Gao, J. J.; Caputo, T. D. *Tetrahedron Lett.* **2000**, *41*, 1–5. (b) Li, G.; Gao, J.; Wei, H.-X.; Enright, M. *Org. Lett.* **2000**, *2*, 617–620. (c) Wei, H.-X.; Kim, S.; Caputo, H.; Purkiss, T. D.; Li, D. W. G. *Tetrahedron* **2000**, *56*, 2397–2401. (d) Wei, H.-X.; Gao, J. J.; Li, G. *Tetrahedron Lett.* **2001**, *42*, 9119–9122.

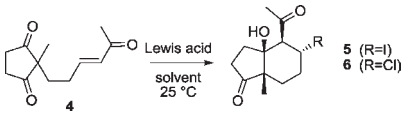
(14) Douelle, F.; Capes, A. S.; Greaney, M. F. *Org. Lett.* **2007**, *9*, 1931–1934 and references cited therein.

(15) (a) Miesch, L.; Welsch, T.; Rietsch, V.; Miesch, M. *Chem.—Eur. J.* **2009**, *15*, 4394–4401. (b) Geoffroy, P.; Ballet, M.-P.; Finck, S.; Marchioni, E.; Miesch, M. *Tetrahedron* **2010**, *66*, 7012–7016.

(16) For reviews concerning the Baylis–Hillman reaction, see: (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811–892. (b) Basavaiah, D.; Veeraraghavaiah, G. *Chem. Soc. Rev.* **2011**DOI: 10.1039/c1cs15174f.

(17) CCDC 784203 contains the supplementary crystallographic data. A copy of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk).

**Table 1.** Optimization of Reaction Conditions for $TiCl_4$ Promoted Michael–Aldol Reaction Starting from Triketone **1**




| entry | conditions | solvent | compd (yield %) |
|---|---|---|---|
| 1 | $TiCl_4$ (1.2 equiv + $n$-$Bu_4NI$ 1.2 equiv)[a] | $CH_2Cl_2$ | **5** (75) |
| 2 | $TiCl_4$ (1.2 equiv) | $CH_2Cl_2$ | **6** (89) |
| 3 | $TiCl_4$ (0.5 equiv) | $CH_2Cl_2$ | **6** (74) |
| 4 | $TiCl_4$ (0.25 equiv) | $CH_2Cl_2$ | **6** (44)[b] |
| 5 | $TiCl_4$ (1.2 equiv) | THF | **6** (40) |
| 6 | $TiCl_4$ (1.5 equiv) | THF | **6** (54) |
| 7 | $TiCl_4$ (2.0 equiv) | THF | **6** (62) |
| 8 | $TiCl_4$ (3.0 equiv)[c] | THF | **6** (84) |
| 9 | $TiCl_4$ (3.0 equiv) | $Et_2O$ | **6** (63) |
| 10 | $TiCl_4$ (3.0 equiv) | dioxane | **6** (59) |

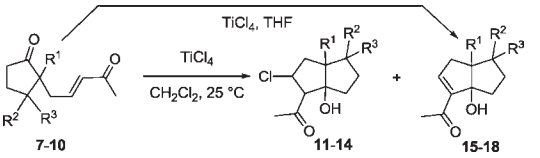
[a] Oshima's reaction conditions (see ref 11b). [b] 36% starting material was recovered. [c] When the reaction was carried out in dichloromethane in the presence of 3 equiv of $TiCl_4$, **6** was isolated in 30% yield.

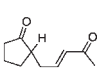
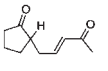
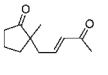
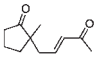
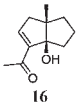
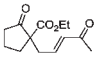
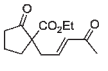
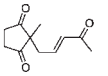
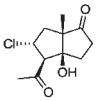
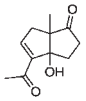
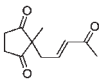
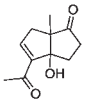
analysis of the crude reaction mixtures, the chloro derivatives **11**–**14** were the major products which were very unstable, except for **13**. Indeed, when silica gel column chromatography was run, an important loss of material was observed and the yields dropped dramatically. During the chromatography, the formation of the α,β-unsaturated ketones **15**–**18** took place. However, these compounds were isolated in poor to good yields. In the presence of 3 equiv of $TiCl_4$ in THF, the formation of **15**–**18**, resulting from a Baylis–Hillman type reaction, took place directly and exclusively except when **7** was used as starting material (Table 2)

Based on these results, ketones **19**–**26** were subjected to the same reaction conditions, leading exclusively to the corresponding chloro derivatives **27**–**34** in 51%–89% yields. In general, the Michael–aldol reaction readily takes place in the presence 0.5 equiv of $TiCl_4$. No products arising from a Baylis–Hillman type reaction were obtained (Table 3).

