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Stepwise approach for sterically hindered C_{sp^3}–C_{sp^3} bond formation by dehydrogenative *O*-alkylation and Lewis acid-catalyzed [1,3]-rearrangement towards the arylalkylcyclopentane skeleton of sesquiterpenes†

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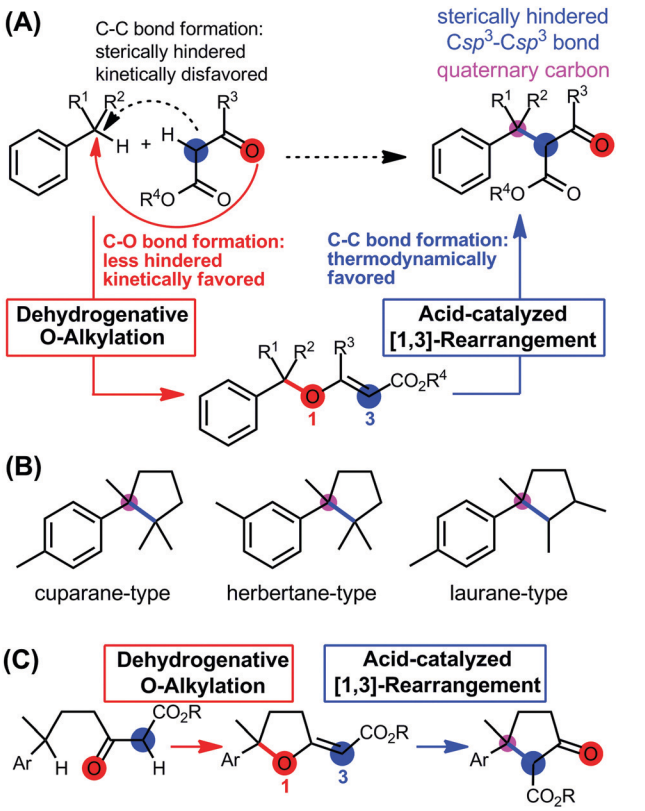
A stepwise dehydrogenative cross-coupling method was developed for the formation of sterically hindered C_{sp^3}–C_{sp^3} bonds. Intramolecular dehydrogenative *O*-alkylation of a β-ketoester by 2,3-dichloro-5,6-dicyano-*p*-benzoquinone to form an oxolane followed by Lewis acid-catalyzed [1,3]-rearrangement furnished the sesquiterpene arylmethylcyclopentane skeleton. The formal syntheses of herbertane-type β-herbertenol, cuparane-type enokipodins A and B were also achieved.

The dehydrogenative C–C bond-forming cross-coupling reaction between two C–H bonds under oxidative conditions is an attractive approach for the construction of organic frameworks since pre-functionalization of C–H bonds of the substrates is not required. While numerous useful dehydrogenative reactions have been developed to date,[1] there are still problems to be overcome. One of these is the difficulty of forming sterically hindered C_{sp^3}–C_{sp^3} bonds such as those with quaternary carbons. For C_{sp^3}–C_{sp^3} bond formation with a quaternary aryltrialkylcarbon, only three metal-catalyzed methods to synthesize β-aromatic α-amino acids,[2a] β-arylethylamines,[2b] and acylimidazoles[3] have been reported by You *et al.* and Ohshima *et al.*, respectively. However, the moderate yields under harsh conditions at high temperatures (80–150 °C) are not satisfactory. To overcome this problem, we propose a stepwise approach consisting of dehydrogenative *O*-alkylation of carbonyl compounds with aryldialkylmethanes[4] and subsequent acid-catalyzed [1,3]-O-to-C-rearrangement[5] to furnish the sterically hindered C_{sp^3}–C_{sp^3} bond with a quaternary carbon under mild conditions (Scheme 1A). Formation of the less hindered C_{sp^3}–O bond is kinetically favored through the nucleophilic attack of the carbonyl oxygen on the oxidatively generated carbocation to give an enol ether. The thermodynamically more stable C_{sp^3}–C_{sp^3} bond is then formed through [1,3]-rearrangement under acidic conditions. As a proof of concept, cuparane-, herbertane-, and laurane-type sesquiterpenes having a quaternary aryltrialkylcarbon structure on a cyclopentane ring were chosen as synthetic targets (Scheme 1B), since a variety of their derivatives have been produced through biosynthesis.[6,7] Their broad useful biological activities