The addition of $TiCl_4$ to the keto derivatives **19**, **21**, and **22** took place with total diastereoselectivity leading exclusively to the *cis*-hydrindanes **27**, **29**, and **30**. However, starting from compound **20**, the *cis*-hydrindane **28** was isolated along with the corresponding trans isomer (*cis*/*trans* ratio: 8.5/1). For the decaline derivatives, the formation of compounds bearing a *trans* and a *cis* ring

**Table 2.** Optimization of Reaction Conditions for $TiCl_4$ Promoted Michael–Aldol Reaction Starting from Keto Derivatives **7**–**10**




| starting material | $TiCl_4$, solvent | Michael-aldol product (yield) | Baylis-Hillman product (yield) |
|---|---|---|---|
|  **7** | 0.5 equiv $CH_2Cl_2$ |  **11** (quant.[a], 38%[b]) |  **15** (19%)[b] |
|  **7** | 3.0 equiv THF |  **11** (quant.[a], 37%[b]) |  **15** (50%; dr=1.8:1) |
|  **8** | 1.2 equiv $CH_2Cl_2$ |  **12** (quant.) | / |
|  **8** | 3.0 equiv THF | / |  **16** (64%) |
|  **9** | 0.5 equiv $CH_2Cl_2$ |  **13** (77%) |  **17** (6%)[c] |
|  **9** | 3.0 equiv THF | |  **17** (76%) |
|  **10** | 0.5 equiv. $CH_2Cl_2$ |  **14** (quant.)[c] |  **18** (79%, dr=7.8:1)[b] |
|  **10** | 3.0 equiv THF | / |  **18** (63%, dr=3.8:1) |

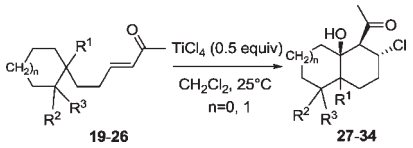
[a] Crude yield: quant. [b] The yields referred to isolated compounds (silica gel column chromatography). [c] In the presence of 0.5 equiv of $TiCl_4$, the reaction proved to be sluggish. [c] In the presence of 0.5 equiv of $TiCl_4$, the reaction proved to be sluggish.

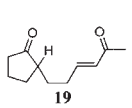
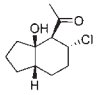
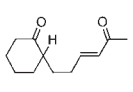
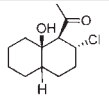
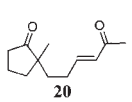
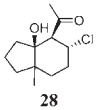
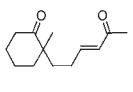
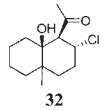
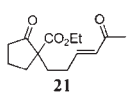
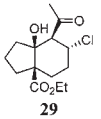
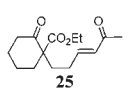
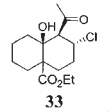
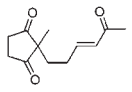
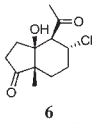
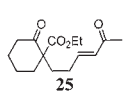
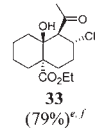
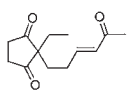
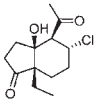
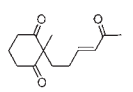
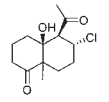
junction always took place. The *trans*-derivatives were the major products except for compound **34**. The structures of compounds **27**, **32**, and **34a** (*cis* ring junction) and **34b** (*trans* ring junction) were confirmed by X-ray analysis.[18]

It should be noted that the addition of $TiCl_4$ to acyclic ketones **35** tethered to α,β-unsaturated ketones readily afforded the corresponding polyfunctionalized cyclohexanes

(18) Compounds **27**, **32**, **34a**, **34b**, **36**, and **37**: see respectively CCDC 843422, CCDC 843424, CCDC 796191, CCDC 796192, CCDC 843425, and CCDC 843426 which contain the supplementary crystallographic data. A copy of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk).