Scheme 1 (A) Stepwise dehydrogenative cross-coupling approach for sterically hindered C_{sp^3}–C_{sp^3} bonds consisting of dehydrogenative *O*-alkylation of β-ketoesters with aryldialkylmethanes and acid-catalyzed [1,3]-rearrangement. (B) Skeletons of cuparane-, herbertane-, laurane-type sesquiterpenes possessing sterically hindered C_{sp^3}–C_{sp^3} bonds with quaternary carbons. (C) Intramolecular dehydrogenative *O*-alkylation and acid-catalyzed [1,3]-rearrangement to arylmethylcyclopentanones.

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have been reported such as antimicrobial, cytotoxic and neurotrophic properties.[7] In this paper, we report the synthesis of arylmethylcyclopentanones by stepwise C_{sp^3}–C_{sp^3} bond formation through intramolecular dehydrogenative *O*-alkylation of a β-ketoester by 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) to give oxolane intermediates and subsequent Lewis-acid catalyzed [1,3]-rearrangement of the oxolanes. The formal syntheses of herbertane-type β-herbertenol[6b] and cuparane-type enokipodins A and B[7d] are also described.

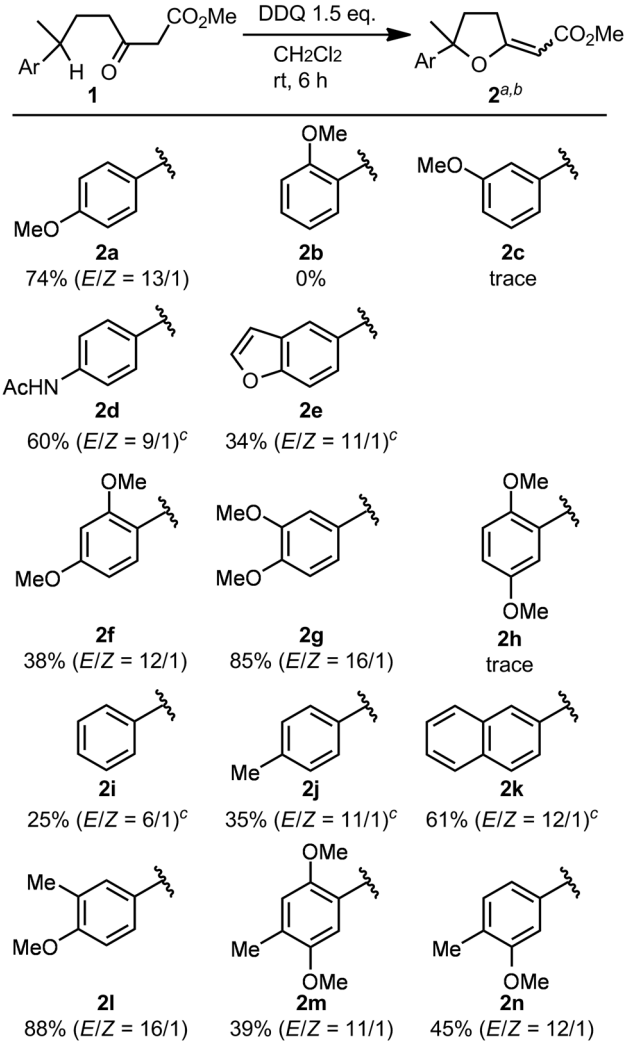
The dehydrogenative *O*-alkylation of ketones with arylmethanes to form enol ethers has not been reported, whereas some redox reactions of benzoquinones[4] are known. First, the intramolecular dehydrogenative *O*-alkylation of β-ketoester **1a** (keto/enol = 10/1) with a 4-methoxyphenyl group was screened, using DDQ, Ph_3CBF_4, $PhI(OAc)_2$, $PhI(OCOCF_3)_2$, $FeCl_3$/^{t}BuOO^{t}Bu, $Mn(OAc)_3$, and $(NH_4)_2[Ce(NO_3)_6]$ as oxidants (Scheme 2).[8] Desired oxolane **2a** was obtained only when DDQ was used. Under conditions using 1.5 eq. DDQ in CH_2Cl_2 at room temperature for 6 h, 74% yield (*E*/*Z* = 13/1) of **2a** was achieved with 7% recovery of **1a**. Using 3.0 eq. DDQ, **1a** was completely consumed and the yield of **2a** was increased up to 87%. While dehydrogenative α-benzylation of 1,3-dicarbonyl compounds with the partial arylmethane structure by $FeCl_2$/^{t}BuOO^{t}Bu, $Cu(ClO_4)_2$/bathophenanthroline/^{t}BuOOCOPh, and DDQ has been reported,[9] **3a** was not observed in our screenings.

With the oxolane **2a** in hand, we attempted the [1,3]-rearrangement of **2a** to cyclopentanone **3a** in the presence of an acid (Scheme 2 and Table S1 in ESI†).[10] The desired **3a** was formed from (*E*)-**2a** by various acids such as TfOH, $BF_3{\cdot}OEt_2$, $BiCl_3$, and Me_3SiOTf at room temperature for 6–18 h, and the best 94% yield was obtained with 100 mol% $Sc(OTf)_3$ for 13 h. Since **3a** was a mixture of keto and enol forms (keto/enol = 2.3/1) as well as the diastereomers of the keto forms (dr = 1.3/1) as judged by ^{1}H NMR, the structure was fully identified only after conversion to a ketone by dealkoxycarboxylation (see ESI†). The amount of $Sc(OTf)_3$ could be reduced to 30 mol% with a similar yield (86%) for 6 h. (*Z*)-**2a** also afforded **3a** in 87% yield under the same conditions.

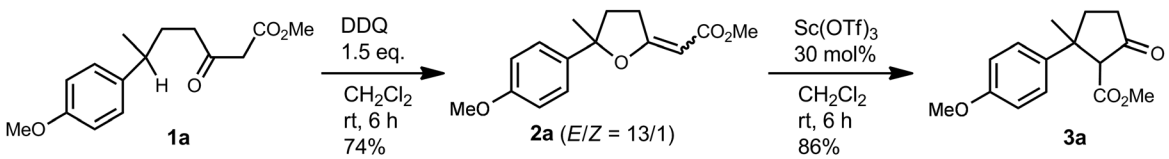
The reactions will proceed through a benzylic cationic intermediate (Scheme S1 in ESI†). At 1st reaction, DDQ oxidation of **1a** generates an intermediate cation and kinetically favored nucleophilic attack of oxygen of the carbonyl group affords the oxolane **2a**. At 2nd reaction, the intermediate cation is generated by acid and the nucleophilic attack of the enolate gives the thermodynamically favored **3a**.

With the successful development of the stepwise method from **1a** with a 4-methoxyphenyl group to **3a** through the oxolane **2a**, we investigated the applicability to the substrates **1** with other substituted phenyl groups. The results of dehydrogenative *O*-alkylation to oxolanes by 1.5 eq. DDQ in CH_2Cl_2 at room temperature are shown in Table 1. In contrast to the high yield of **2a**, the yields of **2b** and **2c** with 2- and 3-methoxy groups were 0% and a trace amount, and **1b** and **1c** were recovered in 95% and 73% yields, respectively. The reaction of **1d** with electron-donating 4-acetoamido group and **1e** with electron-rich benzofuryl group afforded **2d** in 60% and **2e** in 34% yield with the recovery of **1d** in 18% and **1e** in 48%, respectively. The reaction proceeded with substrates **1f** and **1g** with 2,4- and 3,4-dimethoxy groups, giving **2f** and **2g** in 38% and 85% yields. Only a trace

Table 1 Dehydrogenative *O*-alkylation to oxolanes **2**



[a] *E*/*Z* ratio was determined by ^{1}H NMR. [b] Combined yield of both isomers. [c] 24 h.