**Table 3.** Formation of Hydrindanes and Decalines Starting fom Triketones **19**–**26**



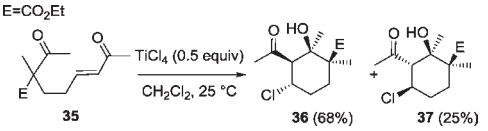

| starting material | Michael-aldol product (yield) | starting material | Michael-aldol product (yield) |
|---|---|---|---|
|  **19** |  **27** (57%)[a] |  **23** |  **31** (75%, dr= 7.3:1)[f] |
|  **20** |  **28** (57%, dr=8.5:1)[b,g] |  **24** |  **32** (86%, dr=2.4:1)[f] |
|  **21** |  **29** (52%)[c] |  **25** |  **33** (50%, dr=4:1)[f] |
|  **4** |  **6** (74%)[d] |  **25** |  **33** (79%)[e,f] |
|  **22** |  **30** (74%) |  **26** |  **34** (50%, dr=4:1)[g] |

[a] 13% starting material was recovered. [b] 15% starting material was recovered. [c] This reaction has to be carried out in the presence of 1.2 equiv of $TiCl_4$. [d] In the presence of 1.2 equiv of $TiCl_4$, **6** was isolated in 89% yield. [e] In the presence of 3 equiv of $TiCl_4$, **33** was isolated in 79% yield. [f] Trans ring junction compounds are major compounds. [g] Cis ring junction compounds are major compounds.

**36** and **37** bearing two vicinal quaternary stereogenic centers. The stuctures of both compounds were confirmed by X-ray analysis (Scheme 2).[18]

To explain our results, it is reasonable to postulate that the formation of the Michael–aldol products takes place via the formation of a *Z*-titanium enolate which undergoes an intramolecular aldol reaction via a chelated six-membered transition state **A** (*cis* ring junction) or **B** (*trans* ring junction).[11b,14] The fact that 0.5 equiv of $TiCl_4$ is sufficient to promote the Michael–aldol reaction could be explained by the putative formation of dimers **C** or **D**. In general, *cis*-diquinanes, *cis*-hydrindanes, and *trans*-decalines (the most stable compounds) were obtained as major products. The formation of the corresponding *trans* and *cis* isomers as minor products is probably due to subtle conformation changes induced by either the presence of different

**Scheme 2.** $TiCl_4$ Promoted Michael–Aldol Reaction Starting from Diketone **35**




substituents at the ring junction or the presence of two carbonyl groups (Figure 2).

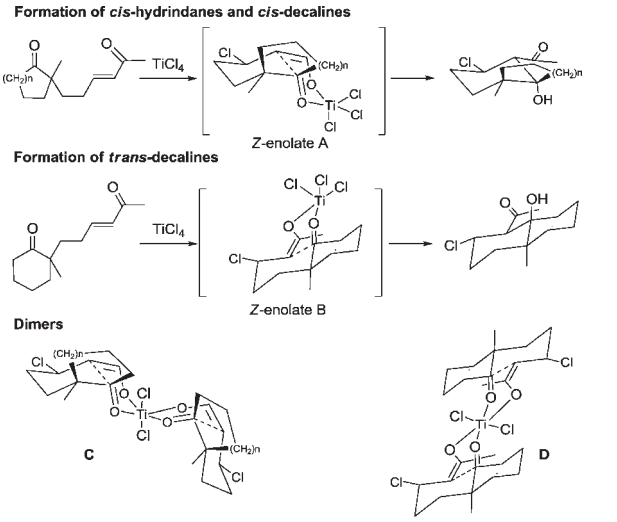



**Figure 2.** Proposed intermediates for the formation of Michael–aldol products.

In summary, we report herein an efficient intramolecular Michael–aldol reaction starting from (di)ketones tethered to α,β-unsaturated ketones. The starting material is easily available (two steps starting from commercially available ketones; no protecting groups are necessary), and 0.5 equiv of $TiCl_4$ is sufficient to promote at rt the Michael–aldol reaction with high or total diastereoselectivity. Further development of our tandem Michael–aldol reaction will be reported in due course.

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**Supporting Information Available.** Analytical data for compounds; $^1H$ and $^{13}C$ spectra for compounds **5**, **6**, **11**–**17**, **27**–**34**; and cif files for compounds **6**, **27**, **32**, **34a**, **34b**, **36**, and **37**. This material is available free of charge via the Internet at http://pubs.acs.org.