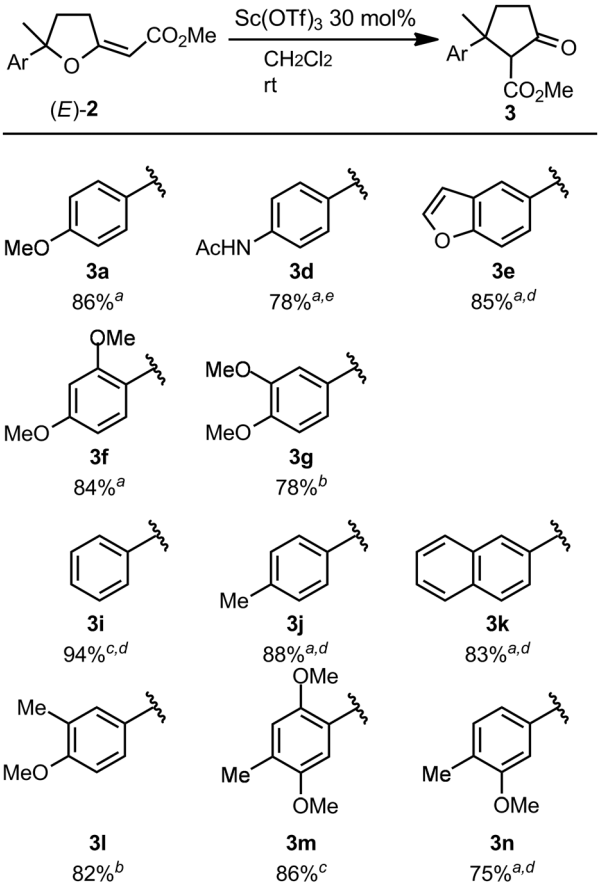


Scheme 2 Intramolecular dehydrogenative *O*-alkylation to an oxolane **2a** and Lewis acid-catalyzed [1,3]-rearrangement to cyclopentanone **3a**.

amount of **2h** was formed in the reaction of **1h** with a 2,5-dimethoxy group. In the case of **1i** with an unsubstituted phenyl group, **2i** was obtained in 25% yield for 24 h. The reaction of **1j** with a weaker electron-donating 4-methyl group compared to the methoxy group afforded **2j** in 35% yield for 24 h. The substrates **1i** and **1j** were recovered in 49% and 38% yields, respectively. The reaction of **1k** with naphthyl group gave **2k** in better 61% yield. Judging from these results, the reaction using DDQ as the oxidant is sensitive to the oxidation potential and the steric hindrance of the substituents, and the electron-rich aryl group stabilizing the intermediate cation is necessary to afford the desired oxolane **2** in high yield. Next, the reaction was applied to the conversion from **1l**, **1m**, and **1n** to the corresponding oxolanes, which can be used as the synthetic precursors for β-herbertenol,[12a] enokipodins A and B,[12b] respectively. The desired **2l**, **2m**, and **2n** were obtained in 88%, 39%, and 45% yields, respectively. **1m** with 2,5-dimethoxy and 4-methyl groups and **1n** with 3-methoxy and 4-methyl groups showed similar reactivities as **2j** with a 4-methyl group rather than **2h** with 2,5-dimethoxy groups or **2c** with a 3-methoxy group.

Next, $Sc(OTf)_3$-catalyzed [1,3]-rearrangement from the obtained (*E*)-**2** to **3** was investigated (Table 2). In all entries, the desired cyclopentanones **3** were obtained in good yields. Under conditions using 30 mol% $Sc(OTf)_3$ in CH_2Cl_2 at room temperature, **2a**, **2f**, and **2g** were converted to **3a**, **3f**, and **3g**, in 86%, 84%, and 78% yields, respectively. Oxolanes **2d**, **2e**, **2i**, **2j**, and **2k** were converted to **3d**, **3e**, **3i**, **3j** and **3k** in 78%, 85%, 94%, 88%, and 83% yield at 40 or 80 °C, respectively. **3l**, **3m**, and **3n** were also obtained in 82%, 86%, and 75% yields. Concerning the reactivity, the oxolanes with less electron-rich aryl groups stabilizing the intermediate cation showed lower reactivity, requiring higher temperature and/or longer reaction time.

Table 2 [1,3]-Rearrangement from oxolanes **2** to cyclopentanones **3**

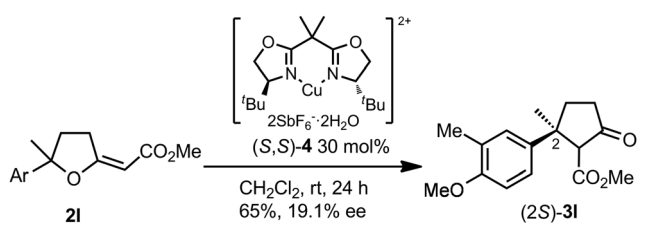


[a] 6 h. [b] 2 h. [c] 24 h. [d] 40 °C. [e] 80 °C.

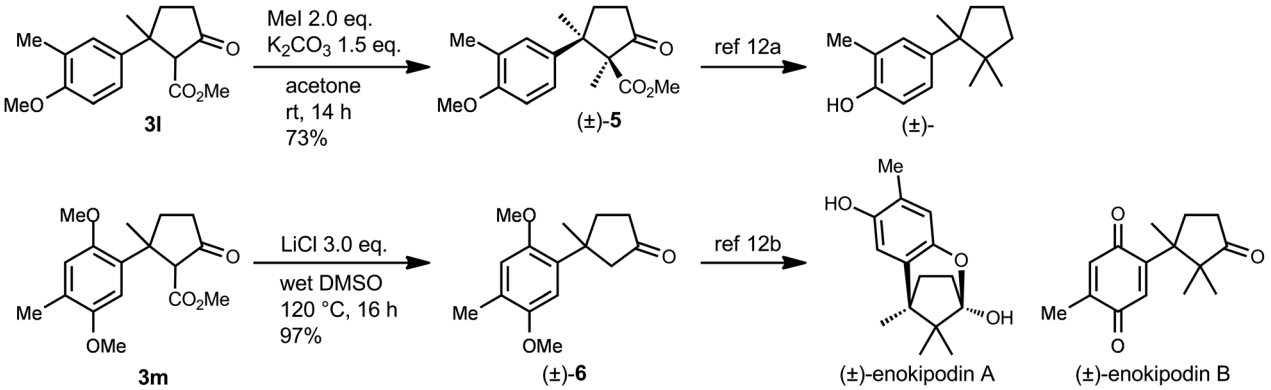
On the basis of the stepwise conversion from **1** to cyclopentanones **3** through oxolanes **2**, the one-pot conversion from **1** to **3** without isolation of **2** was also attempted. Using **1l** as the substrate, which afforded high yields for both reactions, the reaction to **3l** in one-pot was carried out by two methods: (A) addition of DDQ and $Sc(OTf)_3$ at the beginning; (B) stepwise addition of DDQ and $Sc(OTf)_3$ (Scheme 3). In method (A), DDQ and $Sc(OTf)_3$ were added at the start of the reaction. On thin layer chromatography (TLC), formation of **2l** and **3l** was observed. After 8 h, **2l** disappeared on TLC and **3l** was obtained in 52% yield with 19% recovery of **1l**. In method (B), $Sc(OTf)_3$ was added after the confirmation by TLC of the conversion from **1l** to **2l** in 6 h. In 2 h after the addition of $Sc(OTf)_3$, **2l** disappeared and **3l** was obtained in 64% yield. In each method, the yields were slightly lower than the 72% yield for the stepwise method. In method A, the consumption of **1l** was slower than that without $Sc(OTf)_3$, suggesting that the coordination of the Lewis acid to **1l** lowers the oxidation potential and suppresses the oxidation by DDQ. In both methods, the hydrobenzoquinone of DDQ generated *in situ* is suspected to cause side reactions during the [1,3]-rearrangement resulting in the slightly lower yields of **3l**.

To explore the applicability of our developed method to catalytic enantioselective syntheses, we investigated the asymmetric induction on the [1,3]-rearrangement step (Scheme 4). Using an asymmetric Cu(II) catalyst (*S*,*S*)-**4** with a (*S*,*S*)-^{t}Bu-BOX ligand,[11] (2*S*)-**3l** was formed with 19.1% ee (see ESI†). Although the enantiomeric excess was not practical, the applicability of

Scheme 3 One-pot conversion by (A) addition of DDQ and Sc(OTf) from the beginning and (B) stepwise addition of DDQ and $Sc(OTf)_3$.



Scheme 4 [1,3]-Rearrangement of **2l** to **3l** using an asymmetric Cu catalyst (*S*,*S*)-**4**.



Scheme 5 Formal syntheses of (±)-β-herbertenol, (±)-enokipodins A and B.

this method to catalytic enantioselective synthesis was demonstrated in principle.

Finally, **3l** and **3m** were further derivatized to reported synthetic intermediates **5**[12a] and **6**[12b] for β-herbertenol, enokipodins A and B, respectively (Scheme 5). Methylation of **3l** by K_2CO_3 and MeI in acetone afforded the intermediate **5** stereoselectively in 73% yield. Decarboxylation of **3m** by LiCl in wet DMSO gave the intermediate **6** in 97% yield. Thus, the formal syntheses of β-herbertenol, enokipodins A and B were achieved.

In summary, we succeeded in developing a stepwise dehydrogenative cross-coupling method for the sterically hindered C_{sp^3}–C_{sp^3} bond formation consisting of intramolecular dehydrogenative *O*-alkylation of β-ketoesters **1** by DDQ to oxolanes **2** and [1,3]-rearrangement of **2** by $Sc(OTf)_3$ to arylcyclopentanones **3**. Using an asymmetric Cu catalyst, asymmetric induction in the [1,3]-rearrangement step was demonstrated. Formal syntheses of β-herbertenol, enokipodins A and B were also accomplished by the derivatization of **3**. Although the method still has a limitation on the oxidation potentials of the aryl groups owing to the oxidizing ability of DDQ, the approach was proven to be effective for the construction of sterically hindered C_{sp^3}–C_{sp^3} bonds with quaternary carbons. This method is expected to be applicable for the construction of other skeletons. The developed dehydrogenative *O*-alkylation of carbonyl compounds also would be attractive for syntheses of oxolane derivatives. This approach is a safer method to form sterically hindered C_{sp^3}–C_{sp^3} bonds between 1,3-dicarbonyl compounds and arylmethanes compared to the metal-catalyzed insertion into the C–H bond of arylmethanes of a carbene generated from potentially explosive diazocarbonyl compounds.[12a]

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 Reviews; (*a*) S. A. Girard, T. Knauber and C.-J. Li, *Angew. Chem., Int. Ed.*, 2014, **53**, 74; (*b*) R. Narayan, K. Matcha and A. P. Antonchick, *Chem. – Eur. J.*, 2015, **21**, 14678.
2 (*a*) K. Li, Q. Wu, J. Lan and J. You, *Nat. Commun.*, 2015, **6**, 8404; (*b*) M. Tan, K. Li, J. Yin and J. You, *Chem. Commun.*, 2018, **54**, 1221.
3 T. Tanaka, K. Hashiguchi, T. Tanaka, R. Yazaki and T. Ohshima, *ACS Catal.*, 2018, **8**, 8430.
4 For benzoquinones' redox reactions with arylmethanes to form hydroquinones' ethers, see the following references; (*a*) G. Song, Z. Zheng, Y. Wang and X. Yu, *Org. Lett.*, 2016, **18**, 6002; (*b*) M. A. Hossain, K. Akiyama, K. Goto and K. Sugiura, *ChemistrySelect*, 2016, **1**, 3784; (*c*) Y. Ando, T. Matsumoto and K. Suzuki, *Synlett*, 2017, 1040; (*d*) G. A. Shevchenko, B. Oppelaar and B. List, *Angew. Chem., Int. Ed.*, 2018, **57**, 10756.
5 Reviews; (*a*) S. J. Meek and J. P. A. Harrity, *Tetrahedron*, 2007, **63**, 3081; (*b*) C. G. Nasveschuk and T. Rovis, *Org. Biomol. Chem.*, 2008, **6**, 240.
6 (*a*) A. Matsuo, S. Yuki and M. Nakayama, *J. Chem. Soc., Chem. Commun.*, 1981, 864; (*b*) Y. Asakawa, R. Matsuda, W. B. Schofield and S. F. Grandstein, *Phytochemistry*, 1982, **21**, 2471; (*c*) T. Suzuki, H. Kikuchi and E. Kurosawa, *Bull. Chem. Soc. Jpn.*, 1982, **55**, 1561.
7 (*a*) A. Matsuo, S. Yuki and M. Nakayama, *J. Chem. Soc., Perkin Trans. 1*, 1986, 701; (*b*) Y. Fukuyama and Y. Asakawa, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2737; (*c*) N. K. Ishikawa, K. Yamaji, S. Tahara, Y. Fukushi and K. Takahashi, *Phytochemistry*, 2000, **54**, 777; (*d*) L. Harinantenaina and Y. Asakawa, *Chem. Pharm. Bull.*, 2004, **52**, 1382; (*e*) L. Harinantenaina, D. N. Quang, T. Nishizawa, T. Hashimoto, C. Kohchi, G. Soma and Y. Asakawa, *Phytomedicine*, 2007, **14**, 486; (*f*) I. Komala, T. Ito, F. Nagashima, Y. Yagi and Y. Asakawa, *J. Nat. Med.*, 2010, **64**, 417; (*g*) J. Otaka, T. Shimizu, Y. Futamura, D. Hashizume and H. Osada, *Org. Lett.*, 2018, **20**, 6294.
8 Oxolane formation through a nucleophilic attack of a carbonyl group to a cation generated by the other methods than oxidative dehydrogenation of a CH bond; (*a*) K. Ohkata, T. Sakai, Y. Kudo and T. Hanafusa, *J. Org. Chem.*, 1978, **43**, 3070; (*b*) H. Arimoto, S. Nishiyama and S. Yamamura, *Tetrahedron Lett.*, 1990, **31**, 5619; (*c*) R. Tapia, M. J. Cano, H. Bouanou, E. Alvarez, R. Alvarez-Manzaneda, R. Chahboun and E. Alvarez-Manzaneda, *Chem. Commun.*, 2013, **49**, 10257.
9 Dehydrogenative C–C bond formation between arylalkylmethane and 1,3-dicarbonyl compounds: (*a*) Z. Li, L. Cao and C.-J. Li, *Angew. Chem., Int. Ed.*, 2007, **46**, 6505; (*b*) N. Borduas and D. A. Powell, *J. Org. Chem.*, 2008, **73**, 7822; (*c*) D. Ramesh, U. Ramulu, S. Rajaram, P. Prabhakar and Y. Venkateswarlu, *Tetrahedron Lett.*, 2010, **51**, 4898.
10 Lewis acid-catalyzed [1,3]-rearrangement of benzyl enol ethers; (*a*) A. Gansäuer, D. Fielenbach and C. Stock, *Adv. Synth. Catal.*, 2002, **344**, 845; (*b*) A. Gansäuer, D. Fielenbach, C. Stock and D. Geich-Gimbel, *Adv. Synth. Catal.*, 2003, **345**, 1017.
11 D. A. Evans, D. M. Barnes, J. S. Johnson, T. Lectka, P. Matt, S. J. Miller, J. A. Murry, R. D. Norcross, E. A. Shaughnessy and K. R. Campos, *J. Am. Chem. Soc.*, 1999, **121**, 7582.
12 (*a*) S. P. Chavan, M. Thakkar, R. K. Kharul, A. B. Pathak, G. B. Bhosekar and M. M. Bhadbhade, *Tetrahedron*, 2005, **61**, 3873; (*b*) J. Buter, R. Moezelaar and A. J. Minnaard, *Org. Biomol. Chem.*, 2014, **12**, 5883.

